SUPPLEMENTARY MATERIAL

*Porzia cum Radix Pini* Rescues Barium chloride-induced Arrhythmia by Regulating the ADORA1-Involved cGMP-PKG Signalling Pathway in Zebrafish

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Abstract:

The traditional Chinese medicine *Porzia cum Radix Pini* (PRP) is a fungal medicinal material that has been proven to play an important role in the treatment of arrhythmia. However, the mechanism of its effect on arrhythmia is still unclear. In this study, network pharmacology and metabolomics correlation analysis methods were used to determine the key targets, metabolites and potential pathways involved in the effects of PRP on arrhythmia. The results showed that PRP can significantly improve cardiac congestion, shorten the SV-BA interval and reduce the apoptosis of myocardial cells induced by barium chloride in zebrafish. By upregulating the expression of the ADORA1 protein and the levels of adenosine and cGMP metabolites in the cGMP-PKG signalling pathway, PRP can participate in ameliorating
arrhythmia. Therefore, we believe that PRP shows great potential for the treatment of arrhythmia.

**Keywords:** Arrhythmia; *Poría cum Radix Pini*; ADORA1; cGMP-PKG signalling pathway; Zebrafish.

**Supplementary File S1**

**S1.1 LC$_{50}$ experiment methods**

The embryos of 72hpf zebrafish were divided into six groups: control group, model group, verapamil positive control group, PRP-high dose, medium dose and low dose group. The arrhythmia model of zebrafish was established using the chemical drug barium chloride, and verapamil hydrochloride injection was used as the positive control group. Sixty zebrafish embryos with normal development after fertilization were taken from each group and placed in 48-well plates. Model group was set at 5 concentrations of 58.3, 52.5, 47.25, 42.5 and 38.25 µg/mL. The positive group was given 5 concentrations of 12.25, 11, 9.9, 8.91 and 6 µg/mL, and the PRP group was given 5 concentrations of 4800, 4320, 3888, 3499 and 3149 µg/mL (2 Wells per concentration, five embryos per well, 2 mL). After 24 h incubation with sterile saline solution of barium chloride, verapamil hydrochloride, or PRP extract, and the survival number of zebrafish embryos was recorded.

**S1.2 LC$_{50}$ experiment and results**

The LC$_{50}$ of the model group was 42 µg/mL, the positive group was 9 µg/mL, and the PRP group was 4878 µg/mL by regression analysis in SPSS 26.0 software. The drug concentration of model group and positive control group was set at 1/20 LC$_{50}$ (2.1 µg/mL and 0.45 µg/mL). The dose of PRP in high, medium and low administration groups were 1/30 LC$_{50}$, 1/40 LC$_{50}$, 1/50 LC$_{50}$ (162.60 µg/mL, 121.95 µg/mL, and 97.56 µg/mL), respectively. Then, zebrafish embryos were randomized divided into six groups and placed on 48-well cell culture plate (ten embryos per group, five embryos per well): control, model (barium chloride sterile saline solution 2.1 µg/mL, 2mL), positive control (model + injection 0.45 µg/mL), and three treatment groups (PRP-H: model + PRP extract 162.60 µg/mL,
PRP-M: model + PRP extract 121.95 µg/mL, PRP-H: model + PRP extract 97.56 µg/mL).
All animal handling and experimental conditions were approved by the Laboratory Animal Care and Use Committee of the Shaanxi University of Chinese Medicine.

**Supplementary File S2**

**Metabolomics Analytical validation**

**S2.1 Sample preparation**

To prepare the calibration curve, appropriate amounts of the adenosine and cGMP reference materials were accurately measured, and a 1:1 methanol: water solution was added to produce a stock solution of 0.1 mg/mL for each reference material. The working standard solution was prepared by continuously diluting the stock solution to obtain the necessary concentration, and all solutions were stored at 4°C until use.

The metabolic sample preparation method was consistent with the nontarget metabolomics sample preparation method.

**S2.2 LC-MS analysis**

Metabolites were quantified with an AB Q Trap 4500-Agilent 1290 liquid chromatography-electrospray ionization/mass spectrometry (LC-ESI/MS) system with an external standard method. An Infinity Lab Poroshell 120HILIC-Z column (100 mm×2.6 mm, 2.7-Micron with column ID) was used under the following conditions: mobile phase A, 0.2% formic acid in H2O; mobile phase B, acetonitrile; linear elution time, 30 min; gradient elution conditions, 0~1.5 min, 10% B, 1.5~23 min, 10%~99% B, 23~24 min, 99% B, 24~27 min, 99%~10% B, 27~30 min, 90% B. The column temperature was maintained at 30°C. ESI positive and negative ion modes were used for scanning, and the detection mode was multi-reaction monitoring. The ion spray voltages of positive and negative ion modes are 5500 V and 4500 V. TEM at 550°C, GS1 and GS2 were nitrogen with 344.738 kPa (50 psi) and CUR 241.316 kPa (35 psi). Collection parameters for compound ion pair optimization: DP, CE and cell exit potential (CXP), as shown in Table S1. All data were analyzed using Analyst Software 1.6.3, and metabolites were quantified using Multiquant Software 2.1.
Table S1 Mass spectrometric information of adenosine and cGMP

| Metabolite | Ion mode | $t_R$/min | Parent ion ($m/z$) | Daughter ion ($m/z$) | DP/V | CE/eV | CXP/V |
|------------|----------|-----------|-------------------|---------------------|------|-------|-------|
| adenosine  | Positive | 0.86      | 268.1             | 136.1               | 235.44 | 21.99 | 6.00  |
| cGMP       | Negative | 1.56      | 344.1             | 150.0               | -104.5 | -29.23 | -9.82 |

S2.3 Method validation

The methodology was investigated from the aspects of precision, limit of detection, limit of quantification, linearity, precision, stability, reproducibility, matrix effect and extraction recovery.

S2.3.1 Precision

The metabolite adenosine and cGMP standard were measured for 6 consecutive times, the RSD values of peak area and retention time were 0.02% and 0.08%, respectively. The RSD values of retention time were 0, which indicated that the precision of the instrument was good.

S2.3.2 LOD and LOQ and Linearity

When the signal-to-noise ratio (S/N) of the analyte is greater than 3:1, the detection limit is obtained; when the signal-to-noise ratio (S/N) is greater than 10:1, the quantification limit is obtained. From this definition, the detection limit and quantification limit of adenosine were 3ng/mL and 15ng/mL, respectively, and the detection limit and quantification limit of cGMP were 0.03ng/mL and 0.1ng/mL, respectively. By diluting the QC samples step by step, the linear regression equation of adenosine was $Y= 112.58 \times +1214$, and the correlation coefficient R was 0.9994. The linear regression equation of cGMP was $Y= 3445 \times +599.45$, and the correlation coefficient R was 0.9999, indicating that the two metabolites had a good linear relationship.

S2.3.3 Repeatability

Six QC samples were prepared in parallel, and the RSD values of adenosine and cGMP peak area were 0.10% and 0.01%, respectively, and the RSD values of retention time were 0.02% and 0.01%, respectively, which indicated that the method had good repeatability.

S2.3.4 Stability
In order to determine the stability of the treated samples, the samples were stored in an automatic sampler at 4°C, and the peak areas were measured at 0, 24 and 48h, respectively. The RSD values of the peak areas of adenosine and cGMP were calculated as 8.36% and 2.87%, respectively, and the retention time RSD values were 0 and 2.18%, respectively, which indicated that the samples had good stability.

S2.3.5 Matrix effect and extraction recovery

By adding the mixed standard solution to the zebrafish metabolic sample in the control group after protein removal, and comparing its peak area with the peak area of each standard in the standard solution, the matrix effects of adenosine and cGMP were calculated to be 90.08% and 85.80%, respectively. It showed that the biological matrix of zebrafish metabolism sample didn’t affect the determination of the sample. By comparing the peak area of the zebrafish metabolic sample in the control group before deproteinization and the peak area of the mixed standard solution after deproteinization, the extraction recovery rates of adenosine and cGMP were calculated to be 81.07% and 80.49%, respectively, which indicated that the extraction method of this sample was stable and reliable.

Supplementary File S3

S3.1 PRP chemical components identification conditions

The concentration of PRP extract was 9.6 mg/mL. The PRP extract solution was analysed on a Waters Acquity H-CLass ultra-performance LC (Waters, MA, USA) / tandem a 5600+ triple-quadruple time-of-flight mass spectrometer (QTOF-MS) system (AB SCIEX, MA, USA) using a Waters BEH C18 column (50 mm × 2.1 mm, 1.7 µm). With a gradient mobile phase of 0.1% formic acid aqueous solution (A) and 0.1% formic acid-acetonitrile solution (B) at a flow rate of 0.3 mL/min and 30°C column temperature. The gradient program was as follows: 0~1 min, 2% B; 1~42 min, 2%~100% B; 42~44 min, 100% B; 44~48 min, 100%~2% B; 48~50 min, 2% B. Full scan and MS/MS experiments were performed under positive and negative modes by using an electrospray ionization (ESI) ion source. Information-dependent data (IDA) acquisition mode was used to switch automatically between MS and MS/MS acquisition with the following parameters: ionspray voltage
floating: +5500 V or -4500 V, declustering potential (DP): 40 V, ion source gas 1 and ion source gas 2 both set as nitrogen: 50 psi; curtain gas: 35 psi; source temperature: 500°C. The scanning range of parent ions (TOF-MS) was 50 to 2000 m/z. The eight strongest peaks exceeding 100 cps were collected by MS2, and the subion scanning range was 1000~2000 m/z. Data were acquired using Analyst TF software (version 1.7.1, AB SCIEX). Components identification was performed by using Peakview software (version 2.2, AB SCIEX), and Masterview software (version 1.1, AB SCIEX) coupled with TCM library 1.0 database.

### S3.2 UPLC/Q-TOF-MS components identification of PRP

Under the optimized chromatographic and mass spectrometry conditions, UPLC/Q-TOF-MS in positive and negative detection modes was used to analyse the alcohol extract of PRP. The results showed that 31 compounds were identified in positive ion mode and 5 in negative ion mode (Table S2). According to the molecular weight, retention time, and MS/MS data of the four compounds analysed using UPLC-TOF-MS chromatography, four compounds of PRP were identified: pachymic acid, glycyrrhetinic acid, oleanolic acid and adenosine (Figure S1 A-D) (Table S3).

#### Table S2 Compounds identified by MS in positive/negative ion mode

| NO | Name               | Molecular Formula | Extraction Mass (Da) | Found at RT(min) | Adduct |
|----|--------------------|-------------------|----------------------|------------------|--------|
| 1  | Pachymic acid      | C_{33}H_{52}O_{5}  | 529.38875            | 30.31            | +H     |
| 2  | Schisandrin A      | C_{24}H_{32}O_{6}  | 417.22716            | 25.86            | +H     |
| 3  | Vitamin K1         | C_{15}H_{26}O_{2}  | 451.35707            | 30.31            | +H     |
| 4  | Alisol B 23-acetate| C_{32}H_{58}O_{5}  | 515.37312            | 29.09            | +H     |
| 5  | Hydroxycamptothecine| C_{20}H_{16}N_{2}O_{5} | 365.1132          | 0.5              | +H     |
| 6  | Glycyrrhetinic acid| C_{18}H_{32}O_{6}  | 471.34688            | 19.85            | +H     |
| 7  | Oleanolic acid     | C_{30}H_{48}O_{3}  | 457.36763            | 33.02            | +H     |
| 8  | Schisandrin B      | C_{23}H_{32}O_{6}  | 401.19588            | 27.48            | +H     |
| 9  | Linoleic acid      | C_{18}H_{32}O_{2}  | 281.24751            | 32.38            | +H     |
| 10 | Schisanhenol       | C_{23}H_{30}O_{6}  | 403.21153            | 23.67            | +H     |
| 11 | Adenosine          | C_{10}H_{13}N_{3}O_{4} | 268.10402         | 0.56             | +H     |
| 12 | Vitamin A acid     | C_{20}H_{38}O_{2}  | 301.2162             | 36.54            | +H     |
| 13 | Aristolone         | C_{18}H_{22}O_{2}  | 219.17434            | 20.56            | +H     |
| 14 | Kaurenoic acid     | C_{26}H_{38}O_{2}  | 303.23186            | 30.14            | +H     |
| 15 | Schisandrin        | C_{24}H_{32}O_{7}  | 433.22209            | 17.7             | +H     |
| 16 | 1,2,3,7-tetramethoxyxanthone | C_{17}H_{16}O_{6} | 317.10197          | 17.64            | +H     |
| 17 | Ligustilide        | C_{12}H_{14}O_{2}  | 191.10666            | 20.42            | +H     |
| No. | Name                                | Molecular Formula | MW    | Purity | Charge |
|-----|-------------------------------------|-------------------|-------|--------|--------|
| 18  | polygalaxanthone III               | C_{25}H_{25}O_{15} | 569.1501 | 8.36   | +H     |
| 19  | 1,2,3,6,7-pentamethoxyxanthone     | C_{10}H_{19}O_{7}  | 347.11253 | 15.54  | +H     |
| 20  | 1,7-dimethoxyxanthone              | C_{16}H_{13}O_{4} | 257.08082 | 16.71  | +H     |
| 21  | Glucosamine Hydrochloride          | C_{6}H_{11}NO_{5}  | 180.08665 | 0.59   | +H     |
| 22  | Tanshinone II A                    | C_{18}H_{15}O_{3} | 295.13286 | 26.3   | +H     |
| 23  | L-Valine                           | C_{3}H_{11}NO_{2} | 118.08626 | 0.56   | +H     |
| 24  | Adenine                            | C_{3}H_{12}N_{3}  | 136.06177 | 0.6    | +H     |
| 25  | guanosine                          | C_{10}H_{13}N_{5}O_{3} | 284.09895 | 0.55   | +H     |
| 26  | Xylitol                            | C_{3}H_{12}O_{5} | 153.07574 | 0.58   | +H     |
| 27  | nicotinamide                       | C_{6}H_{6}N_{2}O   | 123.05529 | 0.75   | +H     |
| 28  | Tectorigenin                       | C_{18}H_{12}O_{6} | 301.07066 | 17.67  | +H     |
| 29  | Trigonelline                       | C_{2}H_{7}NO_{2} | 138.05496 | 0.57   | +H     |
| 30  | Polydatin                          | C_{20}H_{22}O_{8} | 391.13875 | 9.05   | +H     |
| 31  | 2-Methoxycinnamic acid             | C_{10}H_{16}O_{3} | 179.07026 | 31.2   | +H     |
| 32  | Lobetyolin +HCOOH                  | C_{20}H_{22}O_{8} | 441.17662 | 27.35  | -H     |
| 33  | 2-HYDROXYADENOSINE                 | C_{10}H_{13}N_{5}O_{3} | 282.0844 | 0.5    | -H     |
| 34  | Scopolamine Hydrobromide           | C_{17}H_{21}NO_{4} | 302.13979 | 46.47  | -H     |
| 35  | Nuciferin                          | C_{19}H_{21}NO_{2} | 294.14995 | 0.54   | -H     |
| 36  | Peimine                            | C_{27}H_{43}N_{3}O_{3} | 430.33266 | 36.57  | -H     |

![Diagram A](image1.png)

![Diagram B](image2.png)
Figure S1 MS/MS diagram and structural formula of the components contained in the alcohol extract of PRP.

Table S3 Compounds identified by MS2 in positive ion mode

| NO. | Name          | Molecular Formula | Extraction Mass (Da) | Found at RT(min) | Daughter ion          |
|-----|---------------|-------------------|----------------------|------------------|-----------------------|
| 1   | Pachymic acid | C_{33}H_{52}O_{5} | 529.38875            | 30.31            | C_{33}H_{50}O_{4}     |
| 2   | Oleanolic acid| C_{30}H_{48}O_{3} | 457.3676             | 33.02            | C_{30}H_{46}O_{2}, C_{29}H_{46}O, C_{30}H_{44} |
| 3   | Glycyrrhetinic acid | C_{30}H_{46}O_{4} | 471.34688           | 19.85            | C_{30}H_{44}O_{2}     |
| 4   | Adenosine     | C_{10}H_{13}N_{5}O_{4} | 268.10402       | 0.56             | C_{5}H_{5}N_{5}       |

Supplementary File S4

S4.1 Determination of key target of PRP for treatment of arrhythmia

To further explore PRP multicomponent and multi-target therapy functions, all the 58 targets of the PPI network were mapped to ‘component-disease’ connections, and then the ‘component-disease-target’ network of PRP therapy was constructed by Cytoscape software. Since the node size is proportional to the importance of nodes involved in the pathway (Table S4).

Table S4 Compound related targets

| NO. | Compound name | Compound related targets                                                                 |
|-----|---------------|-----------------------------------------------------------------------------------------|
| 1   | Pachymic      | PGR, AR, NR3C2, HMGCR, ESR1, PTGER4, NR3C1, ITGB2, PTGER2, PTGER3, PTGF                  |
| Component | Genes |
|-----------|-------|
| Acid      | R,ANXA1,ITGAL,CYP19A1,HDAC2,ADH1C,AKR1C2,ALOX5,ANXA1, AR, CES1, COX4I1, COX5A,COX5B, COX6A2, COX6B1, COX6C, COX7A1,COX7B, COX7C,COX8A, EFTUD1, ESRI, ESRRG, FABP6, FECH,GPBAR1, GSTP1, HMGCR,HOXA10,HSD11B1, HSD11B2,HSD3B1,IGHG2, ITGAL, ITGB2, MT-CO1, MT-CO2, MT-CO3, NCOA1,NPPB,NR1H4,NR1I2,NR3C1,NR3C2,PGR,PLA2G1B, PTGS1, VDR |
| Oleanolic acid | SRD5A1,CYP17A1,SLC8A1,F12,PRLR,ESR1,TRPV1,PTGER1,PTGER4,PGR,AR, NR3C1,OPRK1,FADS2,FADS1,PTGER2,PTGER3,PTGER5,ELOV4,ANXA 1,NR3C2,ADH1C, AKR1C1,AKR1C2, AR, CES1, CLEC4E, COX4I1, COX5A,COX5B, COX6A2, COX6B1, COX6C, COX7A1,COX7B, COX7C,COX8A, EFTUD1, ESRI, ESRR2,ESRRG, FABP6,IGHG2, GABRA1,GABRA2, GABRA3, GABRA4,GABRA5, GABRA6, GABBR1,GABBR2, GABBR3, GABRD,GABRE,GABRG1, GABRG2, GABRG3, GABRP, GABRQ, GPBAR1,GRN1, GRN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B,GSTP1, HOXA10, HSD11B1, HSD11B2, HSD17B1, IGHG2, LSS,MT-CO1, MT-CO2,MT-CO3, NCOA2,NFKB1,NFKB2, NPPB, NR1H4,NR1I2,NR1I3,NR3C1, NR3C2, PGR, PLA2G1B, PPARA, PRLR, RORA,SHBG,SIGMAR1, SULT2A1, SULT2B1, VDR |
| Glycyrrhetinic acid | HOX1,ICAM1,NQO1,HSD11B1,AR,NR3C1,ANXA1,PTGER1,PTGER4,PTGER 2,PTGER3,CD300A,KIF14,SRD5A1,CYP17A1,SLC8A1,F12,PRLR,ESR1,TRPV1, PPARG,FEAR1,PRG,OPRK1,FADS2,FADS1,PPARD,PTGER3,ACSL4,PTGER5,ELOV L4,ACSL3,NR3C2,ADH1C, AKR1C1,AKR1C2, ALOX5 , ANXA1, AR ,CES1 , COX4I1 , COX5A , COX5B , FECH,COX6B1 ,COX6C ,COX7A1 , COX7B , COX7C , COX8A , EFTUD1 , ESRI , ESRRG , FABP6 ,FECH ,GPBAR1, GSTP1 , HMGCR, HSD11B1,HSD11B2, HSD3B1, IGHG2 , ITGAL , ITGB2 , MT-CO1 , MT-CO2, MT-CO3 ,NCOA1 , NCOA2 , NFKB1, NFKB2 , NPPB,NR1H4 , NR1I2, NR3C1, NR3C2 , PGR , PLA2G1B , PRLR, PTGS1 , SULT2B1 |
| Adenine | ACACB,MTAP,APRT,PECR,SRPK2ACP1,ACACA,FBP1,PRKAB1,ACSS2,ADCY 1,ADK, PDE4D,PRKA1,CREB1,ACSS1,PIM1,PYGL,HINT1,ACSL1,PDE4B,PRKAB2,SRPK1,SRPK3,SHMT1,MTHFD2,MTR,MTHFD1,ALDH1L1,AMT,FBP2,MT FMT,ATIC,PYGM,SHMT,FTCD,MTHFR,PYGB,SCN1A,KNJ8,ADRA1A,SCN1 A,SCNN1G,HTR2A, |
| Ergotamine | COX6A2,ADRA2A,TLR8,ADRBI1,ADRA1D,HRH1,HTR7,HRH2,ADRA1B,SCNN1D,ADRA2C,ACOC3,PH4A1,TLR7,KNJ1,AGTR1,ADRB3,SCNN1B,CYP2B6,ADRA2B,SLC6A2,ASAXO1,ST,UGCG,PKHG2,APLP1,CHRAN7,PNP,ARRB2,RAB7 A,PRKAA2,HTR2C,HSP90AB1,ALDH3A2,INS,CALCOCO2,SLC22A1,AC2,ARR DC3,CALCA,HPRT1,ACTN2,ACACB, ACP1,APRT,MTAP, PECR ,PIM1,PKIA, PRKACA,SRPK2 |
| 5-Hydroxytryptamine | ADRA1A,HTR2A,HTR1F,HTR1A,ADRA1B,ADRA2A,HTR1B,DRD5,DRD1,HTR 2C,ADRA1D,ADRA2B,HTR1D,DRD2,SLC6A2,SLC6A3,DNMT3A,CNR1,INS,SL C22A1,ADRA2C,PKHG2,APLP1,CHRAN7,CD34,CALCA,DRD4,HTR7,PTGER2, PTGER3,DRD3,HTR1E,PTGER1,PTGER4,SLC6A4,SLC6A1,SLC6A13,SLC6A8,SL C6A11,SLC6A12,SLC6A6,SLC6A7,HTR2B,ADR2B,HTR3D,GABRA2,GABRQ,GABRD,GABRB1,GABRG3,GABRB3,HTR3B,GABRA5,HTR3E,GABRA6,HTR3 |
| Adenosine | Lauric Aldehyde |
|-----------|----------------|
| A,GABRA1,HTR6,GABRE,GABRG2,GABRA3,GABRG1,GABRP,SLC2B1,GABRA4,HTR3C,GABRB2 | SCN11A,SCN2B,ABAT,SCN1A,SCN3B,SCN3A,SCN7A,SCN5A,SCN10A,AKR1D1,ALDH5A1,SCN2A,HDAC9,TYR,SCN9A,SCN4A,SCN4B,SRD5A2,ACADSB,SCN8A,SCN1B,OGDH,HDAC2,ABAT,ABL1,ACADSB,ACOX1,ACSL3,ACSL4,ADH5,ALDH5A1,ARF1,ARF6,C8G,CALM1,CNR1,CNR2,CYP2C8,ECI2,ELOV14,FADS1,FADS2,FFAR1,HTR4,FURIN,GLTP,GM2A,GUC1A1,HAO1,HDAC2,HDAC9,HNF4A,HNF4G,INS,LALBA,LIP3,LTBR4,LTBR4L2,LT,LY96,NCOA1,NR1H4,OGDH,PAEP,PKIA,PLA2G1B,PLA2G2A,PLA2G2D,PLA2G2E,PMP2,PPAR,PPARG,PPA_RS05235,PPP3CA,PPP3R1,PPT1,PRKACA,PTGSI,PTGS2,PTVR,CVRN,RKH,RXRA,RXRB,RXRG,S100B,SCN10A,SCN11A,SCN1A,SCN1B,SCN2A,SCN2B,SCN3A,SCN3B,SCN4A,SCN4B,SCN5A,SCN7A,SCN8A,SCN9A,SEC14L2,SLC8A1,SREBF1,TLR4,TM1468,TRAPpc3,TRPV1,VLDLR | ADORA2A,ADORA3,ADORA1,ADORA2B,SLC25A6,SLC25A5,TACR2,RIPK1,CXCR1,ADA,HAP1,ABCC2,AKT1,ACVR1,ASNA1,ADRBK2,ACCS2,PRKAA1,A,BC9,ACSS1,AB1,AFG3L2,ACVR1L,ADY1,CDK15,NT5C2,AMHR2,TNK2,AS1,ASNS,ACVR1B,ACSL1,ABCA1,AB2,ADRBK1,NAE1,APAF1,ABCC8,ALK,ABCB1,ABCG1,A,ARF,FKBPA1,TYR,TYMS,FBPI,PRKAB1,RRM2,POLE,CREB1,PIM1,PYGLO,POLE2,POLE3,HINT1,POLA1,RRM2,ADK,PDE4B,PNP,PRKAB2,POLE4,RMR1,PDE4D,ACNA1C,ACBN1,ACNA1D,SLC6A4,ACNB3,CKNH2,ACNA1F,AKT3,ACNA1A,ABCB4,ACNA1I,ACNA1G,SCN5A,ACNB2,CKJ1,ACNA1S,PRKAA2,ACNB4,AKT2,ACNA1B,CBS,MA1A,CBS,COMT,DK,MA2A,AMD1,GNTM1,PDE5A,UTS2R,HMGCR,DKI,FURIN,UTS2,INS,KHDRBS1,SLC18A3,CRH,ATP1A2,HOMER1,SHANK3,AVPR2,S,PAT2A1,SMO,ADRA2A,CRE2,CRP,CENT1,PIK3CG,TNF,IDO1,AGT,KCNB1,DRD1,SORC3,LTA,SLC4A4,GHRL,NCBP2,PCSK6,DRD2,DRN3M,CHRNA3,SCN9A,PTGRD2,PLAT,PTGR2,CFTR,PTGER2,PTGSI,PLA2G2A,THBD,PTGS2,GL01,PAPAR,PTGER1,PPARA,BCCL2,FABP2,TPK1,SLC19A2,TP02A,DHFR,TP02,SLC6A3,PDE7B,PDE7A,PDE9A,PECR,ADRA1A,PDE4A,RYR1,SLC18A2,ITPR3,SCL12A2,MAPK1,DRD4,PDE4C,PE3A,HTR7,SCL12A7,SCL12A6,SCL12A5,ADRBB2,HTR1A,ADRA1B,ACACB,MTAPI,ITPR1,ADRA2C,BH1,PDE6A,PTGER3,PDE10A,PDE1C,SCL25A31,DRD3,PKD3,PIK3CD,HTR1B,ACSL5,DRD5,ATM,SRPK2,PDE3B,SCL12A1,PTGIS,PDE6B,PIK3C3A,ACVR1C,PIK3R3,PDE2A,PIK3R2,ADRB1,PIK3R1,PDE1A,PTGER4,APRT,ADRB3,TPGFR1,PDE8B,SLC18A1,P,IKC3B,ACP1,SCL12A4,ACBC4,ADRA1D,PDE6C,ITPR2,ADRA2B,PDE11A,P2RY12,PTGER1,PDE1B,P4H,SLC6A2,PDE8A,ACNG1,ACSL6,CUBN,TCN1,AMN,MUT,MXACI,MMAB,MTRP,POLB,MMAA,DNMT1,MTR,FBP2,ATF4,SAXO1,XPB1,AK9,RAA1,BICD1,UGCG,LAG1,ASNSD1,SMAD3,CASP9,TGFB1,CTNNB1,VLDLR,ABCA7,UBA3,GRB2,ABCA1,ABCB1,ABCB11,ABCC2,ABCC1,ABCC2,ABCC4,ABCC6,ABCC8,ACBC9,ABCG1,ABL1,ABL2,ACSL1,ACSS1,ACSS2,ACTA1,ACVR1,ACVR1B,ACVR1L,ADA,ADCY1,ADHC1,ADK,ADORA1,ADORA2A,ADORA2B,ADORA3,ADRBK1,ADRBK2,AFG3L2,AHCY,K1,AK2,Ak8,AKT1,ALK,AMHR2,APAF1,ARAF,ASNA1,ASNS,
ASS1, BAG1, BALF5, CCT3, CDK15, CFTR, COMTD1, CREB1, CSNK1G2, CSNK2A1, CSNK2B, DAM, DAPK1, DCK, DNMT1, DPH5, DTYMK, EEF2, ENPP1, EPHA2, EPHB2, FB1, FHIT, GALK1, GAMT, GAPDH, GAPDHS, GNMT, GSK2, GSK3B, GSS, HCN2, HINT1, HK1, HNMT, HSP90B1, HSPA8, IG1R, IMPDH1, IMPDH2, ITPKA, KIF1A, KIF2C, L, LCK, LSM6, MAFF_RS13750, MAPK10, MAPK12, MAPK3, MTA1, NAE1, NME1, NT5C2, PAPS, PB1, PCMT1, PDE4B, PDE4D, PKFBP4, PK3CA, PIM1, PNMT, PNP, POLA1, POLB, POLE, POLE2, POLE3, POLE4, PPP5C, PRKAA1, PRKAB1, PRKAB2, PRKB1, PRKAR1A, PRKAR2B, PRMT1, PRMT3, PYGL, RAD51, RNASE1, RPL10L1, RPL11, RPL13A, RPL15, RPL23, RPL23A, RPL26L1, RPL3, RPL7, RRM1, RRM2, RRM2B, RSL24D1, SETD7, SIRT3, SIRT5, SLC25A4, SRPK2, STM4606, TK, TLR7, TM0588, TNK2, TOP2B, TRDM1, TRPM7, TTHA0667, TTHA1435, UCK2, VCP, PTGS1, PNP, PTGS2, PTPIN1, ADORA2A

CTSD, ADH1B, ADH1C, PTGS1, PTGS2, NCOA1, BCL2, IL10, TNF, PTEN, GUSB, P3H3, OXCT2, TMLHE, PLOD1, HSD17B6, SLC25A10, P3H3, OXCT1, PLOD3, P4HB, CACNA2D1, PLAT, SLC7A2, CACNA1A, GRIN3B, AC0L1C, AKR1D1, TYR, SRD5A2, SCN1A, SCN1B, ABAT, SCN2A, SCN2B, ACSL3, ACSL4, ADH5, ALDH5A1, ARF1, ARF6, C8G, CALM1, CNR1, CYP2C8, EC12, ELOVL4, FADS1, FADS2, FFAR1, FKBP1A, FURIN, GLTP, GM2A, GUCA1A, HA01, HDA2C, HDAC9, HNF4A, HNF4G, INS, KARS, LALB, LIP3, LT4R4, LT4R2, LT5, LY96, NCOA1, NR1H4, OGDH, PAEP, PKIA, PLA2G1B, PLA2G2A, PLA2G2D, PLA2G2E, PMP2, PPARA, PPARD, PPARF, PPARG, PPAR_RS05235, PPP3CA, PPP3R1, PRKACA, PTGS1, PTGS2, PVR, RCVRN, RHO, RXRA, RXRB, S100B, SCN10A, SCN11A, SCN1A, SCN2A, SCN2B, SCN3A, SCN3B, SCN4A, SCN4B, SCN5A, SCN7A, SCN8A, SLC8A1, SREBF1, TLR4, TM1468, TRAPP3C, TRPV1, VLDLR

palmitic

CTSD, ADH1B, ADH1C, PTGS1, PTGS2, NCOA1, BCL2, IL10, TNF, PTEN, GUSB, P3H3, OXCT2, TMLHE, PLOD1, HSD17B6, SLC25A10, P3H3, OXCT1, PLOD3, P4HB, CACNA2D1, PLAT, SLC7A2, CACNA1A, GRIN3B, AC0L1C, AKR1D1, TYR, SRD5A2, SCN1A, SCN1B, ABAT, SCN2A, SCN2B, ACSL3, ACSL4, ADH5, ALDH5A1, ARF1, ARF6, C8G, CALM1, CNR1, CYP2C8, EC12, ELOVL4, FADS1, FADS2, FFAR1, FKBP1A, FURIN, GLTP, GM2A, GUCA1A, HA01, HDA2C, HDAC9, HNF4A, HNF4G, INS, KARS, LALB, LIP3, LT4R4, LT4R2, LT5, LY96, NCOA1, NR1H4, OGDH, PAEP, PKIA, PLA2G1B, PLA2G2A, PLA2G2D, PLA2G2E, PMP2, PPARA, PPARD, PPARF, PPARG, PPAR_RS05235, PPP3CA, PPP3R1, PRKACA, PTGS1, PTGS2, PVR, RCVRN, RHO, RXRA, RXRB, S100B, SCN10A, SCN11A, SCN1A, SCN2A, SCN2B, SCN3A, SCN3B, SCN4A, SCN4B, SCN5A, SCN7A, SCN8A, SLC8A1, SREBF1, TLR4, TM1468, TRAPP3C, TRPV1, VLDLR

lauric
PHOSPHO1, ACHE, PLD2, BCHE, SUCLG2, SLC13A2, SLC13A1, SUCLG1, HSD17B6, SLC25A10, P3H3, OCT2, TMLHE, PLOD1, SUČNR1, SLC13A3, ASPH, BBOX1, SDHB, OCT1, PLOD3, P4HA1, SDHC, P3H2, SDHA, P4HA2, SUCLA2, SDHD, P3H1, DCT, AKR1C3, CRTAP, SLIT2, AC02, JMJD6, SLC13A4, SDHA2, SLC1A3, SALL1, HS D17B11, TYRP1, HIF1AN, UROS, SLC13A5, P4HB, CaCN2D1, PLAT, SLC7A2, CaNA1A, GRIN3B, CaCN2D2, GRIN2A, TOP1, PLG, CaCN1A1B, GRIN2C, GRIN2B, SLC7A3, KARS, GRIN3A, SLC7A1, SLC7A4, GRIN2D, ADORA1, GRIN1, ABAT, AB1L, ACADS, OX1, ACSL3, ACSL4, ADH5, ALDH5A1, ARF1, ARF6, C8G, CALM1, CN1R1, CN2, CYP2C8, EC12, ELOVL4, FADS1, FADS2, FFA1R, FKBPA1, FURIN, GLTP, GM2A, GAUCA1A, HAO1, HDAC2, HDAC9, HNF4A, HNF4G, INS, LALBA, LIP3, LTBR, LTBR2, LTFL, LY96, NCOA1, NR1H4, OGDH, PAEP, PKIA, PLA2G1B, PLA2G2A, PLA2G2D, PLA2G2E, PMP2, PPARA, PPARD, PPARC, PPA_RS05235, PPP3CA, PPP3R1, PPT1, PRKACA, PTGS1, PTGS2, PVR, RVVRN, RHO, RXRA, RXRB, RXRG, S100B, SNC10A, SCN11A, SCN1A, SCN1B, SCN2A, SCN3A, SCN3B, SCN4A, SCN4B, SCN7A, SCN8A, SCN9A, SEC14L2, SLC8A1, SREBF1, TLR4, TM1468, TRAPPC3, TRPV1, VLDLR, PLA2G7, ADH1B, ADH1C, PPARA, EP300, FABP1, RBP2, AKR1D1, TYR, SRD5A2, SNC11A, SCN2B, ABAT, SCN1A, ESRRG, SCN3B, COX6C, COX5B, COX7C, COX1, SCNA3, A4K1C2, SCN7A, SCN5A, SCN10A, ALDH5A1, SCN2A, COX5A, COX3, AR, COX7A1, FEXH, COX4H1, HDAC9, PLA2G1B, COX6A2, SCN9A, SCN4A, SCN4B, ADH1C, COX6B1, FABP6, CES1, SCN9A, SCN8A, COX7B, SCN1B, COX2, OGDH, HDA C2, COX8A, NR1H4, PLD1, PCYT1A, PCYT1B, PHOSPHO1, ACHE, PLD2, BCHE, SUCLG2, SLC13A2, SLC13A1, SUCLG1, HSD17B6, SLC25A10, P3H3, OCT2, TMLHE, PLOD1, SUČNR1, SLC13A3, ASPH, BBOX1, SDHB, OCT1, PLOD3, P4HA1, SDHC, P3H2, SDHA, P4HA2, SUCLA2, SDHD, P3H1, DCT, AKR1C3, CRTAP, SLIT2, AC02, JMD6, PPARA, PPARD, PPARC, PPA_RS05235, PPP3CA, PPP3R1, PPT1, PRKACA, PTGS1, PTGS2, PVR, RVVRN, RHO, RXRA, RXRB, RXRG, S100B, SNC10A, SCN11A, SCN1A, SCN1B, SCN2A, SCN2B, SCN3A, SCN3B, SCN4A, SCN4B, SCN7A, SCN8A, SCN9A, SEC14L2, SLC8A1, SREBF1, TLR4, TM1468, TRAPPC3, TRPV1, VLDLR

caprylic acid

PLA2G7, ADH1B, ADH1C, PPARA, EP300, FABP1, RBP2, AKR1D1, TYR, SRD5A2, SNC11A, SCN2B, ABAT, SCN1A, ESRRG, SCN3B, COX6C, COX5B, COX7C, COX1, SCNA3, A4K1C2, SCN7A, SCN5A, SCN10A, ALDH5A1, SCN2A, COX5A, COX3, AR, COX7A1, FEXH, COX4H1, HDAC9, PLA2G1B, COX6A2, SCN9A, SCN4A, SCN4B, ADH1C, COX6B1, FABP6, CES1, SCN9A, SCN8A, COX7B, SCN1B, COX2, OGDH, HDA C2, COX8A, NR1H4, PLD1, PCYT1A, PCYT1B, PHOSPHO1, ACHE, PLD2, BCHE, SUCLG2, SLC13A2, SLC13A1, SUCLG1, HSD17B6, SLC25A10, P3H3, OCT2, TMLHE, PLOD1, SUČNR1, SLC13A3, ASPH, BBOX1, SDHB, OCT1, PLOD3, P4HA1, SDHC, P3H2, SDHA, P4HA2, SUCLA2, SDHD, P3H1, DCT, AKR1C3, CRTAP, SLIT2, AC02, JMD6, PPARA, PPARD, PPARC, PPA_RS05235, PPP3CA, PPP3R1, PPT1, PRKACA, PTGS1, PTGS2, PVR, RVVRN, RHO, RXRA, RXRB, RXRG, S100B, SNC10A, SCN11A, SCN1A, SCN1B, SCN2A, SCN2B, SCN3A, SCN3B, SCN4A, SCN4B, SCN7A, SCN8A, SCN9A, SEC14L2, SLC8A1, SREBF1, TLR4, TM1468, TRAPPC3, TRPV1, VLDLR

Tumulosic Acid

NR3C1, SRD5A1, CYP17A1, SLC8A1, F12, PRLR, ESRI, TRPV1, PTGER1, PTGER4, PRGR, AR, PTGIR, OPKR1, FADS2, FADS1, PTGER2, PTGS1, PTGER3, PTGS2, ELOVL4, PTGFR, ANXA1, NR3C2, ADH1C, A1K1C1, A1K1C2, ANXA1, AR, CES1, CLEC4E, COX4I1, COX5A, COX5B, COX6A2, COX6B1, COX6C, COX7A1, COX7B, COX7C, COX8A, CYP27B1, EFUD1, ACADS, ESRRG,
**Table S5** Arrhythmia related targets from three databases.

| Database   | Arrhythmia related targets                                                                 |
|------------|------------------------------------------------------------------------------------------|
| TTD        | ADORA1, F2, F10, PLG, HTR4, ADRB2, ABCC8, CD20, PTA4R, VKORC1, KCNH2, SCN5A, ADORA2B, A   |
|            | DRAD1A, ADRA2A, ADRB2, ADRD2C, ADRB1, F8, RFWD2, EDNRA, EDNRB1, L12B, CACNA1C, KCNA5,    |
|            | ADRB1A, ADRA2A, CALM, SPT, ATP1ase, KCND3, SCN11A, IL18, SLC9A1, TBXAS1, MCHRI, SLC9A3,   |
|            | CACNA1D, HSP70, HSP90, NaC, ADOR, CaC, HCN, KCNN, GPJ, IC, LISC, SLC                        |
| ETCM       | A2ML1, ACTC1, ATF6, BRAF, CACNA1B, CASR, CAV3, COX3, COX7B, CPT1A, CPT2, CREBBP, CTLL4,   |
|            | CYTB, DES, DMD, EFEMP2, ELN, EP300, ERCC6, ERCC8, FBLN5, FXL1, FHL1, FOXC2, GATA1,         |
|            | GDAP1, GJA1, GLA, GNA11, GNAQ, GPC3, GPC4, GPX4, GTPBP3, HBB, HCCS, HD4, HFE, HLA-DBP1,   |
|            | HRAS, KCN, KAT6B, KCNK3, ECP2, MEFV, MGME1, MTO1, MYH6, MYLK2, NAA10, ND1, ND2, ND4, ND4L, |
|            | ND5, ND6, NDUF11, NKX2-5, NRAS, PCCA, PCBA, PCCHB, PEX1, PEX10, PEX11B, PEX12, PEX13,      |
|            | PEX14, PEX16, PEX19, PEX2, PEX3, PEPX3 (HPO), PEX5, PEX6, PEX7, PHOX2B, PHYH, PIK3CA,     |
|            | PGLG2, PRMD1, PRTN3, PSMB8, PTPPN11, PTPRN22, RAF1, RASA2, RIT1, RPL11, RPL15, RPL18,       |
|            | RPL26, RPL27, RPL35, RPL35A, RPL5, RPS10, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS9,  |
|            | RPS7, RARS, SALL4, SCNB1, SCNB4, SCNB5, SCNB1B, SCNB1G, SLC19A2, SLC40A1, SOST, SOST2,     |
|            | SOX10, SPEC1C1L, SYNE2, TAB2, TAZ, TXB3, TMEM70, TXNB, TRNEL, TRNK, TRNL1, TRPM4, TSC1,     |
|            | TSC2, TS22, TTN, TTP, TTPA, VHL, L.                                                                 |
| Genecards  | SCN5A, KCNH2, KCNQ1, ANK2, RYR2, KCNJ2, KCNE2, CACNA1C, KCNE1, LMNA, PKP2, MYH7, DSP,      |
|            | AKAP9, SNTA1, TTN, CAV3, CASQ2, SCN4B, DSG2, KCNJ5, JUP, TMEM43, HC N4, TANGO2, CABN2,      |
|            | MYBPC3, SCN1B, TNN2, MYH6, DSC2, GIA5, DMD, NXX2-5, TRD4, RANGRF, NPPA, TNNI3, CACNA2D1,   |
|            | GJA1, GNB5, SCN3B, KCNA5, HSPG2, PLN, NOS1AP3, KCND3, KCNJ8, KCNE3, DES, TGFBI, GPD1,       |
|            | LDLB3, CALM2, PRKAG2, MYPN, RRM20, CALM1, ABC9C, SCN2B, RYR1, GATA4, CPT2, TECRL, CACNA1S,  |
|            | ACTN2, SYNE2, TPM4, SLC25A20, NEXN, KCNE5, SCN10A, TPM1, CACNA1D, DTNA, ACTC1, SYNE1, TAZ, |
|            | CTNNAS, LAMP2, TTR, LAMMA4, LAMMA2, GATA6, TCAP, ADCAVL, CALM3, TNNC1, SDH A, GYGI, GATA5, |
|            | PPARG, FLNC, AC, CSRPE3, HFE, GAA, HADHA, FHL1, NUP155, AKAP10, MYL3, CAVIN1, SLMAP, RAF1,  |
|            | SCN4A, IFNG, DPP6, PTPN11, TBX5, XK, VCL, PRMD16, TNI3K, MYL4, NPPB, GATA1D, HLA-DRB1, BAG3,|
|            | LOC11021269, KCNO1-AS1, SLC25A4, MECP2, DMPK, FOS, ACADM, ALG10B, MT-TL1, EYA4, ADRB1, B    |
|            | BMP2, CPT1A, TBX3, AKRDI, KCNO1OT1, CTLL4, DNAPC19, MYOT, MYLK2, NAA10, MT-ND4, MT-NDS, SGCD, |
|            | ELN, CRYAB, CAV1, TP53, TBX20, PITX2, FUBP1B, POLG, TWWK, MT-CYB, KCNJ18, SOS1, MYL2, IL6, |
|            | KCNJ11, CRP, MT-CO1, MT-TK, ERCC6, ACADL, POLG2, CACNA1C-AS1, APO E, HRAS, AGPAT2, BSL2,   |
|            | TMEM70, HJV, BVES, MT-ND1, FKTN, SLC25A5, GLA, GSN, PEX1, NR2F2, NDUF2S, TNEF, TMPO, AGTR1, |
|            | BRAF, NDUF11, SGO1, ALB, PIK3CA, HAADH, SLC19A2, RRM2B, SCN11A, PEX6, TTPA, MT-ATP6, JPH2,  |
|            | ATFB2, SDHB, TOP3A, PHYH, PEX7, CNBP, KRAS, ATFB1, ATFB5, SLC40A1, PSEN1, REN, MT-CO3, FBLN5,|
|            | PEX14, PEX10,                                                                                     |
PEX2, PEX3, PEX5, PEX12, PEX13, EDN1, MYOZ2, PDGFRA, DYSF, KCND2, HLA-B, ADRB2, COL4A1, CLCNKB, PSEN2, PPCS, CIZ1, PSMB8, NRAS, CASR, GATA1, HB B, PTRN3, ERCC8, INS, FBV1, MT-CO2, CDH23, SLC12A3, CD2AP, SLC26A4, MT-ND6, MT-ND4L, MEFV, COL1A1, HAND2, RNF207, CHK2, RET, SDHC, EHMT1, ETFDH, PTH, FBXL4

Table S6 58 Common targets from compounds-disease sets

| #  | SYMBOL  | ENTREZID |
|----|---------|----------|
| 1  | COX7B   | 1349     |
| 2  | MT-CO1  | 4512     |
| 3  | MT-CO2  | 4513     |
| 4  | MT-CO3  | 4514     |
| 5  | NPPB    | 4879     |
| 6  | PPARG   | 5468     |
| 7  | SCNN1A  | 6337     |
| 8  | KCNJ8   | 3764     |
| 9  | ADRA1A  | 148      |
| 10 | SCNN1G  | 6340     |
| 11 | ADRB2   | 154      |
| 12 | ADRA2A  | 150      |
| 13 | ADRB1   | 153      |
| 14 | ADRA1D  | 146      |
| 15 | ADRA1B  | 147      |
| 16 | ADRA2C  | 152      |
| 17 | AGTR1   | 185      |
| 18 | SCNN1B  | 6338     |
| 19 | ADRA2B  | 151      |
| 20 | INS     | 3630     |
| 21 | ACTN2   | 88       |
| 22 | HTR4    | 3360     |
| 23 | SCN11A  | 11280    |
| 24 | SCN2B   | 6327     |
| 25 | SCN3B   | 55800    |
| 26 | SCN5A   | 6331     |
| 27 | SCN10A  | 6336     |
| 28 | SCN4A   | 6329     |
| 29 | SCN4B   | 6330     |
| 30 | SCN1B   | 6324     |
| 31 | CALM1   | 801      |
| 32 | ADORA1  | 134      |
| 33 | ADORA2B | 136      |
| 34 | ABCC9   | 10060    |
| 35 | ABCC8   | 6833     |
| 36 | SLC25A4 | 291      |
| 37 | RRM2B   | 50484    |
| #cluster | method | cluster | cluster color | gene count | protein name | protein identifier | protein description |
|----------|--------|---------|---------------|------------|--------------|-------------------|---------------------|
| 1        | kmeans | 1       | Red           | 25         | ABCC8        | 9606.ENSP000003039 60 | ATP-binding cassette sub-family C member 8; Subunit of the beta-cell ATP-sensitive potassium channel (KATP). Regulator of ATP-sensitive K(+) channels and insulin release; ATP binding cassette subfamily C |
| 1        | kmeans | 1       | Red           | 25         | ADORA1       | 9606.ENSP000003562 05 | Adenosine receptor A1; Receptor for adenosine. The activity of this receptor is mediated by G proteins which inhibit adenyl cyclase; Belongs to the G-protein coupled receptor 1 family |
| 1        | kmeans | 1       | Red           | 25         | ADORA2B      | 9606.ENSP000003045 | Adenosine receptor A2b; |
| kmeans  | Red | ADRA1A  | 9606.ENSP000003699 | 60 |
|---------|-----|---------|-------------------|----|
|         |     | Receptor for adenosine. The activity of this receptor is mediated by G proteins which activate adenylyl cyclase |
| Alpha-1A adrenergic receptor; This alpha-adrenergic receptor mediates its action by association with G proteins that activate a phosphatidylinositol-calcium second messenger system. Its effect is mediated by G(q) and G(11) proteins. Nuclear ADRA1A-ADRA1B heterooligomers regulate phenylephrine(PE)-stimulated ERK signaling in cardiac myocytes; Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily. |

| kmeans  | Red | ADRA1B  | 9606.ENSP000003066 | 62 |
|---------|-----|---------|-------------------|----|
| Alpha-1B adrenergic receptor; This alpha-adrenergic receptor mediates its action by association with G proteins that activate a phosphatidylinositol-calcium second messenger system. Its effect is mediated by G(q) and G(11) proteins. Nuclear ADRA1A-ADRA1B heterooligomers regulate phenylephrine (PE)-stimulated ERK signaling in cardiac myocytes; Belongs to the G-protein coupled receptor 1 family. Adrenergic |
Adrenoceptors

| kmeans | Rank | Red | 25 | ADRA1D | 9606.ENSP00000368766 | ADRA1B sub-family receptor | Alpha-1D adrenergic receptor; This alpha-adrenergic receptor mediates its effect through the influx of extracellular calcium; Adrenoceptors |
|--------|------|-----|-----|--------|-----------------------|-----------------------------|

| kmeans | Rank | Red | 25 | ADRA2A | 9606.ENSP00000280155 | Alpha-2A adrenergic receptor; Alpha-2 adrenergic receptors mediate the catecholamine-induced inhibition of adenylate cyclase through the action of G proteins. The rank order of potency for agonists of this receptor is oxymetazoline > clonidine > epinephrine > norepinephrine > phenylephrine > dopamine > p-syneprine > p-tyramine > serotonin = p-octopamine. For antagonists, the rank order is yohimbine > phentolamine = mianserine > chlorpromazine = spiperone = prazosin > propanolol > alprenolol = pindolol; Adrenoceptors |
|--------|------|-----|-----|--------|-----------------------|-----------------------------|

| kmeans | Rank | Red | 25 | ADRA2B | 9606.ENSP00000480573 | Alpha-2B adrenergic receptor; Alpha-2 adrenergic receptors mediate the catecholamine-induced inhibition of adenylate cyclase through the action of G proteins. The rank order of potency for agonists of this receptor is clonidine > norepinephrine > epinephrine = |
| kmeans | Red | 25 | ADRA2C | 9606.ENSP000003860069 |
|--------|-----|----|--------|----------------------|
|        |     |    | Alpha-2C adrenergic receptor; Alpha-2 adrenergic receptors mediate the catecholamine-induced inhibition of adenylate cyclase through the action of G proteins; Adrenoceptors |

| kmeans | Red | 25 | ADRB1 | 9606.ENSP00000358301 |
|--------|-----|----|-------|----------------------|
|        |     |    | Beta-1 adrenergic receptor; Beta-adrenergic receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. This receptor binds epinephrine and norepinephrine with approximately equal affinity. Mediates Ras activation through G(s)-alpha- and cAMP-mediated signaling; Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily. |

| kmeans | Red | 25 | ADRB2 | 9606.ENSP000003053 |
|--------|-----|----|-------|-------------------|
|        |     |    | Beta-2 adrenergic receptor; |

oxymetazoline >
dopamine > p-tyramine =
phenylephrine > serotonin >
p-synephrine /
p-octopamine. For antagonists, the rank order is yohimbine > chlorpromazine >
phentolamine >
mianserine > spiperone >
prazosin > alprenolol >
propanolol > pindolol;
Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily. ...[...]

kmeans 1 Red 25 ADRB1 9606.ENSP00000358301

Beta-1 adrenergic receptor; Beta-adrenergic receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. This receptor binds epinephrine and norepinephrine with approximately equal affinity. Mediates Ras activation through G(s)-alpha- and cAMP-mediated signaling; Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily. ADRB1 sub-subfamily
Beta-adrenergic receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. The beta-2-adrenergic receptor binds epinephrine with an approximately 30-fold greater affinity than it does norepinephrine; Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily. ADRB2 sub-family

| kmeans  | 1    | Red  | 25  | AGTR1 9606.ESNP000004194 | 22 |
|---------|------|------|-----|--------------------------|----|
| kmeans  | 1    | Red  | 25  | CACNA1B 9606.ESNP000003604| 23 |

Type-1 angiotensin II receptor; Receptor for angiotensin II. Mediates its action by association with G proteins that activate a phosphatidylinositol-calcium second messenger system

Voltage-dependent N-type calcium channel subunit alpha-1B; Voltage-sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death. The isoform alpha-1B gives rise to N-type calcium currents. N-type calcium channels belong to the 'high-voltage activated' (HVA) group and are blocked by
Omega-conotoxin-GVIA (omega-CTx-GVIA) and by omega-agatoxin-IIIA (omega-Aga-IIIA). Th [...] Voltage-dependent L-type calcium channel subunit alpha-1C; Voltage-sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death. The isoform alpha-1C gives rise to L-type calcium currents. Long-lasting (L-type) calcium channels belong to the 'high-voltage activated' (HVA) group. They are blocked by dihydropyridines (DHP), phenylalkylamines, benzothiazepines, and by o [...] Voltage-dependent L-type calcium channel subunit alpha-1D; Voltage-sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and
cell death. The isoform alpha-1D gives rise to L-type calcium currents. Long-lasting (L-type) calcium channels belong to the 'high-voltage activated' (HVA) group. They are blocked by dihydropyridines (DHP), phenylalkylamines, benzothiazepines, and by o ...

Voltage-dependent L-type calcium channel subunit beta-2; The beta subunit of voltage-dependent calcium channels contributes to the function of the calcium channel by increasing peak calcium current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting

C-reactive protein; Displays several functions associated with host defense: it promotes agglutination, bacterial capsular swelling, phagocytosis and complement fixation through its calcium-dependent binding to phosphorylcholine. Can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells; Short pentraxins

Histone acetyltransferase p300; Functions as histone acetyltransferase and
regulates transcription via chromatin remodeling. Acetylates all four core histones in nucleosomes. Histone acetylation gives an epigenetic tag for transcriptional activation. Mediates cAMP-gene regulation by binding specifically to phosphorylated CREB protein. Mediates acetylation of histone H3 at 'Lys-122' (H3K122ac), a modification that localizes at the surface of the histone octamer and stimulates transcription, possibly by promoting nucleosome instability. Mediates acetylation of histone H3 at 'Lys-27' (H3K27ac), a modification that localizes at the surface of the histone octamer and stimulates transcription, possibly by promoting nucleosome instability.

5-hydroxytryptamine receptor 4; This is one of the several different receptors for 5-hydroxytryptamine (serotonin), a biogenic hormone that functions as a neurotransmitter, a hormone, and a mitogen. The activity of this receptor is mediated by G proteins that stimulate adenylate cyclase; 5-hydroxytryptamine receptors, G protein-coupled. Insulin; Insulin decreases blood glucose concentration. It increases cell permeability to monosaccharides, amino acids and fatty acids. It
accelerates glycolysis, the pentose phosphate cycle, and glycogen synthesis in liver

ATP-sensitive inward rectifier potassium channel 11; This receptor is controlled by G proteins. Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it. Their voltage dependence is regulated by the concentration of extracellular potassium; as external potassium is raised, the voltage range of the channel opening shifts to more positive voltages. The inward rectification is mainly due to the blockage of outward current by internal magnesium. Can be blocked by extracellular barium (By similarity).

Natriuretic peptides B; Cardiac hormone which may function as a paracrine antifibrotic factor in the heart. Also plays a key role in cardiovascular homeostasis through natriuresis, diuresis, vasorelaxation, and inhibition of renin and aldosterone secretion. Specifically binds and stimulates the cGMP production of the NPR1 receptor. Binds the clearance receptor NPR3;
| kmeans | 1 | Red | 25 | PIK3CA | 9606.ENSP000002639 |
|--------|---|-----|-----|--------|-------------------|
|        |   |     |     |        | Belongs to the natriuretic peptide family |
|        |   |     |     |        | Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; |
|        |   |     |     |        | Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol) |
|        |   |     |     |        | PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). |
|        |   |     |     |        | PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to [...] |

| kmeans | 1 | Red | 25 | PLG | 9606.ENSP000003089 |
|--------|---|-----|-----|-----|-------------------|
|        |   |     |     |     | Plasminogen; Plasmin dissolves the fibrin of blood clots and acts as a proteolytic factor in a variety of other processes including embryonic development, tissue remodeling, tumor invasion, and inflammation. |
|        |   |     |     |     | In ovulation, weakens the walls of the Graafian follicle. It activates the urokinase-type plasminogen activator, collagenases and |
several complement zymogens, such as C1 and C5. Cleavage of fibronectin and laminin leads to cell detachment and apoptosis. Also cleaves fibrin, thrombospondin and von Willebrand factor. Its role in tissue remodeling and tumor invasion may be modulated by:[...]

Peroxisome proliferator-activated receptor gamma; Nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the nuclear receptor binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis. ARF6 acts as a key regulator of the tissue-specific adipocyte P2 (aP2) enhancer. Acts as a critical regulator of gut ho [...]

ATP-binding cassette sub-family C member 9; Subunit of ATP-sensitive potassium channels (KATP). Can form cardiac and smooth muscle-type KATP channels with
KCNJ11. KCNJ11 forms the channel pore while ABCC9 is required for activation and regulation; Belongs to the ABC transporter superfamily, ABCC family. Conjugate transporter (TC 3.A.1.208) subfamily

**kmeans 2**  
**Green 24**  
**ACTN2**  
9606.ENSP00000443495  
Alpha-actinin-2; F-actin cross-linking protein which is thought to anchor actin to a variety of intracellular structures. This is a bundling protein; Actinins

**kmeans 2**  
**Green 24**  
**CACNA1S**  
9606.ENSP00000355192  
Voltage-dependent L-type calcium channel subunit alpha-1S; Pore-forming, alpha-1S subunit of the voltage-gated calcium channel that gives rise to L-type calcium currents in skeletal muscle. Calcium channels containing the alpha-1S subunit play an important role in excitation-contraction coupling in skeletal muscle via their interaction with RYR1, which triggers Ca(2+) release from the sarcoplasmic reticulum and ultimately results in muscle contraction. Long-lasting (L-type) calcium channels belong to the 'high-voltage activated' (HVA) group

**kmeans 2**  
**Green 24**  
**CACNA2D**  
9606.ENSP00000349320  
Voltage-dependent calcium channel subunit alpha-2/delta-1; The alpha-2/delta subunit of voltage-dependent calcium channels regulates calcium current density and
activation/inactivation kinetics of the calcium channel. Plays an important role in excitation-contraction coupling (By similarity)

Calmodulin-1; Calmodulin mediates the control of a large number of enzymes, ion channels, aquaporins and other proteins through calcium-binding. Among the enzymes to be stimulated by the calmodulin-calcium complex are a number of protein kinases and phosphatases. Together with CCP110 and centrin, is involved in a genetic pathway that regulates the centrosome cycle and progression through cytokinesis. Mediates calcium-dependent inactivation of CACNA1C. Positively regulates calcium-activated potassium channel activity of KCNN2.

Potassium voltage-gated channel subfamily H member 2; Pore-forming (alpha) subunit of voltage-gated inwardly rectifying potassium channel. Channel properties are modulated by cAMP and subunit assembly. Mediates the rapidly activating component of the delayed rectifying potassium current in heart (IKr)
ATP-sensitive inward rectifier potassium channel 8; This potassium channel is controlled by G proteins. Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it. Their voltage dependence is regulated by the concentration of extracellular potassium; as external potassium is raised, the voltage range of the channel opening shifts to more positive voltages. The inward rectification is mainly due to the blockage of outward current by internal magnesium. Can be blocked by external barium (By similarity); Belon [...] 

60S ribosomal protein L11; Component of the ribosome, a large ribonucleoprotein complex responsible for the synthesis of proteins in the cell. The small ribosomal subunit (SSU) binds messenger RNAs (mRNAs) and translates the encoded message by selecting cognate aminoacyl-transfer RNA (tRNA) molecules. The large subunit (LSU) contains the ribosomal catalytic site termed the peptidyl transferase center (PTC), which catalyzes the formation of peptide bonds, thereby polymerizing the amino acids delivered by
tRNAs into a polypeptide chain. The nascent polypeptides leave the ribosome through […]

| kmeans | Gene | Chromosome | Ensembl ID | Description |
|--------|------|------------|------------|-------------|
| 2      | Green 24 | RPL15 | 9606.ENSP00000309334 | Ribosomal protein L15 |
| 2      | Green 24 | RRM2B | 9606.ENSP00000251810 | Ribonucleoside-diphosphate reductase subunit M2 B; Plays a pivotal role in cell survival by repairing damaged DNA in a p53/TP53-dependent manner. Supplies deoxyribonucleotides for DNA repair in cells arrested at G1 or G2. Contains an iron-tyrosyl free radical center required for catalysis. Forms an active ribonucleotide reductase (RNR) complex with RRM1 which is expressed both in resting and proliferating cells in response to DNA damage. |
| 2      | Green 24 | RYR1 | 9606.ENSP00000352608 | Ryanodine receptor 1; Calcium channel that mediates the release of Ca(2+) from the sarcoplasmic reticulum into the cytoplasm and thereby plays a key role in triggering muscle contraction following depolarization of T-tubules. Repeated very high-level exercise increases the open probability of the channel and leads to Ca(2+) leaking into the cytoplasm. Can also mediate the release of Ca(2+) from intracellular stores in neurons, and may thereby promote prolonged […] |
Ca(2+) signaling in the brain. Required for normal embryonic development of muscle fibers and skeletal muscle. Required for [nor [...] 

Sodium channel protein type 10 subunit alpha; Tetrodotoxin-resistant channel that mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which sodium ions may pass in accordance with their electrochemical gradient. Plays a role in neuropathic pain mechanisms; Sodium voltage-gated channel alpha subunits

Sodium channel protein type 11 subunit alpha; This protein mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which sodium ions may pass in accordance with their electrochemical gradient. It is a tetrodotoxin-resistant
sodium channel isoform. Also involved, with the contribution of the receptor tyrosine kinase NTRK2, in rapid BDNF-evoked neuronal depolarization; Sodium voltage-gated channel alpha subunits

Sodium channel subunit beta-1; Crucial in the assembly, expression, and functional modulation of the heterotrimeric complex of the sodium channel. The subunit beta-1 can modulate multiple alpha subunit isoforms from brain, skeletal muscle, and heart. Its association with NFASC may target the sodium channels to the nodes of Ranvier of developing axons and retain these channels at the nodes in mature myelinated axons; Immunoglobulin like domain containing

Sodium channel subunit beta-2; Crucial in the assembly, expression, and functional modulation of the heterotrimeric complex of the sodium channel. The subunit beta-2 causes an increase in the plasma membrane surface area and in its folding into microvilli. Interacts with TNR may play a crucial role in clustering and regulation of activity of sodium channels at nodes of Ranvier (By similarity); Belongs to the sodium
| kmeans 2 Green 24 SCN3B 9606.ENSP00000376523 | Sodium channel subunit beta-3; Modulates channel gating kinetics. Causes unique persistent sodium currents. Inactivates the sodium channel opening more slowly than the subunit beta-1. Its association with NFASC may target the sodium channels to the nodes of Ranvier of developing axons and retain these channels at the nodes in mature myelinated axons (By similarity); Belongs to the sodium channel auxiliary subunit SCN3B (TC 8.A.17) family. |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| kmeans 2 Green 24 SCN4A 9606.ENSP00000396320 | Sodium channel protein type 4 subunit alpha; This protein mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na(+) ions may pass in accordance with their electrochemical gradient. This sodium channel may be present in both denervated and innervated skeletal muscle; Belongs to the sodium channel (TC 1.A.1.10) family. Nav1.4/SCN4A subfamily |
Sodium channel subunit beta-4; Modulates channel gating kinetics. Causes negative shifts in the voltage dependence of activation of certain alpha sodium channels, but does not affect the voltage dependence of inactivation. Modulates the susceptibility of the sodium channel to inhibition by toxic peptides from spider, scorpion, wasp and sea anemone venom; Sodium voltage-gated channel beta subunits

Sodium channel protein type 5 subunit alpha; This protein mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na(+) ions may pass in accordance with their electrochemical gradient. It is a tetrodotoxin-resistant Na(+) channel isoform. This channel is responsible for the initial upstroke of the action potential. Channel inactivation is regulated by intracellular calcium levels; Sodium voltage-gated channel beta subunits

Amiloride-sensitive sodium channel subunit alpha; Sodium permeable
non-voltage-sensitive ion channel inhibited by the diuretic amiloride. Mediates the electrodiffusion of the luminal sodium (and water, which follows osmotically) through the apical membrane of epithelial cells. Plays an essential role in electrolyte and blood pressure homeostasis, but also in airway surface liquid homeostasis, which is important for proper clearance of mucus. Controls the reabsorption of sodium in kidney, colon, lung and eccrine sweat glands. Also plays a role in taste perception; Belongs to the amiloride-sensit [..]
| kmeans | Color | Rank | Gene Symbol | Accession Number | Description |
|--------|-------|------|-------------|------------------|-------------|
| 2      | Green | 24   | SCNN1G      | 9606.ENSP00000300061 | Amiloride-sensitive sodium channel subunit gamma; Sodium permeable non-voltage-sensitive ion channel inhibited by the diuretic amiloride. Mediates the electrodiffusion of the luminal sodium (and water, which follows osmotically) through the apical membrane of epithelial cells. Plays an essential role in electrolyte and blood pressure homeostasis, but also in airway surface liquid homeostasis, which is important for proper clearance of mucus. Controls the reabsorption of sodium in kidney, colon, lung and sweat glands. Also plays a role in taste perception. |
| 2      | Green | 24   | SLC19A2     | 9606.ENSP00000236137 | Thiamine transporter 1; High-affinity transporter for the intake of thiamine; Solute carriers |
| 2      | Green | 24   | SLC25A4     | 9606.ENSP00000281456 | ADP/ATP translocase 1; Involved in mitochondrial ADP/ATP transport. Catalyzes the exchange of cytoplasmic ADP with mitochondrial ATP across the mitochondrial inner membrane; Belongs to the mitochondrial carrier (TC 2.A.29) family |
| 3      | Blue  | 9    | COX7B       | 9606.ENSP00000417656 | Cytochrome c oxidase subunit 7B, mitochondrial; This protein is one of the nuclear-coded polypeptide chains of cytochrome c oxidase, the terminal oxidase in mitochondrial |
electron transport. Plays a role in proper central nervous system (CNS) development in vertebrates. Cytochrome c oxidase subunit 1; Cytochrome c oxidase is the component of the respiratory chain that catalyzes the reduction of oxygen to water. Subunits 1-3 form the functional core of the enzyme complex. CO I is the catalytic subunit of the enzyme. Electrons originating in cytochrome c are transferred via the copper A center of subunit 2 and heme A of subunit 1 to the bimetallic center formed by heme A3 and copper B.

Cytochrome c oxidase subunit 2; Cytochrome c oxidase is the component of the respiratory chain that catalyzes the reduction of oxygen to water. Subunits 1-3 form the functional core of the enzyme complex. Subunit 2 transfers the electrons from cytochrome c via its binuclear copper A center to the bimetallic center of the catalytic subunit 1.

Cytochrome c oxidase subunit 3; Subunits I, II and III form the functional core of the enzyme complex; Mitochondrial complex IV: cytochrome c oxidase subunits.

Prostaglandin G/H synthase 1; Converts arachidonate to
prostaglandin H2 (PGH2), a committed step in prostanoid synthesis. Involved in the constitutive production of prostanoids in particular in the stomach and platelets. In gastric epithelial cells, it is a key step in the generation of prostaglandins, such as prostaglandin E2 (PGE2), which plays an important role in cytoprotection. In platelets, it is involved in the generation of thromboxane A2 (TXA2), which promotes platelet activation and aggregation, vasoconstriction and proliferation of vascular smooth muscle cells; Belongs to th [...]

Succinate dehydrogenase flavoprotein subunit, mitochondrial; Flavoprotein (FP) subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q). Can act as a tumor suppressor; Belongs to the FAD-dependent oxidoreductase 2 family. FRD/SDH subfamily

Succinate dehydrogenase iron-sulfur subunit, mitochondrial; Iron-sulfur protein (IP) subunit of succinate
Succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q); Belongs to the cytochrome b560 family

Tumor necrosis factor; Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. It is potent pyrogen causing fever by direct action or by stimulation of interleukin-1 secretion and is implicated in the induction of cachexia. Under certain conditions it can stimulate cell proliferation and induce cell differentiation. Impairs regulatory T-cells (Treg) function in individuals with rheumatoid arthritis via FOXP3 dephosphorylation. Upregulates the expression of protein phosphatase 1
Table S8 PRP acts directly on disease targets and topological parameters (Degree>10)

| NO | Gene name | ENTREZID | Degree |
|----|-----------|----------|--------|
| 1  | INS       | 3630     | 33     |
| 2  | CACNA1C   | 775      | 25     |
| 3  | SCN5A     | 6331     | 25     |
| 4  | SCN1B     | 6324     | 25     |
| 5  | SCN10A    | 6336     | 24     |
| 6  | SCN3B     | 55800    | 22     |
| 7  | CACNA2D1  | 781      | 22     |
| 8  | SCN3B     | 55800    | 22     |
| 9  | SCN4B     | 6330     | 21     |
| 10 | ADORA1    | 134      | 21     |
| 11 | ADORA2B   | 136      | 20     |
| 12 | CACNB2    | 154      | 19     |
| 13 | SCN4A     | 6329     | 17     |
| 14 | ABCC9     | 10060    | 17     |
| 15 | TNF       | 7124     | 16     |
| 16 | CACNA1B   | 774      | 16     |
| 17 | KCNJ8     | 3764     | 16     |
| 18 | KCNJ11    | 3767     | 15     |
| 19 | CACNA1S   | 779      | 13     |
| 20 | SDHC      | 6391     | 13     |
| 21 | ADRB2     | 154      | 13     |
| 22 | AGTR1     | 185      | 13     |
| 23 | PPARG     | 5468     | 13     |
| 24 | SCNN1A    | 6337     | 12     |
| 25 | RYR1      | 6261     | 12     |
| 26 | SCN11A    | 11280    | 11     |
| 27 | CALM1     | 801      | 11     |
| 28 | ADRA1B    | 147      | 10     |
| 29 | ADRA1A    | 148      | 10     |

Table S9 Gene Ontology annotations of biological processes (BP); cellular components (CC) and molecular functions (MF)

| ON ID | Description | GeneRat geneID | GOIO | BgRratio | pval | p.adjusted | qvalue | genelD | Cnt | Cnt | Cnt |
|-------|-------------|----------------|------|----------|------|------------|--------|--------|-----|-----|-----|
| GO:19035 | regulation of | 25/57 | 297/297 | 2.49 | 5.12 | 3.38E-2 | 148/150 | 65800/6331 | 25 | 154/153/14/7/152/152/185/151/6/327/55800/6331 |
| GO:00069 | muscle contraction | 26/57 |
|---------|-------------------|-------|
| BP 36  | 360/7.46 7.66 5.06E-2 | 186 E-30 E-27 7  |
|         | 70  | 3764/148/154/1 26 |
|         | 50/147/152/151/88/6327/55800/6331/6336/6329/6330/6324/801/134/136/775/77 | |
|         | 6/375/783/779/6261/5290/781 90/781 | |

| GO:000600 | heart contraction | 23/57 |
|-----------|------------------|-------|
| BP 47    | 280/1.51 1.03 6.83E-2 | 186 E-27 E-24 5 |
|           | 70  | 3764/148/153/1 23 |
|           | 47/6327/55800/6331/6336/6330/6324/801/134/10060/775/776/3757/783/3767/79/774/6261/52 | |
|           | 90/781  |

| GO:00030 | heart process | 23/57 |
|----------|---------------|-------|
| BP 15   | 290/3.44 1.77 1.17E-2 | 186 E-27 E-24 4 |
|          | 70  | 3764/148/153/1 23 |
|          | 47/6327/55800/6331/6336/6330/6324/801/134/10060/775/776/3757/783/3767/79/774/6261/52 | |
|          | 90/781  |

| GO:00030 | muscle system process | 26/57 |
|----------|-----------------------|-------|
| BP 12   | 465/6.03 2.48 1.64E-2 | 186 E-27 E-24 4 |
|          | 70  | 3764/148/154/1 26 |
|          | 50/147/152/151/88/6327/55800/6331/6336/6329/6330/6324/801/134/136/775/77 | |
|          | 6/3757/783/779/6261/5290/781 90/781 | |

| GO:00080 | regulation of heart contraction | 21/57 |
|----------|---------------------------------|-------|
| BP 16   | 251/2.98 1.02 6.73E-2 | 186 E-25 E-22 3 |
|          | 70  | 148/153/147/63 21 |
|          | 27/55800/6331/636/6330/6324/801/134/10060/775/776/3757/708/3767/779/77 | |
|          | 4/6261/781  | |
| BP  | GO:00860 | membrane depolarization during action potential | 13/57 | 37/1 | 1.55 | 4.53 | 2.99E-2 | 11280/6327/558 | 13 |
|-----|----------|-----------------------------------------------|-------|------|------|------|----------|----------------|----|
|     |          |                                               |       | 867  | E-24 | E-22 | 2         | 0/6331/6336/6  |    |
|     |          |                                               |       |      |      |      |           | 329/6330/6324/ |    |
|     |          |                                               |       |      |      |      |           | 775/776/3757/7 |    |
|     |          |                                               |       |      |      |      |           | 83/781         |    |
| BP  | GO:00600 | cardiac muscle contraction                     | 17/57 | 137/ | 2.03 | 5.21 | 3.44E-2  | 3764/148/147/6 | 17 |
|     |          |                                               |       | 186  | E-23 | E-21 | 1         | 327/55800/6331 |    |
|     |          |                                               |       |      |      |      |           | /6336/6330/632 |    |
|     |          |                                               |       |      |      |      |           | 4/801/134/775/7|    |
|     |          |                                               |       |      |      |      |           | 76/3757/783/52 |    |
|     |          |                                               |       |      |      |      |           | 90/781         |    |
| BP  | GO:00069 | striated muscle contraction                    | 18/57 | 174/ | 2.60 | 5.92 | 3.91E-2  | 3764/148/147/6 | 18 |
|     |          |                                               |       | 186  | E-23 | E-21 | 1         | 327/55800/6331 |    |
|     |          |                                               |       |      |      |      |           | /6336/6329/633 |    |
|     |          |                                               |       |      |      |      |           | 0/6324/801/134/|    |
|     |          |                                               |       |      |      |      |           | 775/776/3757/7 |    |
|     |          |                                               |       |      |      |      |           | 83/5290/781    |    |
| BP  | GO:00356 | multicellular organismal signaling             | 18/57 | 204/ | 4.92 | 1.01 | 6.67E-2  | 11280/6327/558 | 18 |
|     |          |                                               |       | 186  | E-22 | E-19 | 0         | 0/6331/6336/6  |    |
|     |          |                                               |       |      |      |      |           | 329/6330/6324/ |    |
|     |          |                                               |       |      |      |      |           | 801/10060/775/ |    |
|     |          |                                               |       |      |      |      |           | 776/3757/783/3 |    |
|     |          |                                               |       |      |      |      |           | 767/779/6261/7 |    |
|     |          |                                               |       |      |      |      |           | 81             |    |
| BP  | GO:00613 | cardiac conduction                            | 16/57 | 146/ | 3.71 | 6.92 | 4.57E-1  | 6327/55800/633 | 16 |
|     |          |                                               |       | 186  | E-21 | E-19 | 9         | 1/6336/6330/6  |    |
|     |          |                                               |       |      |      |      |           | 24/801/10060/7 |    |
|     |          |                                               |       |      |      |      |           | 75/776/3757/78 |    |
|     |          |                                               |       |      |      |      |           | 3/3767/779/626 |    |
|     |          |                                               |       |      |      |      |           | 1/781          |    |
| BP  | GO:00518 | membrane depolarization                       | 14/57 | 91/1 | 9.75 | 1.67 | 1.10E-1  | 11280/6327/558 | 14 |
|     |          |                                               |       | 867  | E-21 | E-18 | 8         | 0/6331/6336/6  |    |
|     |          |                                               |       |      |      |      |           | 329/6330/6324/ |    |
|     |          |                                               |       |      |      |      |           | 775/776/3757/7 |    |
|     |          |                                               |       |      |      |      |           | 83/774/781     |    |
| BP  | GO:00423 | regulation of membrane potential               | 21/57 | 434/ | 3.02 | 4.76 | 3.15E-1  | 3764/148/154/1 | 21 |
|     |          |                                               |       | 186  | E-20 | E-18 | 8         | 53/88/11280/63 |    |
|     |          |                                               |       |      |      |      |           | 27/55800/6331/ |    |
|     |          |                                               |       |      |      |      |           | 6336/6329/6330 |    |
|     |          |                                               |       |      |      |      |           | /6324/134/775/7|    |
|     |          |                                               |       |      |      |      |           | 76/3757/783/37 |    |
|     |          |                                               |       |      |      |      |           | 67/774/781     |    |
| BP  | GO:00020 | regulation of heart rate                      | 14/57 | 101/ | 4.58 | 6.43 | 4.25E-1  | 148/153/6327/5 | 14 |
|     |          |                                               |       | 186  | E-20 | E-18 | 8         | 5800/6331/6336 |    |
|     |          |                                               |       |      |      |      |           | 11280/6327/558 |    |
| BP GO:00015 | action potential | 15/57 | 70 | 133/186 | 4.70 E-20 | 6.43 E-18 | 4.25E-18 | 3764/3757/783/781 | 15 |
| BP GO:00347 | regulation of ion transmembrane transport | 21/57 | 70 | 483/186 | 2.73 E-18 | 3.51 E-17 | 2.32E-17 | 3764/6327/55800/6330/134/775/776/3757/783/781 | 21 |
| BP GO:00860 | cardiac muscle cell contraction | 12/57 | 0 | 69/867 | 1.47 E-18 | 1.78 E-16 | 1.17E-16 | 3764/6327/55800/6330/775/776/3757/783/781 | 12 |
| BP GO:00860 | cardiac muscle cell action potential | 12/57 | 0 | 74/867 | 3.62 E-18 | 4.13 E-17 | 2.73E-17 | 3764/6327/55800/6330/775/776/3757/783/781 | 12 |
| BP GO:00860 | membrane depolarization during cardiac muscle cell action potential | 9/57 | 0 | 23/867 | 9.39 E-18 | 1.01 E-16 | 6.70E-16 | 6327/55800/6330/775/776/3757/783/781 | 9 |
| BP GO:00860 | cardiac muscle cell action potential involved in contraction | 11/57 | 0 | 56/867 | 1.03 E-17 | 1.06 E-15 | 7.01E-15 | 3764/6327/55800/6330/775/776/3757/783/781 | 11 |
| BP GO:00860 | regulation of heart rate by cardiac conduction | 10/57 | 0 | 38/867 | 1.35 E-17 | 1.32 E-15 | 8.74E-15 | 6327/55800/6330/775/776/3757/783/781 | 10 |
| BP GO:00702 | actin-mediated cell contraction | 13/57 | 70 | 116/186 | 2.01 E-17 | 1.87 E-15 | 1.24E-15 | 3764/88/6327/5800/6330/775/776/3757/783/781 | 13 |
| BP  | GO:00300   | actin filament-based movement | 13/57 | 138/186 | 2.05 E-16 | 1.83 E-14 | 1.21E-10 | 3764/5800/6327/7600/6331/6330 | 13 |
|-----|-------------|-------------------------------|-------|---------|-----------|-----------|----------|--------------------------------|-----|
| BP  | GO:00860   | cell-cell signaling involved in cardiac conduction | 9/57 | 32/867 | 3.16 E-16 | 2.50 E-14 | 1.65E-10 | 55800/6331/6330 | 9 |
| BP  | GO:00352   | regulation of tube diameter | 13/57 | 143/186 | 3.29 E-16 | 2.50 E-14 | 1.65E-10 | 4879/148/154/150/153/152/151/6331/6330/6336 | 13 |
| BP  | GO:00508   | regulation of blood vessel size | 13/57 | 143/186 | 3.29 E-16 | 2.50 E-14 | 1.65E-10 | 4879/148/154/150/153/152/151/6331/6330/6336 | 13 |
| BP  | GO:00977   | regulation of blood vessel diameter | 13/57 | 143/186 | 3.29 E-16 | 2.50 E-14 | 1.65E-10 | 4879/148/154/150/153/152/151/6331/6330/6336 | 13 |
| BP  | GO:00351   | regulation of tube size | 13/57 | 144/186 | 3.61 E-16 | 2.64 E-14 | 1.75E-10 | 4879/148/154/150/153/152/151/6331/6330/6336 | 13 |
| BP  | GO:00860   | cell communication involved in cardiac conduction | 10/57 | 56/867 | 9.78 E-16 | 6.92 E-14 | 4.57E-10 | 55800/6331/6330 | 10 |
| BP  | GO:00069   | regulation of muscle contraction | 13/57 | 171/186 | 3.47 E-15 | 2.38 E-13 | 1.57E-10 | 148/154/150/152/151/6331/6336/6329/801/134/16 | 13 |
| BP  | GO:00300   | vascular process in circulatory system | 13/57 | 173/186 | 4.04 E-15 | 2.68 E-13 | 1.77E-10 | 4879/148/154/150/152/151/6331/6336/6329/801/134/16 | 13 |
| BP  | GO:00109   | regulation of metal ion transport | 16/57 | 394/186 | 3.01 E-14 | 1.93 E-12 | 1.27E-10 | 154/150/150/88/632/75/783/78/775/776/774/781 | 16 |
| Term | GO:00718 | adenylate cyclase-activating adrenergic receptor signaling pathway | 8/57 | 31/1  | 3.38  | 2.10  | 1.39E-1  | 148/154/150/15  | 8 |
|------|-----------|---------------------------------------------------------------|------|-------|-------|-------|----------|------------------|---|
|      | GO:00432  | positive regulation of ion transport                        | 14/57| 275/1 | 7.10  | 4.17  | 2.75E-1  | 154/150/88/558  | 14 |
|      |           |                                                               |      | 186/1 | E-14  | E-12  | 2        | 00/6331/6330/6  |    |
|      |           |                                                               |      | 70    |       |       |          | 324/801/134/77  |    |
|      |           |                                                               |      |       |       |       |          | 6/3757/783/376  |    |
|      |           |                                                               |      |       |       |       |          | 7/781           |    |
|      | GO:19040  | regulation of cation transmembrane transport                  | 15/57| 342/1 | 7.11  | 4.17  | 2.75E-1  | 154/150/88/632  | 15 |
|      |           |                                                               |      | 186/1 | E-14  | E-12  | 2        | 7/55800/6331/6  |    |
|      |           |                                                               |      | 70    |       |       |          | 330/6324/801/7  |    |
|      |           |                                                               |      |       |       |       |          | 75/776/3757/78  |    |
|      |           |                                                               |      |       |       |       |          | 3/3767/781      |    |
|      | GO:00718  | adrenergic receptor signaling pathway                         | 8/57 | 34/1  | 7.72  | 4.40  | 2.91E-1  | 148/154/150/15  | 8  |
|      |           |                                                               |      | 867/1 | E-14  | E-12  | 2        | 3/146/147/152/1  |    |
|      |           |                                                               |      | 0     |       |       |          | 3/146/147/152/1  |    |
|      | GO:00324  | regulation of transporter activity                            | 14/57| 283/1 | 1.05  | 5.84  | 3.86E-1  | 5468/154/150/3  | 14 |
|      |           |                                                               |      | 186/1 | E-13  | E-12  | 2        | 630/88/6327/55  |    |
|      |           |                                                               |      | 70    |       |       |          | 800/6330/6324/7  |    |
|      |           |                                                               |      |       |       |       |          | 801/776/783/37  |    |
|      |           |                                                               |      |       |       |       |          | 67/781          |    |
|      | GO:00230  | signal release                                                | 16/57| 462/1 | 3.49  | 1.88  | 1.24E-1  | 148/150/152/18  | 16 |
|      |           |                                                               |      | 186/1 | E-13  | E-11  | 1        | 5/151/3630/134/  |    |
|      |           |                                                               |      | 70    |       |       |          | 136/6833/291/7  |    |
|      |           |                                                               |      |       |       |       |          | 75/776/783/376  |    |
|      |           |                                                               |      |       |       |       |          | 7/774/7124      |    |
|      | GO:00357  | sodium ion transmembrane transport                            | 11/57| 140/1 | 3.89  | 2.05  | 1.35E-1  | 6337/6340/6338  | 11 |
|      |           |                                                               |      | 186/1 | E-13  | E-11  | 1        | /11280/6327/55  |    |
|      |           |                                                               |      | 70    |       |       |          | 800/6331/6326/7  |    |
|      |           |                                                               |      |       |       |       |          | 6329/6330/6324  |    |
|      | GO:00902  | regulation of muscle system process                           | 13/57| 259/1 | 7.42  | 3.81  | 2.52E-1  | 148/154/150/14  | 13 |
|      |           |                                                               |      | 186/1 | E-13  | E-11  | 1        | 7/152/151/6331/  |    |
|      |           |                                                               |      | 70    |       |       |          | 6336/6329/801/7  |    |
|      |           |                                                               |      |       |       |       |          | 134/136/775     |    |
|      | GO:00228  | regulation of transmembrane transporter activity              | 13/57| 268/1 | 1.15  | 5.74  | 3.79E-1  | 154/150/3630/8  | 13 |
|      |           |                                                               |      | 186/1 | E-12  | E-11  | 1        | 8/6327/55800/6  |    |
|      |           |                                                               |      | 70    |       |       |          | 330/6324/801/7  |    |
|      |           |                                                               |      |       |       |       |          | 76/783/3767/78  |    |
|      |           |                                                               |      |       |       |       |          | 1             |    |
|      | GO:00068  | sodium ion transmembrane transport activity                   | 12/57| 218/1 | 2.11  | 1.03  | 6.82E-1  | 6337/6340/154/  | 12 |
|      |           |                                                               |      |       |       |       |          | 1             |    |
| BP  | GO:00199 | second-messenger-mediated signaling | 15/57 | 439/15 | 2.62 | 1.25 | 8.26E-1 | 4879/148/154/1 | 15 |
| BGP | GO:00977 | negative regulation of blood vessel diameter | 9/57 | 84/1 | 3.67 | 1.71 | 1.13E-1 | 148/150/147/15 | 9 |
| BGP | GO:00071 | G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger | 12/57 | 256/12 | 1.40 | 6.38 | 4.21E-1 | 148/154/150/15 | 12 |
| BGP | GO:00324 | regulation of ion transmembrane transporter activity | 12/57 | 260/12 | 1.68 | 7.48 | 4.94E-1 | 154/150/88/632 | 12 |
| BGP | GO:00069 | regulation of smooth muscle contraction | 8/57 | 65/1 | 2.00 | 8.72 | 5.76E-1 | 148/154/150/14 | 8 |
| BGP | GO:00468 | regulation of hormone secretion | 12/57 | 266/12 | 2.19 | 9.35 | 6.17E-1 | 150/152/185/15 | 12 |
| BGP | GO:00996 | cardiac muscle cell membrane repolarization | 7/57 | 42/1 | 4.19 | 1.74 | 1.15E-0 | 3764/6331/6330/6324 | 7 |
| BGP | GO:00199 | cyclic-nucleotide-mediated signaling | 11/57 | 215/11 | 4.24 | 1.74 | 1.15E-0 | 4879/148/154/1 | 11 |
| BGP | GO:00603 | regulation of atrial cardiac | 5/57 | 10/1 | 5.52 | 2.22 | 1.47E-0 | 6327/55800/6330/6324 | 5 |
| BP     | GO          | Description                                                                 | p-value | BP     | GO          | Description                                                                 | p-value |
|--------|-------------|-----------------------------------------------------------------------------|---------|--------|-------------|-----------------------------------------------------------------------------|---------|
| 88     | GO:00071    | muscle cell membrane depolarization                                          | 0       | 88     | GO:00071    | adenylate cyclase-modulating G protein-coupled receptor signaling pathway    |         |
|        |             |                                                                             |         |        |             |                                                                             |         |
| 89     | GO:00071    |                                                                           | 11/57   | 11/57  |             |                                                                             |         |
|        |             |                                                                             | 221/11  | 186    |             |                                                                             |         |
|        |             |                                                                             | 5.70    | E-11   |             |                                                                             |         |
|        |             |                                                                             | 2.25    | E-09   |             |                                                                             |         |
|        |             |                                                                             | 1.49E-0 | 9      |             |                                                                             |         |
|        |             |                                                                             | 148/154/150/15 |     | 3/146/147/152/1 |                                                                             |         |
|        |             |                                                                             | 51/134/136/776 |      |         |                                                                             |         |
| 16     | GO:00860    | AV node cell action potential                                                | 0       | 16     | GO:00860    | AV node cell to bundle of His cell signaling                                | 5       |
|        |             |                                                                             | 11/1    | 11/1   | 867         |                                                                             |         |
|        |             |                                                                             | 1.01    | 1.01   | E-10        |                                                                             |         |
|        |             |                                                                             | 3.84    | 3.84   | E-09        |                                                                             |         |
|        |             |                                                                             | 2.54E-0 | 2.54E-0 | 6331/6336/6330 |                                                                             |         |
|        |             |                                                                             | /775/783 |        | 7          |                                                                             |         |
| 27     | GO:00860    | AV node cell action potential                                                | 0       | 27     | GO:00860    | AV node cell to bundle of His cell signaling                                | 5       |
|        |             |                                                                             | 11/1    | 11/1   | 867         |                                                                             |         |
|        |             |                                                                             | 1.01    | 1.01   | E-10        |                                                                             |         |
|        |             |                                                                             | 3.84    | 3.84   | E-09        |                                                                             |         |
|        |             |                                                                             | 2.54E-0 | 2.54E-0 | 6331/6336/6330 |                                                                             |         |
|        |             |                                                                             | /775/783 |        | 7          |                                                                             |         |
| 79     | GO:00468    | hormone secretion                                                           | 12/57   | 79     | GO:00468    | hormone secretion                                                           | 12      |
|        |             |                                                                             | 312/12  | 186    |             |                                                                             |         |
|        |             |                                                                             | 1.39    | 1.39   | E-10        |                                                                             |         |
|        |             |                                                                             | 5.18    | 5.18   | E-09        |                                                                             |         |
|        |             |                                                                             | 3.42E-0 | 3.42E-0 | 150/152/185/15 |                                                                             |         |
|        |             |                                                                             | 12      |        | 1/3630/134/683 |                                                                             |         |
|        |             |                                                                             | 3/291/775/776/3 |   | 767/7124 |                                                                             |         |
| 09     | GO:00860    | membrane repolarization                                                     | 0       | 09     | GO:00860    | membrane repolarization                                                     | 7       |
|        |             |                                                                             | 50/1    | 50/1   | 867         |                                                                             |         |
|        |             |                                                                             | 1.52    | 1.52   | E-10        |                                                                             |         |
|        |             |                                                                             | 5.58    | 5.58   | E-09        |                                                                             |         |
|        |             |                                                                             | 3.69E-0 | 3.69E-0 | 3764/6331/6330 |                                                                             |         |
|        |             |                                                                             | /6324/776/3757/781 | | 781 |                                                                             |         |
| 67     | GO:00860    | AV node cell to bundle of His cell signaling                                 | 0       | 67     | GO:00860    | AV node cell to bundle of His cell signaling                                 | 5       |
|        |             |                                                                             | 12/1    | 12/1   | 867         |                                                                             |         |
|        |             |                                                                             | 1.73    | 1.73   | E-10        |                                                                             |         |
|        |             |                                                                             | 6.22    | 6.22   | E-09        |                                                                             |         |
|        |             |                                                                             | 4.11E-0 | 4.11E-0 | 6331/6336/6330 |                                                                             |         |
|        |             |                                                                             | /775/783 |        | 7          |                                                                             |         |
| 17     | GO:00082    | regulation of blood pressure                                                | 10/57   | 17     | GO:00082    | regulation of blood pressure                                                | 10      |
|        |             |                                                                             | 182/10  | 186    |             |                                                                             |         |
|        |             |                                                                             | 1.76    | 1.76   | E-10        |                                                                             |         |
|        |             |                                                                             | 6.22    | 6.22   | E-09        |                                                                             |         |
|        |             |                                                                             | 4.11E-0 | 4.11E-0 | 4879/5468/148/154/153/147/18 |                                                                             |         |
|        |             |                                                                             | 5/151/134/774 |      | 767/7124 |                                                                             |         |
| 14     | GO:00099    | hormone transport                                                           | 12/57   | 14     | GO:00099    | hormone transport                                                           | 12      |
|        |             |                                                                             | 322/12  | 186    |             |                                                                             |         |
|        |             |                                                                             | 1.99    | 1.99   | E-10        |                                                                             |         |
|        |             |                                                                             | 6.94    | 6.94   | E-09        |                                                                             |         |
|        |             |                                                                             | 4.58E-0 | 4.58E-0 | 150/152/185/15 |                                                                             |         |
|        |             |                                                                             | 12      |        | 1/3630/134/683 |                                                                             |         |
|        |             |                                                                             | 3/291/775/776/3 |   | 767/7124 |                                                                             |         |
| 33     | GO:00199    | cAMP-mediated signaling                                                     | 10/57   | 33     | GO:00199    | cAMP-mediated signaling                                                     | 10      |
|        |             |                                                                             | 187/10  | 186    |             |                                                                             |         |
|        |             |                                                                             | 2.29    | 2.29   | E-10        |                                                                             |         |
|        |             |                                                                             | 7.84    | 7.84   | E-09        |                                                                             |         |
|        |             |                                                                             | 5.18E-0 | 5.18E-0 | 148/154/150/15 |                                                                             |         |
|        |             |                                                                             | 3/146/147/152/1 |      | 51/801/136 |                                                                             |         |
| 89     | GO:00071    | adenylate cyclase-activating G protein-coupled receptor signaling pathway     | 9/57    | 89     | GO:00071    | adenylate cyclase-activating G protein-coupled receptor signaling pathway     | 9       |
|        |             |                                                                             | 139/9   | 186    |             |                                                                             |         |
|        |             |                                                                             | 3.60    | 3.60   | E-10        |                                                                             |         |
|        |             |                                                                             | 1.21    | 1.21   | E-08        |                                                                             |         |
|        |             |                                                                             | 7.99E-0 | 7.99E-0 | 148/154/150/15 |                                                                             |         |
|        |             |                                                                             | 3/146/147/152/1 |      | 51/136 |                                                                             |         |
| BP      | GO:000069 | regulation of striated muscle contraction | 8/57 | 97/1 | 5.30 | 1.70 | 1.12E-0 | 148/147/6331/6 | 8  |
|---------|------------|------------------------------------------|------|------|------|------|---------|-----------------|----|
|         | BP GO:00069 | regulation of cell membrane repolarization | 6/57 | 39/1 | 1.86 | 5.71 | 3.77E-0 | 6331/6330/6324 | 6  |
|         | BP GO:00030 | regulation of systemic arterial blood pressure | 5/57 | 19/1 | 2.49 | 7.53 | 4.97E-0 | 4879/148/154/1 | 5  |
|         | BP GO:00551 | regulation of aerobic respiration | 7/57 | 82/1 | 5.38 | 1.60 | 1.06E-0 | 148/147/6331/6 | 7  |
|         | BP GO:00550 | regulation of sodium ion homeostasis | 6/57 | 52/1 | 1.13 | 3.26 | 2.15E-0 | 4879/6337/6340 | 6  |
|         | BP GO:00030 | regulation of systemic arterial blood pressure | 7/57 | 93/1 | 1.31 | 3.67 | 2.43E-0 | 4879/148/154/1 | 7  |
|         | BP GO:00029 | regulation of cell membrane repolarization | 6/57 | 32/1 | 5.26 | 1.70 | 1.12E-0 | 6331/6330/6324 | 6  |
|         | BP GO:00096 | regulation of cardiac muscle cell membrane repolarization | 6/57 | 31/1 | 4.29 | 1.42 | 9.37E-0 | 3764/6331/6330 | 6  |
|         | BP GO:00030 | signaling pathway | 6/57 | 867 | E-10 | E-08 | 9       | /6324/3757/781 |    |
|         | BP GO:00030 | regulation of cardiac muscle cell membrane repolarization | 6/57 | 867 | E-10 | E-08 | 9       | /776/3757/781  |    |
|         | BP GO:00069 | regulation of smooth muscle contraction | 8/57 | 110/ | 1.46 | 4.54 | 3.00E-0 | 148/154/150/14 | 8  |
|         | BP GO:00075 | regulation of excretion | 7/57 | 63/1 | 8.18 | 2.59 | 1.71E-0 | 4879/148/6340/7 | 7  |
|         | BP GO:00069 | regulation of membrane repolarization | 6/57 | 39/1 | 1.86 | 5.71 | 3.77E-0 | 6331/6330/6324 | 6  |
|         | BP GO:00030 | regulation of negative systemic arterial blood pressure | 5/57 | 19/1 | 2.49 | 7.53 | 4.97E-0 | 4879/148/154/1 | 5  |
|         | BP GO:00551 | regulation of cardiac muscle contraction | 7/57 | 82/1 | 5.38 | 1.60 | 1.06E-0 | 148/147/6331/6 | 7  |
|         | BP GO:00090 | regulation of aerobic respiration | 7/57 | 87/1 | 8.17 | 2.40 | 1.58E-0 | 1349/4512/4513 | 7  |
|         | BP GO:00550 | regulation of sodium ion homeostasis | 6/57 | 52/1 | 1.13 | 3.26 | 2.15E-0 | 4879/6337/6340 | 6  |
|         | BP GO:00096 | regulation of cardiac muscle cell membrane repolarization | 6/57 | 31/1 | 4.29 | 1.42 | 9.37E-0 | 3764/6331/6330 | 6  |
|         | BP GO:00030 | regulation of signaling pathway | 6/57 | 867 | E-10 | E-08 | 9       | /6324/3757/781 |    |
|         | BP GO:00030 | regulation of cell membrane repolarization | 6/57 | 867 | E-10 | E-08 | 9       | /776/3757/781  |    |
| BP  | GO:00159 | energy derivation by oxidation of organic compounds | 10/57 | 285/  | 1.35  | 3.73  | 2.47E-07 | 1349/4512/4513/4514/3630/801/5290/6390/6391/6389 |
|-----|----------|-----------------------------------------------------|-------|-------|-------|-------|-----------|-----------------------------------------------|
| BP  | GO:00603 | regulation of ventricular cardiac muscle cell membrane repolarization | 5/57  | 27/1  | 1.70  | 4.65  | 3.07E-07 | 6331/6330/6324/3757/781 |
| BP  | GO:00192 | regulation of vasoconstriction | 6/57  | 58/1  | 2.21  | 5.98  | 3.95E-07 | 148/150/147/151/2/185/151 |
| BP  | GO:00068 | potassium ion transport | 9/57  | 240/  | 4.34  | 1.16  | 7.64E-07 | 3764/150/88/133/76/3757/3767 |
| BP  | GO:00507 | regulation of insulin secretion | 8/57  | 176/  | 5.93  | 1.56  | 1.03E-06 | 150/152/6833/2/91/775/776/376 |
| BP  | GO:00300 | regulation of peptide hormone secretion | 9/57  | 250/  | 6.16  | 1.60  | 1.06E-07 | 150/152/3630/6/833/291/775/776/3767/7124 |
| BP  | GO:00229 | regulation of respiratory electron transport chain activity | 7/57  | 117/  | 6.46  | 1.66  | 1.10E-07 | 1349/4512/4513/7/6390/639 |
| BP  | GO:20012 | regulation of cation channel activity | 6/57  | 70/1  | 6.97  | 1.77  | 1.17E-06 | 154/88/801/783/6376/781 |
| BP  | GO:00457 | regulation of blood pressure | 5/57  | 37/1  | 8.97  | 2.22  | 1.46E-05 | 148/153/147/15/1/134 |
| BP  | GO:20002 | regulation of signaling receptor activity | 5/57  | 37/1  | 8.97  | 2.22  | 1.46E-05 | 154/150/152/15/0/1/775/3757 |
| BP  | GO:00860 | regulation of ventricular cardiac muscle cell action potential | 5/57  | 38/1  | 1.03  | 2.52  | 1.66E-05 | 3764/55800/633/1775/3757 |
| BP  | GO:00514 | regulation of cytosolic calcium ion | 10/57 | 357/  | 1.12  | 2.70  | 1.79E-07 | 148/147/185/80/1/134/775/776/7/83/6261/781 |

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| Gene ID | GO Term | Term Description | BP | GO Term | Concentration |
|---------|---------|------------------|----|---------|---------------|
| BP:00423 | GO:00423 | vasoconstriction | 6/57 | 10 | 1.15 | 2.73 | 1.81E-07 | 148/150/147/15 | 6 |
| BP:00453 | GO:00453 | cellular respiration | 8/57 | 33 | 1.21 | 2.85 | 1.88E-07 | 1349/4512/4513 | 8 |
| BP:00459 | GO:00459 | negative regulation of smooth muscle contraction | 4/57 | 86 | 1.38 | 3.22 | 2.13E-06 | 154/152/134/13 | 4 |
| BP:00705 | GO:00705 | calcium ion import | 6/57 | 09 | 1.56 | 3.60 | 2.38E-07 | 775/776/783/77 | 6 |
| BP:00347 | GO:00347 | positive regulation of transmembrane transport | 8/57 | 64 | 1.85 | 4.22 | 2.79E-06 | 154/3630/88/80 | 8 |
| BP:00300 | GO:00300 | insulin secretion | 8/57 | 73 | 2.07 | 4.67 | 3.08E-06 | 91/775/776/376 | 8 |
| BP:00020 | GO:00020 | regulation of sodium ion transport | 6/57 | 28 | 2.24 | 5.01 | 3.31E-06 | 154/6327/55800 | 6 |
| BP:19040 | GO:19040 | positive regulation of cation transmembrane transport | 7/57 | 64 | 2.69 | 5.93 | 3.92E-07 | 154/88/801/375 | 7 |
| BP:00027 | GO:00027 | regulation of peptide secretion | 11/57 | 91 | 2.76 | 5.97 | 3.94E-07 | 150/152/3630 | 11 |
| BP:00457 | GO:00457 | negative regulation of blood pressure | 5/57 | 76 | 2.76 | 5.97 | 3.94E-07 | 4879/148/154/1 | 5 |
| BP:00860 | GO:00860 | atrial cardiac muscle cell action potential | 4/57 | 14 | 3.65 | 7.64 | 5.04E-06 | 55800/6331/775 | 4 |
| BP:00860 | GO:00860 | atrial cardiac muscle cell to AV node cell signaling | 4/57 | 26 | 3.65 | 7.64 | 5.04E-06 | 55800/6331/775 | 4 |
| BP | GO:00860 | atrial cardiac muscle cell to AV node cell communication |
|----|-----------|-------------------------------------------------------|
| 66 |           | 4/57                                                  |
|    |           | 20/1                                                  |
|    |           | 3.65                                                  |
|    |           | 7.64                                                  |
|    |           | 5.04E-0                                               |
|    |           | 5580/6331/775/783/4                                   |
| BP | GO:00030 | regulation of systemic arterial blood pressure mediated by a chemical signal |
| 44 |           | 5/57                                                  |
|    |           | 49/1                                                  |
|    |           | 3.82                                                  |
|    |           | 7.83                                                  |
|    |           | 5.17E-0                                               |
|    |           | 148/154/153/14/5                                      |
| BP | GO:00032 | regulation of membrane depolarization |
| 54 |           | 5/57                                                  |
|    |           | 49/1                                                  |
|    |           | 3.82                                                  |
|    |           | 7.83                                                  |
|    |           | 5.17E-0                                               |
|    |           | 6327/6336/6324/6                                       |
| BP | GO:00550 | monovalent inorganic cation homeostasis |
| 67 |           | 7/57                                                  |
|    |           | 154/1                                                  |
|    |           | 4.24                                                  |
|    |           | 8.62                                                  |
|    |           | 5.69E-0                                               |
|    |           | 4879/6337/6340/6                                       |
| BP | GO:00705 | calcium ion transmembrane transport |
| 88 |           | 9/57                                                  |
|    |           | 315/1                                                  |
|    |           | 4.37                                                  |
|    |           | 8.79                                                  |
|    |           | 5.80E-0                                               |
|    |           | 150/801/775/776/9                                      |
| BP | GO:00061 | mitochondrial electron transport, cytochrome c to oxygen |
| 23 |           | 4/57                                                  |
|    |           | 21/1                                                  |
|    |           | 4.49                                                  |
|    |           | 8.87                                                  |
|    |           | 5.86E-0                                               |
|    |           | 1349/4512/4513/4                                     |
| BP | GO:00196 | aerobic electron transport chain |
| 46 |           | 4/57                                                  |
|    |           | 21/1                                                  |
|    |           | 4.49                                                  |
|    |           | 8.87                                                  |
|    |           | 5.86E-0                                               |
|    |           | 1349/4512/4513/4                                     |
| BP | GO:00347 | positive regulation of ion transmembrane transport |
| 67 |           | 7/57                                                  |
|    |           | 156/1                                                  |
|    |           | 4.63                                                  |
|    |           | 9.05                                                  |
|    |           | 5.97E-0                                               |
|    |           | 154/88/801/375/7                                    |
| BP | GO:00072 | positive regulation of cytosolic calcium ion concentration |
| 04 |           | 9/57                                                  |
|    |           | 319/1                                                  |
|    |           | 4.85                                                  |
|    |           | 9.40                                                  |
|    |           | 6.21E-0                                               |
|    |           | 148/147/185/80/9                                     |
| BP | GO:00427 | mitochondrial ATP synthesis coupled electron |
| 75 |           | 6/57                                                  |
|    |           | 97/1                                                  |
|    |           | 4.93                                                  |
|    |           | 9.46                                                  |
|    |           | 6.25E-0                                               |
|    |           | 1349/4512/4513/6                                    |

| BP | GO:00030 | regulation of systemic arterial blood pressure mediated by a chemical signal | 5/57 |
| BP | GO:00550 | monovalent inorganic cation homeostasis | 7/57 |
| BP | GO:00705 | calcium ion transmembrane transport | 9/57 |
| BP | GO:00061 | mitochondrial electron transport, cytochrome c to oxygen | 4/57 |
| BP | GO:00196 | aerobic electron transport chain | 4/57 |
| BP | GO:00347 | positive regulation of ion transmembrane transport | 7/57 |
| BP | GO:00072 | positive regulation of cytosolic calcium ion concentration | 9/57 |
| BP | GO:00427 | mitochondrial ATP synthesis coupled electron | 6/57 |
| BP   | GO:00427 | transport                                      | 6/57 | 98/1 | 5.24 | 9.96 | 6.58E-0 | 1349/4512/4513 | 6 |
|      | GO:00509 | negative regulation of lipid catabolic process | 4/57  | 23/1 | 6.62 | 1.25 | 8.23E-0 | 150/3630/134/7 | 4 |
|      | GO:00068 | calcium ion transport                          | 16/57 | 434/1 | 6.76 | 1.26 | 8.33E-0 | 148/150/801/77 | 10 |
|      | GO:00068 | cellular calcium ion homeostasis               | 74/57 | 186/1 | 6.62 | 1.25 | 8.23E-0 | 150/3630/134/7 | 4 |
|      | GO:20012 | regulation of cation channel activity         | 57/57 | 178/1 | 1.13 | 1.99 | 1.32E-0 | 154/88/3630/801/783/ | 6 |
|      | GO:00459 | negative regulation of transporter activity   | 11/57 | 112/1 | 1.15 | 2.02 | 1.34E-0 | 154/88/3630/801/783/ | 6 |
|      | GO:19023 | regulation of sodium ion transport            | 5/57  | 62/1  | 1.26 | 2.19 | 1.44E-0 | 6327/55800/633 | 5 |
|      | GO:00459 | negative regulation of transporter activity   | 5/57  | 27/1  | 1.30 | 2.22 | 1.47E-0 | 154/152/134/13 | 4 |
| GO   | BP      | Description                                         | Rank | Fold Change | p value | P value 2-tail | P value 1-tail |
|------|---------|-----------------------------------------------------|------|-------------|---------|----------------|----------------|
| 32   | BP:00519| regulation of muscle contraction negative           | 4/57 | 1.30        | 2.22    | 1.47E-0        | 1.47E-0        |
| 53   | BP:00550| negative regulation of amine transport              | 74   | 1.42        | 2.40    | 1.59E-0        | 1.59E-0        |
| 08   | BP:00507| regulation of protein secretion                      | 10/57| 1.44        | 2.43    | 1.60E-0        | 1.60E-0        |
| 00   | BP:00229| electron transport chain                             | 7/57 | 1.51        | 2.52    | 1.66E-0        | 1.66E-0        |
| 88   | BP:00468| negative regulation of hormone secretion            | 5/57 | 1.72        | 2.85    | 1.88E-0        | 1.88E-0        |
| 38   | BP:00708| divalent metal ion transport                         | 10/57| 1.78        | 2.92    | 1.93E-0        | 1.93E-0        |
| 11   | BP:00725| divalent inorganic cation transport                 | 10/57| 1.98        | 3.23    | 2.14E-0        | 2.14E-0        |
| 03   | BP:00725| cellular divalent inorganic cation homeostasis      | 10/57| 2.13        | 3.45    | 2.28E-0        | 2.28E-0        |
| 11   | BP:00423| vasodilation                                       | 4/57 | 2.63        | 4.22    | 2.79E-0        | 2.79E-0        |
| 26   | BP:00192| transmission of nerve impulse                        | 5/57 | 2.65        | 4.22    | 2.79E-0        | 2.79E-0        |
| 24   | BP:19035| positive regulation of blood circulation             | 5/57 | 2.84        | 4.49    | 2.96E-0        | 2.96E-0        |
| 3    | BP:00860| SA node cell to                                     | 3/57 | 3.19        | 5.00    | 3.30E-0        | 3.30E-0        |
| BP    | GO:00107 | atrial cardiac muscle cell communication | 0  | 867 | E-06 | E-05 |
|-------|-----------|------------------------------------------|----|-----|------|------|
| GO:00192 | neuronal action potential | 0  | 867 | E-06 | E-05 | 5    |
| GO:00321 | activation of protein kinase B activity | 0  | 867 | E-06 | E-05 | 5    |
| GO:019035 | negative regulation of secretion by cell | 0  | 186 | E-06 | E-05 | 5    |
| GO:00718 | cellular potassium ion transport | 70 | 217/ | 4.20 | 6.29 | 4.16E-0 |
| GO:00718 | potassium ion transmembrane transport | 70 | 217/ | 4.20 | 6.29 | 4.16E-0 |
| GO:00107 | macrophage derived foam cell differentiation | 0  | 867 | E-06 | E-05 | 5    |
| GO:00900 | foam cell differentiation | 0  | 36/1 | 4.28 | 6.31 | 4.17E-0 |
| GO:00061 | oxidative phosphorylation | 0  | 145/ | 5.18 | 7.60 | 5.02E-0 |
| GO:00986 | inorganic cation import across plasma membrane | 0  | 83/1 | 5.37 | 7.76 | 5.13E-0 |
| GO:00995 | inorganic ion import across plasma membrane | 0  | 83/1 | 5.37 | 7.76 | 5.13E-0 |
| GO:00026 | negative regulation of | 0  | 867 | E-06 | E-05 | 5    |

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| GO:00508 | acute inflammatory response | 0 | 9/57 | 436/ | 6.34 | 9.04 | 5.97E-05 | 148/154/3630/1 | 9 |
| GO:00991 | modulation of chemical synaptic transmission | 186 | E-06 | E-05 | 5 | 34/136/776/783/774/7124 |
| GO:00510 | regulation of trans-synaptic signaling | 186 | E-06 | E-05 | 5 | 34/136/776/783/774/7124 |
| GO:19905 | negative regulation of secretion | 867 | E-06 | 012 | 5 | 7/3767 |
| GO:00860 | bundle of His cell to Purkinje myocyte communication | 14/1 | 9.59 | 0.00 | 8.78E-09 | 6331/6336/781/78 |
| GO:00519 | regulation of calcium ion transport | 186 | E-05 | 016 | 7 | 6/783/774/781 |
| GO:00336 | negative regulation of catecholamine secretion | 15/1 | 1.20 | 0.00 | 0.0001 | 150/152/151/18 |
| GO:00091 | nucleoside triphosphate metabolic process | 186 | E-05 | 018 | 9 | 1349/4512/4513/8 |
| GO:00072 | phospholipase C-activating G protein-coupled receptor signaling pathway | 186 | E-05 | 018 | 9 | 148/150/147/18 |
| GO:00101 | potassium ion import | 867 | E-05 | 018 | 1 | 7/3767 |
| GO:00432 | positive regulation of | 48/1 | 1.37 | 0.00 | 0.00012 | 150/88/134/375/4 |

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| BP   | GO:00104 | regulation of potassium ion transport | 6/57 | 173/186 | 1.42/0.00 | 0.00012/0.018 | 154/150/152/15 | 6 | 9 |
| BP GO:00140 | regulation of norepinephrine secretion | 3/57 | 16/867 | 1.47/0.00 | 0.00012/0.019 | 150/152/15 | 3 | 8 |
| BP GO:00094 | response to cold | 4/57 | 50/867 | 1.62/0.00 | 0.00013/0.021 | 4513/5468/154/15 | 4 | 9 |
| BP GO:00192 | sensory perception of pain | 5/7 | 104/186 | 1.62/0.00 | 0.00013/0.021 | 152/11280/5580 | 5 | 9 |
| BP GO:00432 | regulation of potassium ion transport | 5/7 | 105/186 | 1.70/0.00 | 0.00014/0.021 | 150/188/134/776 | 5 | 9 |
| BP GO:00310 | response to caffeine | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 5468/779/6261 | 3 | 9 |
| BP GO:00316 | heat generation | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 154/153/7124 | 3 | 9 |
| BP GO:00362 | response to diuretic | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 5468/779/6261 | 3 | 9 |
| BP GO:00482 | norepinephrine secretion | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 150/152/15 | 3 | 9 |
| BP GO:00615 | calcium ion transport via high voltage-gated calcium channel | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 775/783/781 | 3 | 9 |
| BP GO:00995 | regulation of presynaptic cytosolic calcium ion concentration | 3/57 | 17/867 | 1.78/0.00 | 0.00014/0.022 | 134/776/783 | 3 | 9 |
| BP GO:20006 | regulation of sodium ion | 4/57 | 52/867 | 1.89/0.00 | 0.00015/0.023 | 6327/55800/633 | 4 | 5 |
| BP       | GO:00987 | import across plasma membrane | 110/70  | 2.13/1  | 0.00/1  | 0.00017/3  | 3764/10060/375/7 | 5/4  |
|----------|----------|-------------------------------|---------|---------|---------|-----------|------------------|-----|
| BP       | GO:00509 | regulation of lipid catabolic process | 54/1/867 | 2.20/0.026/8 | 0.00017/124 |        | 150/3630/134/7 | 4/1  |
| BP       | GO:00171 | regulation of calcium ion-dependent exocytosis | 112/70 | 2.32/0.028/6 | 0.00018/6/783 |        | 148/150/136/77 | 5/3  |
| BP       | GO:00989 | regulation of action potential | 55/1/867 | 2.37/0.028/9 | 0.00018/148/6331/775/7 | 4/1  |
| BP       | GO:00108 | negative regulation of lipid storage | 19/1/867 | 2.53/0.030/3 | 0.0002/5468/1401/7124 | 3/1  |
| BP       | GO:00030 | renal system process | 120/1/867 | 3.23/0.038/5 | 0.00025/4879/148/185/1 | 5/1  |
| BP       | GO:00158 | norepinephrine transport | 21/1/867 | 3.45/0.040/9 | 0.00026/150/152/151 | 3/1  |
| BP       | GO:00358 | regulation of renal sodium excretion | 21/1/867 | 3.45/0.040/9 | 0.00026/4879/185/134 | 3/1  |
| BP       | GO:00460 | ATP metabolic process | 305/1/867 | 3.81/0.044/5 | 0.00029/1349/4512/4513 | 7/1  |
| BP       | GO:00312 | positive regulation of cyclase activity | 22/1/867 | 3.99/0.046/7 | 0.0003/136/775/776 | 3/1  |
| BP       | GO:00989 | negative regulation of catabolic process | 308/1/867 | 4.05/0.047/7 | 0.00031/148/150/3630/1 | 7/1  |
| BP       | GO:00347 | negative regulation of transmembrane transport | 128/1/867 | 4.41/0.050/6 | 0.00033/150/88/801/375 | 5/1  |
| BP       | GO:00358 | renal sodium transport | 23/1/867 | 4.58/0.050/6 | 0.00034/4879/185/134 | 3/1  |
| 12 | excretion | 867 | E-05 | 052 | 5 |
|----|-----------|-----|------|-----|---|
| BP | GO:00513  | 3/57|      |     |   |
| 49 | positive  | 23/1| 4.58 | 0.00| 0.00034 |
| BP | regulation of lyase activity | 867 | E-05 | 052 | 5 |
| 3/57| 0 | 2 | |
| BP | GO:00440  | 3/57|      |     |   |
| 62 | regulation of excretion | 24/1 | 5.22 | 0.00| 0.00039 |
| BP | GO:00454  | 6/57|      |     |   |
| 44 | fat cell differentiation | 223/ | 5.93 | 0.00| 0.00044 |
| BP | GO:00104  | 3/57|      |     |   |
| 60 | positive regulation of heart rate | 26/1 | 6.67 | 0.00| 0.00049 |
| BP | GO:00719  | 7/57|      |     |   |
| 02 | positive regulation of protein serine/threonine kinase activity | 334/ | 6.76 | 0.00| 0.00049 |
| BP | GO:0092   | 7/57|      |     |   |
| 05 | purine ribonucleoside triphosphate metabolic process | 335/ | 6.88 | 0.00| 0.00050 |
| BP | GO:19037  | 4/57|      |     |   |
| 79 | regulation of cardiac conduction | 73/1 | 7.26 | 0.00| 0.00052 |
| BP | GO:0091   | 7/57|      |     |   |
| 67 | purine ribonucleoside monophosphate metabolic process | 340/ | 7.55 | 0.00| 0.00054 |
| BP | GO:0091   | 7/57|      |     |   |
| 26 | purine ribonucleoside monophosphate metabolic process | 341/ | 7.69 | 0.00| 0.00055 |
| BP | GO:0091   | 7/57|      |     |   |
| 99 | ribonucleoside triphosphate metabolic process | 341/ | 7.69 | 0.00| 0.00055 |
| BP | GO:0091   | 7/57|      |     |   |
| 44 | purine nucleoside | 342/ | 7.84 | 0.00| 0.00055 |

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| BP   | GO:       | Term                                      | Count 1 | Count 2 | Count 3 | Count 4 | Count 5 | Count 6 | p-value 1  | p-value 2  | p-value 3  | p-value 4  | p-value 5  |
|------|-----------|-------------------------------------------|---------|---------|---------|---------|---------|---------|------------|------------|------------|------------|------------|
| 34   | GO:00458  | triphosphate metabolic process             | 70      | 7       | 1/6389  | 5       |
| 93   | GO:00425  | glucose homeostasis                        | 6/57    | 241/    | 9.10    | 0.00    | 0.0064  | 5468/150/147/3 | 6       |
| 00   | GO:00335  | carbohydrate homeostasis                   | 6/57    | 242/    | 9.31    | 0.00    | 0.0065  | 5468/150/147/3 | 6       |
| 00   | GO:20003  | regulation of synaptic vesicle exocytosis  | 4/57    | 78/1    | 9.41    | 0.00    | 0.0065  | 148/136/775/78 | 4       |
| 66   | GO:00092  | response to temperature stimulus           | 6/57    | 243/    | 9.52    | 0.00    | 0.0066  | 4513/5468/154/3 | 6       |
| 69   | GO:19031  | regulation of calcium ion transmembrane   | 5/57    | 151/    | 9.66    | 0.00    | 0.0066  | 150/801/775/78 | 5       |
| 61   | GO:0091   | ribonucleoside monophosphate metabolic process | 7/57    | 354/    | 9.72    | 0.00    | 0.0066  | 1349/4512/4513 | 7       |
| 13   | GO:00620  | regulation of small molecule metabolic process | 5/57    | 153/    | 0.00    | 0.00    | 0.0070  | 4513/5468/3630 | 5       |
| 43   | GO:00107  | regulation of macrophage derived foam cell differentiation | 3/57    | 30/1    | 0.00    | 0.00    | 0.0070  | 5468/185/1401 | 3       |
| 71   | GO:00488  | multicellular organismal homeostasis        | 8/57    | 485/    | 0.00    | 0.00    | 0.0071  | 6337/6340/154/3 | 8       |
| 56   | GO:00171  | calcium ion regulated exocytosis            | 5/57    | 154/    | 0.00    | 0.00    | 0.0071  | 148/150/136/77 | 5       |
| BP   | GO:00860 | membrane repolarization during action potential | 3/57 | 31/1 | 0.00 | 0.00 | 0.00076 | 3764/3757/781 | 3 |
| BP   | GO:00432 | negative regulation of ion transport | 5/57 | 157/1 | 0.00 | 0.00 | 0.00077 | 150/88/801/134/57 | 5 |
| BP   | GO:00604 | calcium ion transport into cytosol | 5/57 | 158/1 | 0.00 | 0.00 | 0.00079 | 148/801/775/62 | 5 |
| BP   | GO:19028 | regulation of synaptic vesicle transport | 4/57 | 84/1 | 0.00 | 0.00 | 0.00082 | 148/136/776/78 | 4 |
| BP   | GO:00459 | positive regulation of vasoconstriction | 3/57 | 32/1 | 0.00 | 0.00 | 0.00082 | 148/147/152 | 3 |
| BP   | GO:00459 | positive regulation of smooth muscle contraction | 3/57 | 32/1 | 0.00 | 0.00 | 0.00082 | 148/147/151 | 3 |
| BP   | GO:19033 | regulation of regulated secretory pathway | 5/57 | 160/1 | 0.00 | 0.00 | 0.00082 | 148/150/136/77 | 5 |
| BP   | GO:00726 | protein localization to plasma membrane | 6/57 | 260/1 | 0.00 | 0.00 | 0.00089 | 3630/88/55800/6 | 6 |
| BP   | GO:00091 | nucleoside monophosphate metabolic process | 7/57 | 375/1 | 0.00 | 0.00 | 0.00089 | 1349/4512/4513 | 7 |
| BP   | GO:00060 | tricarboxylic acid cycle | 3/57 | 34/1 | 0.00 | 0.00 | 0.00096 | 6390/6391/6389 | 3 |
| BP   | GO:00700 | neuron cellular homeostasis | 3/57 | 34/1 | 0.00 | 0.00 | 0.00096 | 134/776/783 | 3 |
| BP   | GO:19010 | regulation of calcium ion transmembrane transporter | 4/57 | 89/1 | 0.00 | 0.00 | 0.001 | 150/801/783/78 | 4 |
| BP GO:19016 | activity | 7/57 | 385/0.00/0.00/0.00102/5468/154/185/3 | 7 |
| BP GO:00072 | cellular response to peptide | 53 | 186/016/155/9 | 630/88/5290/78 |
| BP GO:19035 | neurotransmitter secretion | 69 | 186/016/155/9 | 3/774 |
| BP GO:00061 | 7/57 | 385/0.00/0.00/0.00102/148/136/776/78 | 5 |
| BP GO:00061 | citrate metabolic process | 01 | 0.00/0.00/0.00102/6390/6391/6389 | 3 |
| BP GO:00988 | regulation of renal system process | 3/57 | 35/1/0.00/0.00102/4879/185/134 | 3 |
| BP GO:00996 | signal release from synapse | 43 | 170/0.00/0.00102/148/136/776/78 | 5 |
| BP GO:19040 | negative regulation of cation transmembrane transport | 63 | 91/1/0.00/0.00102/150/88/801/375 | 4 |
| BP GO:00604 | cytosolic calcium ion transport | 01 | 171/0.00/0.00102/148/801/775/62 | 5 |
| BP GO:00458 | regulation of lipid metabolic process | 33 | 92/1/0.00/0.00102/150/3630/134/7 | 4 |
| BP GO:00148 | release of sequestered calcium ion into cytosol by sarcoplasmic reticulum | 08 | 36/1/0.00/0.00102/801/775/6261 | 3 |
| BP GO:00432 | positive regulation of protein complex disassembly | 43 | 37/1/0.00/0.00102/154/88/7124 | 3 |
| BP GO:19035 | release of sequestered calcium ion into cytosol by endoplasmic reticulum | 14 | 37/1/0.00/0.00102/801/775/6261 | 3 |
| BP     | GO:00519 | regulation of reticulum 4/57 | 95/1 | 0.00 | 0.00 | 0.00121 | 150/152/151/13 | 4 |
| BP     | GO:00071 | activation of amine transport 3/57 | 38/1 | 0.00 | 0.00 | 0.00126 | 154/153/136 | 3 |
| BP     | GO:19010 | positive regulation of calcium ion transmembrane activity 3/57 | 38/1 | 0.00 | 0.00 | 0.00126 | 801/783/781 | 3 |
| BP     | GO:00519 | regulation of sensory perception of pain 3/57 | 39/1 | 0.00 | 0.00 | 0.00135 | 152/11280/134 | 3 |
| BP     | GO:00723 | tricarboxylic acid metabolic process 3/57 | 39/1 | 0.00 | 0.00 | 0.00135 | 6390/6391/6389 | 3 |
| BP     | GO:00458 | positive regulation of heart contraction 3/57 | 40/1 | 0.00 | 0.00 | 0.00144 | 148/153/55800 | 3 |
| BP     | GO:00519 | regulation of sensory perception of pain 3/57 | 40/1 | 0.00 | 0.00 | 0.00144 | 152/11280/134 | 3 |
| BP     | GO:00508 | brown fat cell differentiation 3/57 | 41/1 | 0.00 | 0.00 | 0.00153 | 154/153/1630 | 3 |
| BP     | GO:00158 | amine transport 4/57 | 102/ | 0.00 | 0.00 | 0.00153 | 150/152/151/13 | 4 |
| BP     | GO:20003 | positive regulation of reactive oxygen species metabolic process 4/57 | 102/ | 0.00 | 0.00 | 0.00153 | 4513/185/1401/7124 | 4 |
| BP     | GO:00347 | negative regulation of ion transmembrane activity 4/57 | 103/ | 0.00 | 0.00 | 0.00159 | 150/88/801/375 | 4 |
| BP   | GO:00469  | regulation of neurotransmitter secretion | 4/57 | 104/0.00 0.00 0.00164 148/136/776/78 4 | 28 |
|------|-----------|------------------------------------------|------|----------------------------------------|----|
| BP   | GO:00312  | regulation of cyclase activity            | 3/57 | 43/0.00 0.00 0.00173 136/775/776 3 | 79 |
| BP   | GO:00702  | sarcoplasmic reticulum calcium ion transport | 3/57 | 43/0.00 0.00 0.00173 801/775/6261 3 | 96 |
| BP   | GO:00860  | regulation of cardiac muscle contraction  | 3/57 | 43/0.00 0.00 0.00173 6331/134/775 3 | 04 |
| BP   | GO:00510  | positive regulation of secretion          | 7/57 | 428/0.00 0.00 0.00176 4879/3630/134/775 7 | 47 |
| BP   | GO:20003  | regulation of reactive oxygen species metabolic process | 5/57 | 195/0.00 0.00 0.00178 4513/185/3630/775 5 | 77 |
| BP   | GO:00513  | regulation of oxidoreductase activity      | 4/57 | 107/0.00 0.00 0.00178 185/3630/801/7 4 | 41 |
| BP   | GO:19007  | protein localization to cell periphery     | 6/57 | 311/0.00 0.00 0.00201 3630/88/55800/775 6 | 78 |
| BP   | GO:00108  | regulation of lipid storage                | 3/57 | 46/0.00 0.00 0.00204 5468/1401/7124 3 | 83 |
| BP   | GO:00308  | positive regulation of nucleotide biosynthetic process | 3/57 | 46/0.00 0.00 0.00204 4513/3630/136 3 | 10 |
| BP   | GO:00513  | regulation of lyase activity               | 3/57 | 46/0.00 0.00 0.00204 136/775/776 3 | 39 |
| BP   | GO:19003  | positive regulation of purine nucleotide   | 3/57 | 46/0.00 0.00 0.00204 4513/3630/136 3 | 73 |
| GO Term       | Description                                                                 | List Size | Log2 Fold Change | p-value | Benjamini Corrected p-value | FDR Corrected p-value |
|---------------|------------------------------------------------------------------------------|-----------|------------------|---------|-----------------------------|-----------------------|
| GO:00986      | regulation of synaptic vesicle cycle                                         | 4/57      | 112/186          | 0.00    | 0.00207                     | 4/3                   |
| GO:00069      | acute-phase response                                                         | 3/57      | 47/867           | 0.00    | 0.00215                     | 3/112/3630/1401/7124 |
| GO:19031      | regulation of actin filament-based movement                                  | 3/57      | 47/867           | 0.00    | 0.00215                     | 3/6331/134/775       |
| GO:00445      | relaxation of smooth muscle                                                  | 2/57      | 10/867           | 0.00    | 0.00216                     | 2/134/136           |
| GO:00457      | positive regulation of epidermal growth factor-activated receptor activity   | 2/57      | 10/867           | 0.00    | 0.00216                     | 2/150/134           |
| GO:00704      | regulation of uterine smooth muscle contraction                              | 2/57      | 10/867           | 0.00    | 0.00216                     | 2/152/151           |
| GO:00713      | cellular response to caffeine                                                | 2/57      | 10/867           | 0.00    | 0.00216                     | 2/779/6261          |
| GO:00459      | positive regulation of muscle contraction                                   | 3/57      | 48/867           | 0.00    | 0.00225                     | 3/148/147/151       |
| GO:00060      | glucose metabolic process                                                    | 5/57      | 209/186          | 0.00    | 0.00231                     | 5/3630/3767/7124    |
| GO:00160      | synaptic vesicle exocytosis                                                  | 4/57      | 119/186          | 0.00    | 0.00251                     | 4/148/136/776/78    |
| GO:00338      | regulation of NAD(P)H oxidase activity                                        | 2/57      | 11/867           | 0.00    | 0.00255                     | 2/185/3630          |
| GO:00400      | negative                                                                     | 2/57      | 11/867           | 0.00    | 0.00255                     | 2/154/153           |
| ID  | Term                                      | GO ID     | P.Value | FDR  | q.Value | EBP | GO ID   | FDR  | q.Value | EBP |
|-----|-------------------------------------------|-----------|---------|------|---------|-----|---------|------|---------|-----|
| 15  | regulation of multicellular organism growth | GO:00704  | 0.000   | 0.000 | 0.00255 | 11/1| 0.000   | 0.000 | 0.00255 | 152/151 |
| 71  | uterine smooth muscle contraction          | GO:00996  | 0.000   | 0.000 | 0.00255 | 11/1| 0.000   | 0.000 | 0.00255 | 6331/776 |
| 24  | atrial cardiac muscle cell membrane repolarization | GO:19028 | 0.000   | 0.000 | 0.00255 | 11/1| 0.000   | 0.000 | 0.00255 | 776/783 |
| 35  | maintenance of location                   | GO:00512  | 0.000   | 0.000 | 0.00255 | 330/| 0.000   | 0.000 | 0.00255 | 5468/801/775/1 |
| 99  | regulation of nitric-oxide synthase activity | GO:00509 | 0.000   | 0.000 | 0.00260 | 51/1| 0.000   | 0.000 | 0.00260 | 3630/801/7124 |
| 57  | regulation of exocytosis                  | GO:00171  | 0.000   | 0.000 | 0.00265 | 217/| 0.000   | 0.000 | 0.00265 | 148/150/136/77 |
| 28  | positive regulation of calcium ion transport | GO:00519 | 0.000   | 0.000 | 0.00275 | 123/| 0.000   | 0.000 | 0.00275 | 801/776/783/78 |
| 26  | acute inflammatory response                | GO:00025  | 0.000   | 0.000 | 0.00280 | 220/| 0.000   | 0.000 | 0.00280 | 5468/3630/134/ |
| 07  | positive regulation of regulated secretory pathway | GO:19033 | 0.000   | 0.000 | 0.00286 | 53/1| 0.000   | 0.000 | 0.00286 | 136/776/783 |
| 24  | diet induced thermogenesis                 | GO:00020  | 0.000   | 0.000 | 0.00296 | 12/1| 0.000   | 0.000 | 0.00296 | 154/153 |
| 60  | positive regulation of action              | GO:00457  | 0.000   | 0.000 | 0.00296 | 12/1| 0.000   | 0.000 | 0.00296 | 148/6331 |
| BP  | GO:19013 | potential positive regulation of voltage-gated calcium channel activity | 2/57 | 12/1 | 0.00 | 0.00 | 0.00296 | 783/781 | 2 |
| BP  | GO:00513 | positive regulation of oxidoreductase activity | 3/57 | 54/1 | 0.00 | 0.00 | 0.00297 | 185/3630/7124 | 3 |
| BP  | GO:19046 | response to amyloid-beta | 3/57 | 54/1 | 0.00 | 0.00 | 0.00297 | 154/774/781 | 3 |
| BP  | GO:00610 | positive regulation of protein tyrosine kinase activity | 3/57 | 55/1 | 0.00 | 0.00 | 0.00312 | 148/150/134 | 3 |
| BP  | GO:00019 | adenosine receptor signaling pathway | 2/57 | 13/1 | 0.00 | 0.00 | 0.00340 | 134/136 | 2 |
| BP  | GO:00030 | positive regulation of systemic arterial blood pressure | 2/57 | 13/1 | 0.00 | 0.00 | 0.00340 | 148/134 | 2 |
| BP  | GO:00107 | negative regulation of macrophage derived foam cell differentiation | 2/57 | 13/1 | 0.00 | 0.00 | 0.00340 | 5468/1401 | 2 |
| BP  | GO:00714 | cellular response to purine-containing compound | 2/57 | 13/1 | 0.00 | 0.00 | 0.00340 | 779/6261 | 2 |
| BP  | GO:00459 | positive regulation of nucleotide metabolic process | 3/57 | 57/1 | 0.00 | 0.00 | 0.00340 | 4513/3630/136 | 3 |
| BP  | GO:19005 | positive | 3/57 | 57/1 | 0.00 | 0.00 | 0.00340 | 4513/3630/136 | 3 |
| ID   | BP GO:00015 | Description                                                                 | Members | FDR  | P-value | p(|d|) | p(|t|) | p(|f|) |
|------|-------------|-----------------------------------------------------------------------------|---------|------|---------|------|------|------|
| 44   | regulation of purine nucleotide metabolic process | 867 070 515 1 0 2 | 6/57 354/ 0.00 0.00 0.00345 148/136/776/78 6 | 70 6 9 | 186 071 522 3 | 3/774/7124 |
| BP   | GO:00316    | regulation of neurological system process | 4/57 137/ 0.00 0.00 0.00388 154/152/11280/ 4 | 70 1 4 | 186 081 588 6 | 134 |
| BP   | GO:00381    | angiotensin-activated signaling pathway | 2/57 14/1 0.00 0.00 0.00388 185/88 2 | 0 4 4 | 867 081 588 6 | |
| BP   | GO:00991    | presynaptic modulation of chemical synaptic transmission | 2/57 14/1 0.00 0.00 0.00388 776/783 2 | 0 4 4 | 867 081 588 6 | |
| BP   | GO:00515    | regulation of neurotransmitter transport | 4/57 139/ 0.00 0.00 0.00406 148/136/776/78 4 | 70 6 8 | 186 085 614 3 | 3 |
| BP   | GO:19059    | negative regulation of lipid localization | 3/57 61/1 0.00 0.00 0.00406 5468/1401/7124 3 | 0 6 8 | 867 085 614 3 | |
| BP   | GO:00975    | calcium ion transmembrane import into cytosol | 4/57 140/ 0.00 0.00 0.00415 801/775/6261/7 4 | 70 9 9 | 186 087 628 3 | 81 |
| BP   | GO:00504    | regulation of catecholamine secretion | 3/57 62/1 0.00 0.00 0.00421 150/152/151 3 | 0 8 | 867 089 638 3 | 150/152/151 |
| BP   | GO:00702    | necrotic cell death | 3/57 62/1 0.00 0.00 0.00421 4513/291/7124 3 | 0 8 | 867 089 638 3 | 4513/291/7124 |
| BP   | GO:00507    | negative regulation of protein secretion | 4/57 141/ 0.00 0.00 0.00422 150/3630/3767/ 4 | 70 3 1 | 186 090 639 1 | 7124 |
| BP   | GO:00307    | sequestering of triglyceride | 2/57 15/1 0.00 0.00 0.00430 5468/7124 2 | 0 7 3 | 867 093 652 8 | |

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| BP                  | GO:00510 | positive regulation of membrane protein ectodomain proteolysis | 2/57 | 15/1 | 0.00 | 0.00 | 0.00430 | 150/7124 | 2 |
|---------------------|----------|---------------------------------------------------------------|------|------|------|------|---------|----------|----|
|                     |          |                                                               |      |      |      |      | 867     | 093      |    |
|                     |          |                                                               |      |      |      |      | 0       | 7        |    |
|                     |          |                                                               |      |      |      |      | 652     | 3        |    |
| BP                  | GO:00550 | fatty acid homeostasis                                         | 2/57 | 15/1 | 0.00 | 0.00 | 0.00430 | 3630/134 | 2 |
|                     |          |                                                               |      |      |      |      | 867     | 093      |    |
|                     |          |                                                               |      |      |      |      | 0       | 7        |    |
|                     |          |                                                               |      |      |      |      | 652     | 8        |    |
| BP                  | GO:19018 | regulation of high voltage-gated calcium channel activity     | 2/57 | 15/1 | 0.00 | 0.00 | 0.00430 | 783/781 | 2 |
|                     |          |                                                               |      |      |      |      | 867     | 093      |    |
|                     |          |                                                               |      |      |      |      | 0       | 7        |    |
|                     |          |                                                               |      |      |      |      | 652     | 8        |    |
| BP                  | GO:19025 | regulation of calcium ion transmembrane transport via high voltage-gated calcium channel | 2/57 | 15/1 | 0.00 | 0.00 | 0.00430 | 783/781 | 2 |
|                     |          |                                                               |      |      |      |      | 867     | 093      |    |
|                     |          |                                                               |      |      |      |      | 0       | 7        |    |
|                     |          |                                                               |      |      |      |      | 652     | 8        |    |
| BP                  | GO:00193 | hexose metabolic process                                       | 5/57 | 249/ | 0.00 | 0.00 | 0.00441 | 3630/767/7124 | 5 |
|                     |          |                                                               |      | 186  | 096  | 668  | 8       | 3630/767/7124 |    |
|                     |          |                                                               |      | 70   | 4    | 9    |         | /5290/2033   |    |
| BP                  | GO:00327 | regulation of monooxygenase activity                           | 3/57 | 64/1 | 0.00 | 0.00 | 0.00448 | 3630/801/7124 | 3 |
|                     |          |                                                               |      | 867  | 098  | 678  | 2       | 3630/801/7124 |    |
|                     |          |                                                               |      | 0    | 5    | 6    |         | 0.00448     |    |
| BP                  | GO:00504 | catecholamine secretion                                        | 3/57 | 64/1 | 0.00 | 0.00 | 0.00448 | 150/152/151  | 3 |
|                     |          |                                                               |      | 867  | 098  | 678  | 2       | 150/152/151  |    |
|                     |          |                                                               |      | 0    | 5    | 6    |         | 0.00448     |    |
| BP                  | GO:00352 | multicellular organism growth                                   | 4/57 | 146/ | 0.00 | 0.00 | 0.00466 | 154/153/5290/2 | 4 |
|                     |          |                                                               |      | 186  | 102  | 705  | 0       | 154/153/5290/2 |    |
|                     |          |                                                               |      | 70   | 8    | 7    |         | 0.033       |    |
| BP                  | GO:00400 | regulation of multicellular organism growth                    | 3/57 | 66/1 | 0.00 | 0.00 | 0.00486 | 154/153/5290 | 3 |
|                     |          |                                                               |      | 867  | 107  | 737  | 8       | 154/153/5290 |    |
|                     |          |                                                               |      | 0    | 7    | 2    |         | 0.00486     |    |
| BP                  | GO:00027 | negative regulation of peptide secretion                       | 4/57 | 148/ | 0.00 | 0.00 | 0.00486 | 150/3630/3767/ | 4 |
|                     |          |                                                               |      | 186  | 108  | 737  | 9       | 150/3630/3767/ |    |
|                     |          |                                                               |      | 70   | 1    | 3    |         | 7124        |    |
| BP                  | GO:00140 | response to                                                    | 4/57 | 149/ | 0.00 | 0.00 | 0.00497 | 5468/3767/779/ | 4 |
|                     |          |                                                               |      | 186  | 108  | 737  | 9       | 5468/3767/779/ |    |
|                     |          |                                                               |      | 70   | 1    | 3    |         | 7124        |    |
| BP     | GO              | PEC    | PEC2   | PEC3   | PEC4   |
|--------|-----------------|--------|--------|--------|--------|
| 74     | purine-containing compound | 186    | 110    | 753    | 5      | 6261   |
|        |                  | 70     | 8      | 4      |        |
| BP GO:00509 | sensory perception of taste | 67/1   | 0.00   | 0.00   | 0.0053 | 6337/6340/6338 |
| 09     |                  | 867    | 112    | 762    | 5      |        |
|        |                 | 0      | 5      | 5      |        |
| BP GO:00434 | positive regulation of MAP kinase activity | 258/   | 0.00   | 0.00   | 0.0053 | 150/151/134/13 |
| 06     |                  | 186    | 113    | 763    | 9      | 6/7124 |
|        |                 |        |        |        |        |        |
| BP GO:00169 | antibiotic metabolic process | 151/   | 0.00   | 0.00   | 0.0051 | 4513/6390/6391 |
| 99     |                  | 186    | 116    | 783    | 6      | /6389  |
|        |                 | 70     | 4      | 7      |        |
| BP GO:00199 | lipid storage | 68/1   | 0.00   | 0.00   | 0.0051 | 5468/1401/7124 |
| 15     |                  | 867    | 117    | 785    | 8      |        |
|        |                 | 0      | 5      | 6      |        |
| BP GO:00508 | multicellular organismal water homeostasis | 68/1   | 0.00   | 0.00   | 0.0051 | 6337/6340/6338 |
| 91     |                  | 867    | 117    | 785    | 8      |        |
|        |                 | 0      | 5      | 6      |        |
| BP GO:00484 | synaptic vesicle transport | 152/   | 0.00   | 0.00   | 0.0052 | 148/136/776/78 |
| 89     |                  | 186    | 119    | 790    | 3      | 3      |
|        |                 | 70     | 3      | 9      |        |
| BP GO:00974 | establishment of synaptic vesicle localization | 152/   | 0.00   | 0.00   | 0.0052 | 148/136/776/78 |
| 80     |                  | 186    | 119    | 790    | 3      | 3      |
|        |                 | 70     | 3      | 9      |        |
| BP GO:00170 | response to insecticide | 17/1   | 0.00   | 0.00   | 0.0052 | 6327/6324 |
| 85     |                  | 867    | 120    | 790    | 3      |        |
|        |                 | 0      | 9      | 9      |        |
| BP GO:00324 | negative regulation of protein oligomerization | 17/1   | 0.00   | 0.00   | 0.0052 | 3630/2033 |
| 60     |                  | 867    | 120    | 790    | 3      |        |
|        |                 | 0      | 9      | 9      |        |
| BP GO:00457 | negative regulation of gluconeogenesis | 17/1   | 0.00   | 0.00   | 0.0052 | 3630/2033 |
| 21     |                  | 867    | 120    | 790    | 3      |        |
|        |                 | 0      | 9      | 9      |        |
| BP GO:00485 | negative regulation of behavior | 17/1   | 0.00   | 0.00   | 0.0052 | 3630/134 |
| 21     |                  | 867    | 120    | 790    | 3      |        |
|        |                 | 0      | 9      | 9      |        |
| BP GO:00158 | organic hydroxy compound | 262/   | 0.00   | 0.00   | 0.0052 | 5468/150/152/1 |
| 50     |                  | 186    | 121    | 790    | 3      | 85/151 |
|        |                 | 70     | 9      |        |        |
| GO ID   | Description                                                                 | Ave FC | Prim FC | P.Value | FDR | Count | pA  |
|---------|-----------------------------------------------------------------------------|--------|---------|---------|-----|-------|------|
| BP GO:00301 | platelet activation                                                          | 4/57   | 153/1  | 0.00    | 0.00 | 0.00526 | 150/152/151/52  |
| BP GO:19044 | positive regulation of calcium ion transport                               | 3/57   | 71/1   | 0.00    | 0.00 | 0.00571 | 801/783/781  |
| BP GO:19059 | regulation of lipid localization                                             | 4/57   | 157/1  | 0.00    | 0.00 | 0.00575 | 5468/185/1401/  |
| BP GO:00026 | regulation of acute inflammatory response                                    | 4/57   | 159/1  | 0.00    | 0.00 | 0.00598 | 5468/3630/134/  |
| BP GO:00301 | water homeostasis                                                            | 3/57   | 74/1   | 0.00    | 0.00 | 0.00635 | 6337/6340/6338  |
| BP GO:00025 | chronic inflammatory response                                               | 2/57   | 19/1   | 0.00    | 0.00 | 0.00637 | 136/7124  |
| BP GO:00989 | membrane repolarization during ventricular cardiac muscle cell action       | 2/57   | 19/1   | 0.00    | 0.00 | 0.00637 | 3764/3757  |
| BP GO:00192 | regulation of lipid metabolic process                                       | 6/57   | 410/1  | 0.00    | 0.00 | 0.00639 | 5468/150/185/3  |
| BP GO:00974 | synaptic vesicle localization                                               | 4/57   | 163/1  | 0.00    | 0.00 | 0.00643 | 148/136/776/78  |
| BP GO:19026 | proton transmembrane transport                                              | 4/57   | 163/1  | 0.00    | 0.00 | 0.00643 | 1349/4512/4513  |
| BP GO:00519 | catecholamine transport                                                     | 3/57   | 77/1   | 0.00    | 0.00 | 0.00699 | 150/152/151  |

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| BP  | GO:00725   |     |    |    |     |     |  |
|-----|------------|-----|----|----|-----|-----|--|
| 93  | GO:00725   |     |    |    |     |     |  |
|     | reactive   | 5/57|    |    |     |     |  |
|     | oxygen species metabolic process | 284/ | 0.00 | 0.01 | 0.00715 | 4513/185/3630/ | 5 |
|     |            | 186 | 172 | 083 | 5    | 1401/7124    |  |
|     |            | 70  | 6   | 5   |      |               |  |
| BP  | GO:00324   |     |    |    |     |     |  |
| 13  | GO:00324   |     |    |    |     |     |  |
|     | negative regulation of ion transmembrane transporter activity | 3/57 | 0.00 | 0.01 | 0.00719 | 150/88/801 | 3 |
|     |            | 78/1| 0.00 | 0.01 | 0.00719 | 150/88/801 | 3 |
|     |            | 174 | 174 | 089 | 2    | 150/88/801   | 3 |
|     |            | 0   | 5   | 5   |      |               |  |
| BP  | GO:00723   |     |    |    |     |     |  |
| 32  | GO:00723   |     |    |    |     |     |  |
|     | intrinsic apoptotic signaling pathway by p53 class mediator | 3/57 | 0.00 | 0.01 | 0.00719 | 50484/6135/203 | 3 |
|     |            | 78/1| 0.00 | 0.01 | 0.00719 | 50484/6135/203 | 3 |
|     |            | 186 | 174 | 089 | 2    | 50484/6135/203 | 3 |
| BP  | GO:00019   |     |    |    |     |     |  |
| 56  | GO:00019   |     |    |    |     |     |  |
|     | positive regulation of neurotransmitter secretion | 2/57 | 21/1 | 0.00 | 0.01 | 0.00761 | 776/783 | 2 |
|     |            | 186 | 152 | 152 | 2    | 186/152/152  | 2 |
|     |            | 0   | 3   | 7   |      |               |  |
| BP  | GO:00971   |     |    |    |     |     |  |
| 93  | GO:00971   |     |    |    |     |     |  |
|     | intrinsic apoptotic signaling pathway by p53 class mediator | 5/57 | 0.00 | 0.01 | 0.00763 | 3630/50484/712 | 5 |
|     |            | 289/| 0.00 | 0.01 | 0.00763 | 3630/50484/712 | 5 |
|     |            | 186 | 155 | 155 | 3    | 186/155/155 | 3 |
|     |            | 70  | 3   | 3   |      |               |  |
| BP  | GO:00016   |     |    |    |     |     |  |
| 59  | GO:00016   |     |    |    |     |     |  |
|     | temperature homeostasis | 4/57 | 173/ | 0.00 | 0.01 | 0.00783 | 154/153/134/71 | 4 |
|     |            | 186 | 186 | 186 | 6    | 186/186/186 | 6 |
|     |            | 70  | 9   | 9   |      |               |  |
| BP  | GO:00059   |     |    |    |     |     |  |
| 96  | GO:00059   |     |    |    |     |     |  |
|     | monosaccharide metabolic process | 5/57 | 292/ | 0.00 | 0.01 | 0.00793 | 3630/3767/7124 | 5 |
|     |            | 292/| 0.00 | 0.01 | 0.00793 | 3630/3767/7124 | 5 |
|     |            | 186 | 201 | 201 | 3    | 186/201/201 | 3 |
|     |            | 70  | 9   | 9   |      |               |  |
| BP  | GO:00517   |     |    |    |     |     |  |
| 02  | GO:00517   |     |    |    |     |     |  |
|     | interaction with symbiont | 3/57 | 82/1 | 0.00 | 0.01 | 0.00817 | 801/5340/2033 | 3 |
|     |            | 82/1| 0.00 | 0.01 | 0.00817 | 801/5340/2033 | 3 |
|     |            | 867 | 201 | 238 | 6    | 867/201/238 | 6 |
|     |            | 0   | 4   | 4   |      |               |  |
| BP  | GO:00059   |     |    |    |     |     |  |
| 80  | GO:00059   |     |    |    |     |     |  |
|     | glycogen catabolic process | 2/57 | 22/1 | 0.00 | 0.01 | 0.00820 | 3630/801 | 2 |
|     |            | 22/1| 0.00 | 0.01 | 0.00820 | 3630/801 | 2 |
|     |            | 867 | 203 | 242 | 8    | 867/203/242 | 8 |
|     |            | 0   | 4   | 4   |      |               |  |
| BP  | GO:00510   |     |    |    |     |     |  |
| 00  | GO:00510   |     |    |    |     |     |  |
|     | positive regulation of nitric-oxide synthase activity | 2/57 | 22/1 | 0.00 | 0.01 | 0.00820 | 3630/7124 | 2 |
|     |            | 22/1| 0.00 | 0.01 | 0.00820 | 3630/7124 | 2 |
|     |            | 867 | 203 | 242 | 8    | 867/203/242 | 8 |
|     |            | 0   | 4   | 4   |      |               |  |
| BP  | GO:00092   |     |    |    |     |     |  |
| 51  | GO:00092   |     |    |    |     |     |  |
|     | glucan catabolic process | 2/57 | 23/1 | 0.00 | 0.01 | 0.00891 | 3630/801 | 2 |
|     |            | 23/1| 0.00 | 0.01 | 0.00891 | 3630/801 | 2 |
|     |            | 867 | 222 | 350 | 9    | 867/222/350 | 9 |
|     |            | 0   | 3   | 5   |      |               |  |
| BP  | GO:00510 | regulation of membrane protein ectodomain proteolysis | 2/57 | 23/1 | 0.00 | 0.01 | 0.00891 | 150/7124 | 2 |
|-----|----------|------------------------------------------------------|------|------|------|------|---------|---------|----|
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
|     |          |                                                      |      |      |      |      |         |         |    |
| BP  | GO:00442 | regulation of systemic arterial blood pressure | cellular polysaccharide catabolic process | 2/57 | 25/1 | 0.00 | 0.01 | 0.01014 | 3630/801 | 2 |
|-----|----------|------------------------------------------------|------------------------------------------|------|------|------|------|----------|----------|---|
|     | GO:00459 | positive regulation of calcium ion-dependent exocytosis | 2/57 | 25/1 | 0.00 | 0.01 | 0.01014 | 776/783 | 2 |
|     | GO:19043 | cellular response to angiotensin | 2/57 | 25/1 | 0.00 | 0.01 | 0.01014 | 185/88 | 2 |
|     | GO:00158 | monoamine transport | 3/57 | 90/1 | 0.00 | 0.01 | 0.01014 | 150/152/151 | 3 |
|     | GO:19013 | regulation of potassium ion transmembrane transport | 3/57 | 90/1 | 0.00 | 0.01 | 0.01014 | 88/776/3757 | 3 |
|     | GO:00620 | regulation of small molecule metabolic process | 6/57 | 459/ | 0.00 | 0.01 | 0.01034 | 4513/5468/3630 | 6 |
|     | GO:00507 | positive regulation of peptidyl-tyrosine phosphorylation | 4/57 | 192/ | 0.00 | 0.01 | 0.01075 | 148/150/134/71 | 4 |
|     | GO:00319 | positive regulation of protein autophosphorylation | 2/57 | 26/1 | 0.00 | 0.01 | 0.01084 | 3630/801 | 2 |
|     | GO:00328 | receptor biosynthetic process | 2/57 | 26/1 | 0.00 | 0.01 | 0.01084 | 5468/7124 | 2 |
|     | GO:00512 | negative regulation of protein | 4/57 | 193/ | 0.00 | 0.01 | 0.01086 | 150/3630/3767/ | 4 |

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| BP    | GO:00075 | transport | body fluid secretion | 3/57 | 93/1 | 0.00 | 0.01 | 0.01094 | 4513/4879/134 | 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| BP | GO:00995 | synaptic vesicle cycle | 4/57 | 194/1 | 0.00 | 0.01 | 0.01100 | 148/136/776/78 | 4 |
| BP | GO:00713 | cellular response to peptide hormone stimulus | 5/57 | 321/1 | 0.00 | 0.01 | 0.01108 | 5468/185/3630/6 | 5 |
| BP | GO:00002 | polysaccharide catabolic process | 2/57 | 27/1 | 0.00 | 0.01 | 0.01140 | 3630/801 | 2 |
| BP | GO:00020 | response to dietary excess | 2/57 | 27/1 | 0.00 | 0.01 | 0.01140 | 154/153 | 2 |
| BP | GO:00020 | regulation of the force of heart contraction | 2/57 | 27/1 | 0.00 | 0.01 | 0.01140 | 148/153 | 2 |
| BP | GO:00071 | regulation of epidermal growth factor-activated receptor activity | 2/57 | 27/1 | 0.00 | 0.01 | 0.01140 | 150/134 | 2 |
| BP | GO:19030 | regulation of protein localization to plasma membrane | 3/57 | 95/1 | 0.00 | 0.01 | 0.01140 | 3630/3767/7124 | 3 |
| BP | GO:19049 | negative regulation of establishment of protein localization | 4/57 | 197/1 | 0.00 | 0.01 | 0.01140 | 150/3630/3767/7124 | 4 |
| BP | GO:00507 | positive regulation of neurogenesis | 6/57 | 474/1 | 0.00 | 0.01 | 0.01166 | 5468/152/151/6 | 6 |
| BP | GO:00327 | positive regulation of monoxygenases | 2/57 | 28/1 | 0.00 | 0.01 | 0.01205 | 3630/7124 | 2 |
| BP  | GO:00457 | 61 | regulation of adenylate cyclase activity | 2/57 | 28/1 | 0.00 | 0.01 | 0.01205 | 775/776 | 2 |
|-----|----------|----|----------------------------------------|------|------|-------|-------|----------|-------|----|
|     |          |    |                                        |      |      | 867   | 329   | 825      |       | 4  |
|     |          |    |                                        |      |      | 0     | 3     |          |       |    |
| BP  | GO:00860 | 13 | membrane repolarization during cardiac muscle cell action potential | 2/57 | 28/1 | 0.00 | 0.01 | 0.01205 | 3764/3757 | 2 |
|     |          |    |                                        |      |      | 867   | 329   | 825      |       | 4  |
|     |          |    |                                        |      |      | 0     | 3     |          |       |    |
| BP  | GO:19907 | 76 | response to angiotensin                | 2/57 | 28/1 | 0.00 | 0.01 | 0.01205 | 185/88 | 2 |
|     |          |    |                                        |      |      | 867   | 329   | 825      |       | 4  |
|     |          |    |                                        |      |      | 0     | 3     |          |       |    |
| BP  | GO:00507 | 27 | regulation of inflammatory response    | 6/57 | 485/ | 0.00 | 0.01 | 0.01278 | 5468/185/3630/ | 6 |
|     |          |    |                                        |      |      | 186   | 352   | 935      |       | 4  |
|     |          |    |                                        |      |      | 70    | 6     | 7        |       |    |
| BP  | GO:00106 | 44 | cell communication by electrical coupling | 2/57 | 29/1 | 0.00 | 0.01 | 0.01278 | 801/775 | 2 |
|     |          |    |                                        |      |      | 867   | 352   | 935      |       | 4  |
|     |          |    |                                        |      |      | 0     | 6     | 7        |       |    |
| BP  | GO:00108 | 82 | regulation of cardiac muscle contraction by calcium ion signaling | 2/57 | 29/1 | 0.00 | 0.01 | 0.01278 | 801/775 | 2 |
|     |          |    |                                        |      |      | 867   | 352   | 935      |       | 4  |
|     |          |    |                                        |      |      | 0     | 6     | 7        |       |    |
| BP  | GO:00458 | 22 | negative regulation of heart contraction | 2/57 | 29/1 | 0.00 | 0.01 | 0.01278 | 148/134 | 2 |
|     |          |    |                                        |      |      | 867   | 352   | 935      |       | 4  |
|     |          |    |                                        |      |      | 0     | 6     | 7        |       |    |
| BP  | GO:00075 | 96 | blood coagulation                      | 5/57 | 336/ | 0.00 | 0.01 | 0.0129  | 150/152/151/52 | 5 |
|     |          |    |                                        |      |      | 186   | 356   | 953      |       | 4  |
|     |          |    |                                        |      |      | 70    | 8     | 3        |       |    |
| BP  | GO:00434 | 05 | regulation of MAP kinase activity      | 5/57 | 337/ | 0.00 | 0.01 | 0.01302 | 150/151/134/13 | 5 |
|     |          |    |                                        |      |      | 186   | 361   | 972      |       | 9  |
|     |          |    |                                        |      |      | 70    | 3     | 9        |       |    |
| BP  | GO:19034 | 26 | regulation of reactive oxygen species biosynthetic process | 3/57 | 101/ | 0.00 | 0.01 | 0.01308 | 4513/3630/7124 | 3 |
|     |          |    |                                        |      |      | 186   | 363   | 981      |       | 4  |
|     |          |    |                                        |      |      | 70    | 8     | 3        |       |    |
| BP  | GO:00990 | 03 | vesicle-mediated transport in synapse   | 4/57 | 207/ | 0.00 | 0.01 | 0.01314 | 148/136/776/78 | 4 |
|     |          |    |                                        |      |      | 186   | 366   | 990      |       | 4  |
|     |          |    |                                        |      |      | 70    | 4     | 3        |       |    |
| BP  | GO:00000 | mitochondrial genome maintenance | 2/57 | 30/1 | 0.00 | 0.02 | 0.01345 | 291/50484 | 2 |
| BP  | GO:00459 | positive regulation of steroid metabolic process | 2/57 | 30/1 | 0.00 | 0.02 | 0.01345 | 185/7124 | 2 |
| BP  | GO:00075 | hemostasis | 5/57 | 341/1 | 0.00 | 0.02 | 0.01351 | 150/152/151/52 | 5 |
| BP  | GO:00508 | coagulation | 5/57 | 342/1 | 0.00 | 0.02 | 0.01365 | 150/152/151/52 | 5 |
| BP  | GO:00457 | positive regulation of epidermal growth factor signaling pathway | 2/57 | 31/1 | 0.00 | 0.02 | 0.01416 | 150/134 | 2 |
| BP  | GO:00900 | relaxation of muscle | 2/57 | 31/1 | 0.00 | 0.02 | 0.01416 | 134/136 | 2 |
| BP  | GO:19022 | regulation of intrinsic apoptotic signaling pathway by p53 class mediator | 2/57 | 31/1 | 0.00 | 0.02 | 0.01416 | 50484/6135 | 2 |
| BP  | GO:00323 | positive regulation of intracellular transport | 4/57 | 215/1 | 0.00 | 0.02 | 0.01472 | 88/136/776/783 | 4 |
| BP  | GO:00108 | regulation of release of sequestered calcium ion into cytosol by sarcoplasmic reticulum | 2/57 | 32/1 | 0.00 | 0.02 | 0.01492 | 801/775 | 2 |
| BP  | GO:00322 | regulation of synaptic | 2/57 | 32/1 | 0.00 | 0.02 | 0.01492 | 148/134 | 2 |
| BP      | GO:00355  | 32/1  | 0.00  | 0.02  | 0.01492 | 134/136  | 2       |
|---------|-----------|-------|-------|-------|---------|----------|---------|
|         | transmission, GABAergic purinergic receptor signaling pathway | 867 | 428  | 260  | 7       |          |         |
| BP      | GO:00197  | 218/  | 0.00  | 0.02  | 0.01531 | 185/801/775/71  | 4       |
|         | calcium-mediated signaling | 186 | 440  | 318  | 1       | 24       |         |
| BP      | GO:00199  | 33/1  | 0.00  | 0.02  | 0.01565 | 4879/136  | 2       |
|         | cGMP-mediated signaling | 867 | 455  | 371  | 8       |          |         |
| BP      | GO:00511  | 33/1  | 0.00  | 0.02  | 0.01565 | 4513/3630  | 2       |
|         | positive regulation of cofactor metabolic process | 867 | 455  | 371  | 8       |          |         |
| BP      | GO:19011  | 33/1  | 0.00  | 0.02  | 0.01565 | 150/134  | 2       |
|         | positive regulation of ERBB signaling pathway | 867 | 455  | 371  | 8       |          |         |
| BP      | GO:19013  | 33/1  | 0.00  | 0.02  | 0.01565 | 88/3757  | 2       |
|         | negative regulation of potassium ion transmembrane transport | 867 | 455  | 371  | 8       |          |         |
| BP      | GO:00432  | 112/  | 0.00  | 0.02  | 0.01668 | 5468/779/6261  | 3       |
|         | response to alkaloid | 186 | 486  | 525  | 1       |          |         |
|         | 70       | 8     |       |         |          |         |         |
| BP      | GO:00432  | 113/  | 0.00  | 0.02  | 0.01705 | 154/88/7124  | 3       |
|         | regulation of protein complex disassembly | 186 | 498  | 582  | 6       |          |         |
|         | 70       | 2     | 6     |         |          |         |         |
| BP      | GO:00713  | 5/1   | 0.00  | 0.02  | 0.0174  | 779/6261  | 2       |
|         | cellular response to alkaloid | 867 | 510  | 634  |         |          |         |
|         | 0        | 8     | 7     |         |          |         |         |
| BP      | GO:19013  | 5/1   | 0.00  | 0.02  | 0.0174  | 783/781  | 2       |
|         | regulation of voltage-gated calcium channel activity | 867 | 510  | 634  |         |          |         |
|         | 0        | 8     | 7     |         |          |         |         |
| BP      | GO:19043  | 115/  | 0.00  | 0.02  | 0.01777 | 3630/3767/7124  | 3       |
|         | regulation of protein | 186 | 523  | 691  | 4       |          |         |
| BP    | GO:0006909 | localization to cell periphery | 70 | 1 | 4 |
|-------|-------------|--------------------------------|----|---|---|
|       | phagocytosis | 5/57                           | 369/0.00/0.02/0.01791/5468/134/1401/7124/5290 | 5 |
|       |             |                                | 186/529/712 |    |
|       |             |                                | 70/7        |    |
| BP    | GO:00356090 | cellular response to drug      | 5/57 | 369/0.00/0.02/0.01791/3757/3767/779/1401/7124/6261 | 5 |
|       |              |                                | 186/529/712 |    |
|       |              |                                | 70/7        |    |
| BP    | GO:0090322  | regulation of superoxide      | 2/57 | 36/1/0.00/0.02/0.01811/1401/7124 | 2 |
|       |              | metabolic process             |             | 867/539/742 |    |
|       |              |                                | 0/8/9       |    |
| BP    | GO:1901020  | negative regulation of calcium | 2/57 | 36/1/0.00/0.02/0.01811/150/801 | 2 |
|       |              | ion transmembrane transporter  |             | 867/539/742 |    |
|       |              | activity                      |             | 0/8/9 |    |
| BP    | GO:2001171  | positive regulation of ATP     | 2/57 | 36/1/0.00/0.02/0.01811/4513/3630 | 2 |
|       |              | biosynthetic process          |             | 867/539/742 |    |
|       |              |                                | 0/8/9       |    |
| BP    | GO:1900371  | regulation of purine nucleotide | 3/57 | 117/0.00/0.02/0.01837/4513/3630/136 | 3 |
|       |              | biosynthetic process          |             | 186/548/781 |    |
|       |              |                                | 70/7/6      |    |
| BP    | GO:0030808  | regulation of nucleotide      | 3/57 | 118/0.00/0.02/0.01876/4513/3630/136 | 3 |
|       |              | biosynthetic process          |             | 186/561/841 |    |
|       |              |                                | 70/8        |    |
| BP    | GO:0007173  | epidermal growth factor receptor signaling pathway | 3/57 | 119/0.00/0.02/0.01915/150/134/5290 | 3 |
|       |              |                                | 186/575/901 |    |
|       |              |                                | 70/1/1      |    |
| BP    | GO:0010939  | regulation of necrotic cell death | 2/57 | 38/1/0.00/0.02/0.01979/4513/291 | 2 |
|       |              |                                | 867/6/996 |    |
|       |              |                                | 0/9         |    |
| BP    | GO:0046676  | negative regulation of insulin secretion | 2/57 | 38/1/0.00/0.02/0.01979/150/3767 | 2 |
|       |              |                                | 867/6/996 |    |
|       |              |                                | 0/9         |    |
| BP    | GO:00515 90 | regulation of neurotransmitter transport | 2/57 | 38/1 | 0.00 | 0.02 | 0.01979 | 776/783 | 2 |
|-------|--------------|------------------------------------------|------|------|------|------|----------|--------|---|
|       | BP GO:19035 23 | negative regulation of blood circulation | 2/57 | 38/1 | 0.00 | 0.02 | 0.01979 | 148/134 | 2 |
|       | BP GO:19034 09 | reactive oxygen species biosynthetic process | 3/57 | 122/ | 0.00 | 0.03 | 0.02027 | 4513/3630/7124 | 3 |
|       | BP GO:00091 65 | nucleotide biosynthetic process | 5/57 | 386/ | 0.00 | 0.03 | 0.02097 | 4513/4879/3630 | 5 |
|       | BP GO:00140 66 | regulation of phosphatidylinositol 3-kinase signaling | 3/57 | 124/ | 0.00 | 0.03 | 0.02105 | 3630/7124/5290 | 3 |
|       | BP GO:00512 09 | release of sequestered calcium ion into cytosol | 3/57 | 124/ | 0.00 | 0.03 | 0.02105 | 801/775/6261 | 3 |
|       | BP GO:20000 08 | regulation of protein localization to cell surface | 2/57 | 40/1 | 0.00 | 0.03 | 0.02161 | 88/7124 | 2 |
|       | BP GO:19012 93 | nucleoside phosphate biosynthetic process | 5/57 | 390/ | 0.00 | 0.03 | 0.02167 | 4513/4879/3630 | 5 |
|       | BP GO:00512 83 | negative regulation of sequestering of calcium ion | 3/57 | 126/ | 0.00 | 0.03 | 0.02184 | 801/775/6261 | 3 |
|       | BP GO:00432 67 | negative regulation of potassium ion transport | 2/57 | 41/1 | 0.00 | 0.03 | 0.02240 | 88/3757 | 2 |
|       | BP GO:19013 81 | positive regulation of potassium ion transport | 2/57 | 41/1 | 0.00 | 0.03 | 0.02240 | 88/3757 | 2 |
| BP  | GO:19031 | negative regulation of calcium ion transmembrane transport | 2/57 | 867 | 695 | 392 | 0.02240 | 150/801 | 2 |
| BP  | GO:00459 | negative regulation of growth | 4/57 | 249/70 | 0.00 | 0.03 | 0.02249 | 4879/5468/154/153 |
| BP  | GO:00025 | platelet degranulation | 3/57 | 128/70 | 0.00 | 0.03 | 0.02249 | 88/801/5340/3 |
| BP  | GO:00512 | regulation of sequestering of calcium ion membrane protein ectodomain proteolysis | 3/57 | 128/70 | 0.00 | 0.03 | 0.02249 | 801/775/6261/3 |
| BP  | GO:00065 | negative regulation of cellular carbohydrate metabolic process | 2/57 | 42/1 | 0.00 | 0.03 | 0.02320 | 3630/2033/2 |
| BP  | GO:19035 | positive regulation of secretion by cell | 5/57 | 399/186 | 0.00 | 0.03 | 0.02325 | 3630/136/776/7 |
| BP  | GO:00512 | sequestering of calcium ion | 3/57 | 131/186 | 0.00 | 0.03 | 0.02374 | 801/775/6261/3 |
| BP  | GO:00324 | regulation of protein oligomerization | 2/57 | 43/1 | 0.00 | 0.03 | 0.02400 | 3630/2033/2 |
| BP  | GO:00508 | positive regulation of calcium-mediated signaling | 2/57 | 43/1 | 0.00 | 0.03 | 0.02400 | 801/7124/2 |
| BP  | GO:19046 | cellular response to amyloid-beta | 2/57 | 43/1 | 0.00 | 0.03 | 0.02400 | 154/781/2 |
| BP  | GO:00455 | regulation of fat cell | 3/57 | 132/186 | 0.00 | 0.03 | 0.02401 | 5468/3630/7124/3 |
| GO ID   | Description                                                             | P-values | q-values | Adjs. P-values | FDR Values |
|---------|-------------------------------------------------------------------------|----------|----------|----------------|------------|
| BP:00507 GO:00507 | regulation of peptidyl-tyrosine phosphorylation                          | 0.00     | 0.03     | 0.008          | 0.10       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00713 GO:00713 | cellular response to glucose stimulus                                    | 0.00     | 0.03     | 0.003          | 0.10       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00353 GO:00353 | positive regulation of protein dephosphorylation                        | 0.00     | 0.03     | 0.02418        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00702 GO:00702 | necroptotic process                                                      | 0.00     | 0.03     | 0.02418        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00713 GO:00713 | cellular response to hexose stimulus                                     | 0.00     | 0.03     | 0.02525        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00510 GO:00510 | positive regulation of DNA-binding transcription factor activity         | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00713 GO:00713 | cellular response to monosaccharide stimulus                             | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00442 GO:00442 | cellular carbohydrate catabolic process                                  | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00519 GO:00519 | synaptic transmission, GABAergic                                         | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:00902 GO:00902 | negative regulation of peptide hormone secretion                        | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
| BP:19002 GO:19002 | regulation of differentiation                                           | 0.00     | 0.03     | 0.02550        | 0.03       |
|         |                                                                         | 0.01     | 0.03     |                |            |
|         |                                                                         | 0.02     | 0.03     |                |            |
|         |                                                                         | 0.03     | 0.03     |                |            |
|   | long-term synaptic potentiation | 867 | 833 | 862 | 7 |
|---|---------------------------------|-----|-----|-----|---|
| BP | negative regulation of cellular catabolic process | 4/57 | 0.00 | 0.03 | 0.02621 |
|    | | 264/ | 186 | 858 | 969 | 6 |
|    | | 148/ | 70 | 5 | 7 | 6135 |
| BP | regulation of protein dephosphorylation | 3/57 | 0.00 | 0.04 | 0.02685 |
|    | | 139/ | 186 | 881 | 066 | 3 |
|    | | 801/ | 70 | 4 | 2 | 134/7124 |
| BP | regulation of postsynaptic membrane potential | 3/57 | 0.00 | 0.04 | 0.02732 |
|    | | 140/ | 186 | 898 | 137 | 1 |
|    | | 154/ | 70 | 8 | 1 | 153/134 |
| BP | regulation of protein autophosphorylation | 2/57 | 0.00 | 0.04 | 0.02743 |
|    | | 47/1 | 867 | 906 | 154 | 4 |
|    | | 3630/ | 0 | 5 | 2 | 801 |
| BP | positive regulation of ATP metabolic process | 2/57 | 0.00 | 0.04 | 0.02743 |
|    | | 47/1 | 867 | 906 | 154 | 4 |
|    | | 4513/ | 0 | 5 | 2 | 3630 |
| BP | positive regulation of catabolic process | 5/57 | 0.00 | 0.04 | 0.02800 |
|    | | 423/ | 186 | 929 | 240 | 4 |
|    | | 154/ | 70 | 5 | 6 | 150/3630/1 |
| BP | regulation of intracellular transport | 5/57 | 0.00 | 0.04 | 0.02800 |
|    | | 423/ | 186 | 929 | 240 | 4 |
|    | | 148/ | 70 | 5 | 6 | 88/136/776/ |
| BP | regulation of ERBB signaling pathway | 3/57 | 0.00 | 0.04 | 0.02801 |
|    | | 142/ | 186 | 934 | 242 | 9 |
|    | | 150/ | 70 | 1 | 8 | 134/5290 |
| BP | regulation of purine nucleotide metabolic process | 3/57 | 0.00 | 0.04 | 0.02801 |
|    | | 142/ | 186 | 934 | 242 | 9 |
|    | | 4513/ | 70 | 1 | 8 | 3630/136 |
| BP | regulation of gluconeogenesis | 2/57 | 0.00 | 0.04 | 0.02819 |
|    | | 48/1 | 867 | 944 | 269 | 4 |
|    | | 3630/ | 0 | 1 | 2 | 2033 |
| BP | negative regulation of | 2/57 | 0.00 | 0.04 | 0.02819 |
|    | | 48/1 | 867 | 944 | 269 | 4 |
|    | | 3630/ | 0 | 1 | 2 | 2033 |
| GO ID     | Description                        | P-value   | q-value | 
|-----------|------------------------------------|-----------|---------|
| GO:00713  | cellular metabolic process          | 0.00      | 0.04    |
| GO:00350  | response to carbohydrate stimulus  | 0.00      | 0.04    |
| GO:00973  | programmed necrotic cell death      | 0.00      | 0.04    |
| GO:00061  | regulation of nucleotide metabolic process | 0.01      | 0.04    |
| GO:00140  | phosphatidylinositol 3-kinase signaling | 0.01      | 0.04    |
| GO:00515  | response to calcium ion             | 0.01      | 0.04    |
| GO:00434  | response to peptide hormone         | 0.01      | 0.04    |
| GO:00507  | negative regulation of immune response | 0.01      | 0.04    |
| GO:00550  | lipid homeostasis                   | 0.01      | 0.04    |
| GO:00001  | activation of MAPK activity         | 0.01      | 0.04    |
| GO:00016  | cellular glucose homeostasis        | 0.01      | 0.04    |
| GO:00347  | cation channel complex              | 2.10      | 3.65    |

**Summary:**
- The carbohydrate metabolic process (BP GO:00713) and cellular response to carbohydrate stimulus (BP GO:00350) are significantly enriched.
- The regulated processes include response to nicotine (BP GO:00973) and programmed necrotic cell death (BP GO:00061).
- Other enriched processes include lipid homeostasis (BP GO:00507) and activation of MAPK activity (BP GO:00001).
- The cation channel complex (CC GO:00347) is also significantly enriched.
| CC  | GO:00347 ion channel complex 24/57 | 301/1 4.87 4.24 2.39E-2 197 E-29 E-27 7 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 24/57 301/1 4.87 4.24 2.39E-2 197 E-29 E-27 7 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 |
| CC  | GO:19024 transmembrane transporter complex 24/57 | 324/1 2.94 1.71 9.61E-2 197 E-28 E-26 7 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 24/57 324/1 2.94 1.71 9.61E-2 197 E-28 E-26 7 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 |
| CC  | GO:19903 transporter complex 24/57 | 332/1 5.33 2.32 1.30E-2 197 E-28 E-26 6 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 24/57 332/1 5.33 2.32 1.30E-2 197 E-28 E-26 6 17 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3764/6340 |
| CC  | GO:00347 sodium channel complex 11/57 | 23/1 5.56 1.93 1.09E-2 971 E-23 E-21 1 7 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3640/6338 11/57 23/1 5.56 1.93 1.09E-2 971 E-23 E-21 1 7 0/6833/775/776/3757/783/3767/779/774/6261/7 81 6337/3640/6338 |
| CC  | GO:00015 voltage-gated sodium channel complex 8/57 | 14/1 8.66 2.51 1.41E-1 971 E-18 E-16 6 7 0/6833/775/776/3757/783/3767/779/774/6261/7 81 11280/6327/55/329/6330/6324 8/57 14/1 8.66 2.51 1.41E-1 971 E-18 E-16 6 7 0/6833/775/776/3757/783/3767/779/774/6261/7 81 11280/6327/55/329/6330/6324 |
| CC  | GO:00303 T-tubule 10/57 | 52/1 2.55 6.35 3.57E-1 971 E-16 E-15 5 7 148/6331/6324/775/776/783/3767/779/774/6261/7 81 148/6331/6324/775/776/783/3767/779/774/6261/7 10/57 52/1 2.55 6.35 3.57E-1 971 E-16 E-15 5 7 148/6331/6324/775/776/783/3767/779/774/6261/7 81 148/6331/6324/775/776/783/3767/779/774/6261/7 |
| CC  | GO:00423 sarcolemma 12/57 | 136/8 3.84 8.36 4.70E-1 148/6331/6324/775/776/783/3767/779/774/6261/7 81 148/6331/6324/775/776/783/3767/779/774/6261/7 12/57 136/8 3.84 8.36 4.70E-1 148/6331/6324/775/776/783/3767/779/774/6261/7 81 148/6331/6324/775/776/783/3767/779/774/6261/7 |
| ID   | GO:         | Type                        | PCT       | E1     | E2   | E3   | p-value       | q-value       |
|------|-------------|-----------------------------|-----------|--------|------|------|---------------|---------------|
| 83   | GO:00347    | calcium channel complex     | 8/57      | 1.48   | 2.85 | 1.60E-1 | 801/775/778/78 | 3/779/774/6261/781 |
| 104  | GO:00058    | voltage-gated calcium       | 7/57      | 3.43   | 5.96 | 3.35E-1 | 775/776/783/77 | 9/774/6261/781 |
| 941  | GO:19904    | L-type voltage-gated calcium| 5/57      | 1.32   | 2.08 | 1.17E-0 | 775/776/783/77 | 9/781         |
| 17   | GO:00300    | sarcomere                   | 10/57     | 3.19   | 4.62 | 2.60E-0 | 148/88/55800/6  | 331/801/10060/775/776/779/62 |
| 104  | GO:00444    | contractile fiber part      | 10/57     | 6.96   | 9.32 | 5.24E-0 | 148/88/55800/6  | 331/801/10060/775/776/779/62 |
| 17   | GO:00300    | myofibril                   | 10/57     | 7.93   | 9.86 | 5.55E-0 | 148/88/55800/6  | 331/801/10060/775/776/779/62 |
| 17   | GO:00432    | contractile fiber           | 10/57     | 1.21   | 1.41 | 7.91E-0 | 148/88/55800/6  | 331/801/10060/775/776/779/62 |
| 17   | GO:00988    | respiratory chain complex   | 7/57      | 4.78   | 5.20 | 2.92E-0 | 1349/4512/4513 | 4/514/6390/639/1/6389 |
| 17   | GO:00316    | I band                      | 8/57      | 7.70   | 7.88 | 4.43E-0 | 148/88/55800/6  | 331/775/777/77 |
| 17   | GO:00704    | respiratory chain           | 7/57      | 1.50   | 1.45 | 8.15E-0 | 1349/4512/4513 | 4/514/6390/639/1/6389 |
| 17   | GO:00300    | Z disc                      | 7/57      | 1.03   | 9.41 | 5.30E-0 | 148/88/55800/6  | 331/775/777/77 |
| 17   | GO:00452    | respiratory                 | 4/57      | 2.94   | 2.56 | 1.44E-0 | 1349/4512/4513 | 4/514/6390/639/1/6389 |

CC: Compound Class
| GO:000700 | chain complex | 77 | E-07 | E-06 | 6 | /4514 |
|---|---|---|---|---|---|---|
| GO:00057 | cytochrome complex | 69 | 4/57 | 2.73 | 2.26 | 1.27E-07 | 1349/4512/4513 |
| GO:00347 | mitochondrial respiratory chain complex | 46 | 5/57 | 5.51 | 4.36 | 2.45E-07 | 1349/4512/6390 |
| GO:00147 | intercalated disc | 54 | 4/57 | 1.31 | 9.49 | 5.34E-07 | 6331/6330/6324 |
| GO:00444 | mitochondrial membrane part | 55 | 6/57 | 5.09 | 0.00 | 0.00019 | 1349/4512/291/ |
| GO:00442 | cell-cell contact zone | 91 | 4/57 | 5.28 | 0.00 | 0.00019 | 6331/6330/6324 |
| GO:00990 | integral component of presynaptic membrane | 56 | 4/57 | 5.89 | 0.00 | 0.00021 | 148/6336/134/ |
| GO:00057 | mitochondrial inner membrane | 43 | 8/57 | 6.09 | 0.00 | 0.00021 | 1349/4512/291/ |
| GO:00996 | integral component of synaptic membrane | 99 | 5/57 | 7.73 | 0.00 | 0.00026 | 148/152/6336/1 |
| GO:00988 | intrinsic component of presynaptic membrane | 89 | 4/57 | 9.28 | 0.00 | 0.00030 | 148/6336/134/7 |
| GO:00992 | intrinsic component of synaptic membrane | 40 | 5/57 | 0.00 | 0.00 | 0.00034 | 148/152/6336/1 |
| GO:00970 | synaptic membrane | 60 | 7/57 | 0.00 | 0.00 | 0.00072 | 148/152/88/633 |
| GO:19902 | oxidoreductase complex | 04 | 4/57 | 0.00 | 0.00 | 0.00091 | 4512/6390/6391 |

85
| CC  | GO:00974 | ribbon synapse | 2/57 | 17 | 9 | 9 | 0.000104 | 776/783 | 2 |
|-----|--------|----------------|------|----|---|---|----------|-------|---|
|     |        |                |      |    |   |   |          |       |   |
| CC  | GO:00987 | presynapse | 7/57 | 491/ | 0.00 | 0.00 | 0.00143 | 148/152/6336/1 | 7 |
|     |        |                |      | 197 | 051 | 254 | 4       | 34/776/783/774 |   |
| CC  | GO:00988 | inner mitochondrial membrane complex | 4/57 | 135/ | 0.00 | 0.00 | 0.00170 | 4512/6390/6391 | 4 |
|     |        |                |      | 197 | 062 | 303 | 5       | /6389   |   |
| CC  | GO:00306 | axolemma | 2/57 | 14/1 | 0.00 | 0.00 | 0.00193 | 134/3767 | 2 |
|     |        |                |      |    | 971 | 073 | 343 | 3       |   |
| CC  | GO:00443 | main axon | 3/57 | 68/1 | 0.00 | 0.00 | 0.00254 | 6324/134/3767 | 3 |
|     |        |                |      |    | 971 | 100 | 460 | 9       |   |
| CC  | GO:00427 | presynaptic membrane | 4/57 | 161/ | 0.00 | 0.00 | 0.00303 | 148/6336/134/7 | 4 |
|     |        |                |      | 197 | 120 | 539 | 3       | 76      |   |
| CC  | GO:00059 | caveola | 3/57 | 80/1 | 0.00 | 0.00 | 0.00393 | 148/147/6331 | 3 |
|     |        |                |      |    | 971 | 160 | 699 | 4       |   |
| CC  | GO:00452 | postsynaptic membrane | 5/57 | 323/ | 0.00 | 0.01 | 0.00569 | 148/152/88/134/1/7 | 5 |
|     |        |                |      | 197 | 238 | 012 | 7       | 775     |   |
| CC  | GO:00430 | neuronal cell body | 6/57 | 497/ | 0.00 | 0.01 | 0.00709 | 152/6324/134/7 | 6 |
|     |        |                |      | 197 | 304 | 260 | 4       | 75/3767/774 |   |
| CC  | GO:00989 | glutamatergic synapse | 5/57 | 349/ | 0.00 | 0.01 | 0.00757 | 148/152/88/633 | 5 |
|     |        |                |      | 197 | 332 | 346 | 6       | 6/136   |   |
| CC  | GO:00448 | plasma membrane raft | 3/57 | 109/ | 0.00 | 0.01 | 0.00861 | 148/147/6331 | 3 |
|     |        |                |      | 197 | 387 | 531 | 4       |   |
| CC  | GO:00990 | integral component of postsynaptic membrane | 3/57 | 117/ | 0.00 | 0.01 | 0.01026 | 148/152/134 | 3 |
|     |        |                |      | 197 | 472 | 825 | 8       |   |
| CC  | GO:00989 | intrinsic component of postsynaptic membrane | 3/57 | 122/ | 0.00 | 0.02 | 0.01128 | 148/152/134 | 3 |
|     |        |                |      | 197 | 530 | 005 | 5       |   |
| CC  | GO ID   | Term                  | Count | FDR | q-value | Gene IDs                                      | Z-score |
|-----|---------|-----------------------|-------|-----|---------|-----------------------------------------------|---------|
|     | GO:00987 | mitochondrial protein complex | 4/57  | 262 | 0.00    | 172, 693, 566, 2                             | 0.01444 |
|     | GO:00325 | neuron projection membrane | 2/57  | 57  | 0.01    | 971, 183, 290, 9                             | 0.02413 |
|     | GO:00451 | membrane raft         | 4/57  | 315 | 0.01    | 197, 299, 572, 3                             | 0.02572 |
|     | GO:00988 | membrane microdomain  | 4/57  | 315 | 0.01    | 197, 313, 572, 3                             | 0.02572 |
|     | GO:00163 | apical plasma membrane | 4/57  | 318 | 0.01    | 197, 341, 578, 7                             | 0.02572 |
|     | GO:00140 | postsynaptic density  | 4/57  | 324 | 0.01    | 197, 428, 702, 8                             | 0.02572 |
|     | GO:00226 | cytosolic large ribosomal subunit | 2/57  | 63  | 0.01    | 971, 432, 702, 8                             | 0.02572 |
|     | GO:00322 | asymmetric synapse     | 4/57  | 328 | 0.01    | 197, 487, 707, 3                             | 0.02572 |
|     | GO:00985 | membrane region        | 4/57  | 328 | 0.01    | 197, 487, 707, 3                             | 0.02572 |
| MF  | GO:00052 | cation channel activity | 23/57 | 319 | 1.06    | 176, E-25, E-23, 3                           | 1.63E-2 |
|     | GO:00052 | ion channel activity   | 23/57 | 416 | 4.80    | 176, E-23, E-21, 1                           | 3.69E-2 |
| MF  | GO:00228 | substrate-speci        | 23/57 | 428 | 9.19    | 176, E-25, E-23, 3                           | 4.71E-2 |
| MF    | GO:00468     | metal ion transmembrane transporter activity | 23/57 | 438/1 | 1.56 | 9.22 | 5.98E-2 | 176 | E-23 | E-21 | 1   | /6338/11280/63   |
|-------|--------------|---------------------------------------------|-------|-------|-------|-------|----------|-----|------|------|-----|-----------------|
|       |              |                                             |       |       |       |       |          |     |      |      |     | 27/55800/6331/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 6336/6329/6330  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | /624/10060/68   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 33/775/776/375  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 7/783/3767/779/  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 774/6261/781    |
| MF    | GO:00228     | ion gated channel activity                 | 21/57 | 334/1 | 3.81 | 1.38 | 8.97E-2 | 176 | E-22 | E-20 | 1   | /6338/11280/63   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 27/55800/6331/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 6336/6329/6330  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | /624/10060/68   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 33/775/776/375  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 7/783/3767/779/  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 774/6261/781    |
| MF    | GO:00152     | channel activity                           | 23/57 | 456/1 | 3.89 | 1.38 | 8.97E-2 | 176 | E-22 | E-20 | 1   | /6338/11280/63   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 27/55800/6331/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 6336/6329/6330  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | /624/10060/68   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 33/775/776/375  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 7/783/3767/779/  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 774/6261/781    |
| MF    | GO:00228     | passive transmembrane transporter activity  | 23/57 | 457/1 | 4.09 | 1.38 | 8.97E-2 | 176 | E-22 | E-20 | 1   | /6338/11280/63   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 27/55800/6331/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 6336/6329/6330  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | /624/10060/68   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 33/775/776/375  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 7/783/3767/779/  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 774/6261/781    |
| MF    | GO:00052     | voltage-gated ion channel activity          | 18/57 | 197/1 | 6.65 | 1.58 | 1.02E-2 | 176 | E-22 | E-20 | 0   | /3764/11280/632  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 27/55800/6331/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 336/6329/6330/   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | /624/10060/68   |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 33/775/776/375  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 7/783/3767/779/  |
|       |              |                                             |       |       |       |       |          |     |      |      |     | 774/6261/781    |
| MF   | GO:00228 | Voltage-gated channel activity | 18/57 | 197/176/97 | 6.65 E-22 E-20 1.02E-2 0 | 79/774/6261/78 1 |
|------|----------|---------------------------------|-------|------------|---------------------------|-------------------|
| MF   | GO:00228 | Gated channel activity          | 21/57 | 343/176/97 | 6.66 E-22 E-20 1.02E-2 0 | 6337/3764/6340 21 |
| MF   | GO:00150 | Monovalent inorganic cation transmembrane transporter activity | 20/57 | 382/176/97 | 1.72 E-19 E-18 2.40E-1 8 | 1349/4512/4513 20 |
| MF   | GO:00052 | Sodium channel activity         | 11/57 | 41/769/7  | 4.07 E-05 E-18 5.22E-1 8 | 6337/6340/6338 11 |
| MF   | GO:00049 | Adrenergic receptor activity    | 8/57  | 17/769/7  | 1.65 E-16 E-15 1.95E-1 5 | 148/154/150/15 8  |
| MF   | GO:00052 | Voltage-gated sodium channel activity | 8/57  | 20/769/7  | 8.48 E-16 E-14 9.31E-1 5 | 11280/6327/5580 8 |
| MF   | GO:00082 | G protein-coupled amine receptor activity | 9/57  | 59/769/7  | 2.14 E-13 E-12 2.19E-1 2 | 148/154/150/15 9  |
| MF   | GO:00150 | Sodium ion transmembrane transporter activity | 11/57 | 149/176/97 | 1.37 E-12 E-11 1.32E-1 1 | 6337/6340/6338 11 |
| MF GO:00443 |
|-------------|
| 25          |
| ion channel binding | 10/57 |
|           | 124/ 6.45 |
|           | 176 E-12 |
|           | 97 E-11  |
|           | 6.45E-1 |
|           | 88/55800/6331/6336/6330/6324 |
|           | 10/57/3/3767 |

| MF GO:00228 |
|-------------|
| 43          |
| voltage-gated cation channel activity | 10/57 |
|           | 142/ 2.52 |
|           | 176 E-11  |
|           | 97 E-10  |
|           | 2.15E-1 |
|           | 3764/775/776/7 |
|           | 7/57/3/3767 |

| MF GO:00083 |
|-------------|
| 31          |
| voltage-gated calcium channel activity | 5/57 |
|           | 10/1 7.21 |
|           | 769 E-11 |
|           | 97 E-10  |
|           | 775/776/783/77 |
|           | 5/77/74/6261/78 |

| MF GO:00052 |
|-------------|
| 45          |
| voltage-gated calcium channel activity | 7/57 |
|           | 48/1 1.63 |
|           | 769 E-10 |
|           | 769 E-09 |
|           | 1.25E-0 |
|           | 775/776/783/77 |
|           | 7/57/7/6261/78 |

| MF GO:19013 |
|-------------|
| 38          |
| catecholamine binding | 5/57 |
|           | 20/1 4.33 |
|           | 769 E-09 |
|           | 769 E-08 |
|           | 3.17E-0 |
|           | 154/150/153/15 |
|           | 7/2/151 |

| MF GO:00990 |
|-------------|
| 94          |
| ligand-gated cation channel activity | 7/57 |
|           | 105/ 4.38 |
|           | 176 E-08 |
|           | 97 E-07  |
|           | 1.25E-0 |
|           | 6337/3764/6340 |
|           | 7/57/7/6261 |

| MF GO:00090 |
|-------------|
| 55          |
| electron transfer activity | 7/57 |
|           | 114/ 7.75 |
|           | 176 E-08 |
|           | 97 E-07  |
|           | 5.18E-0 |
|           | 1349/4512/4513 |
|           | 7/57/7/6261 |

| MF GO:00052 |
|-------------|
| 62          |
| calcium channel activity | 7/57 |
|           | 123/ 1.31 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 8.37E-0 |
|           | 775/776/783/77 |
|           | 7/57/7/6261/78 |

| MF GO:00152 |
|-------------|
| 76          |
| ligand-gated ion channel activity | 7/57 |
|           | 138/ 2.87 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 1.70E-0 |
|           | 6337/3764/6340 |
|           | 7/57/7/6261 |

| MF GO:00228 |
|-------------|
| 34          |
| ligand-gated channel activity | 7/57 |
|           | 138/ 2.87 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 1.70E-0 |
|           | 6337/3764/6340 |
|           | 7/57/7/6261 |

| MF GO:00150 |
|-------------|
| 85          |
| calcium ion transport activity | 7/57 |
|           | 139/ 3.02 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 1.72E-0 |
|           | 775/776/783/77 |
|           | 7/57/7/6261/78 |

| MF GO:00162 |
|-------------|
| 47          |
| channel regulator activity | 7/57 |
|           | 144/ 3.84 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 2.11E-0 |
|           | 154/6327/55800 |
|           | 7/57/7/6261 |

| MF GO:00041 |
|-------------|
| 47          |
| cytochrome-c activity | 4/57 |
|           | 28/1 1.87 |
|           | 176 E-07 |
|           | 97 E-06  |
|           | 9.27E-0 |
|           | 1349/4512/4513 |
|           | 4/57/7/6261 |

90
|   | GO:00150 | oxidase activity | 769 | E-06 | E-05 | 6 | /4514 |
|---|----------|------------------|-----|------|------|---|-------|
| MF| 02       | heme-copper terminal oxidase activity | 4/57| 28/1 | 1.87 | 1.43 | 9.27E-07 | 1349/4512/4513 |
| MF| 06       | oxidoreductase activity, acting on a heme group of donors, oxygen as acceptor | 4/57| 29/1 | 2.16 | 1.60 | 1.04E-07 | 1349/4512/4513 |
| MF| 08       | ligand-gated sodium channel activity | 3/57| 10/1 | 3.74 | 2.69 | 1.74E-07 | 6337/6340/6338 |
| MF| 09       | sodium channel regulator activity | 4/57| 36/1 | 5.27 | 3.68 | 2.38E-07 | 6327/55800/633 |
| MF| 12       | adrenergic receptor binding | 3/57| 19/1 | 2.96 | 0.00 | 0.00013 | 150/153/152 |
| MF| 42       | inward rectifier potassium channel activity | 3/57| 20/1 | 3.47 | 0.00 | 0.00014 | 3764/3757/3767 |
| MF| 06       | ankyrin binding | 3/57| 20/1 | 3.47 | 0.00 | 0.00014 | 6331/776/3767 |
| MF| 09       | ion channel regulator activity | 5/57| 118/ | 3.84 | 0.00 | 0.00015 | 154/55800/6324 |
| MF| 67       | potassium channel activity | 5/57| 123/ | 4.69 | 0.00 | 0.00018 | 3764/10060/683 |
| MF| 06       | WW domain | 3/57| 31/1 | 0.00 | 0.00 | 0.00051 | 6337/6340/6338 |
| MF | GO:00150 | potassium ion transmembrane transporter activity | 5/57 | 159/176/97 | 0.00/0.00/0.0059 | 3764/10060/683 | 5 |
| MF | GO:00082 | ion channel inhibitor activity | 3/57 | 37/769/7 | 0.00/0.022/125 | 55800/6324/801 | 3 |
| MF | GO:00513 | alpha-actinin binding | 3/57 | 37/769/7 | 0.00/0.022/125 | 5468/775/776 | 3 |
| MF | GO:00162 | channel inhibitor activity | 3/57 | 38/769/7 | 0.00/0.024/132 | 55800/6324/801 | 3 |
| MF | GO:00428 | actinin binding | 3/57 | 46/769/7 | 0.00/0.043/229 | 5468/775/776 | 3 |
| MF | GO:19022 | voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization | 2/57 | 12/769/7 | 0.00/0.065/339 | 3764/757/76 | 2 |
| MF | GO:00081 | adenylate cyclase binding | 2/57 | 13/769/7 | 0.00/0.077/391 | 154/801/81 | 2 |
| MF | GO:00166 | oxidoreductase activity, acting on the CH-CH group of donors | 3/57 | 58/769/7 | 0.00/0.086/425 | 6390/6391/6389 | 3 |
| MF | GO:00150 | proton transmembrane transporter activity | 4/57 | 133/176/97 | 0.00/0.088/428 | 1349/4512/4513 | 4 |
| MF | GO:00314 | titin binding | 2/57 | 14/769/7 | 0.00/0.090/428 | 88/801/81 | 2 |
| MF | GO:00860 | voltage-gated | 2/57 | 15/769/7 | 0.00/0.090/428 | 3764/757/76 | 2 |
| MF GO:00016  | protein-coupled receptor binding | 5/57 | 280/1 | 0.00 | 0.00 | 0.00604 | 150/153/152/18 | 5 |
| MF GO:00052  | voltage-gated potassium channel activity | 3/57 | 87/1 | 0.00 | 0.00 | 0.00803 | 3764/3757/3767 | 3 |
| MF GO:00355  | purinergic receptor activity | 2/57 | 25/1 | 0.00 | 0.00 | 0.00829 | 134/136 | 2 |
| MF GO:00080  | protein C-terminus binding | 4/57 | 187/1 | 0.00 | 0.01 | 0.00861 | 5468/3767/774/ | 4 |
| MF GO:00055  | calmodulin binding | 4/57 | 200/1 | 0.00 | 0.01 | 0.01075 | 6331/775/779/6 | 4 |
| MF GO:00305  | neurotransmitter receptor activity | 3/57 | 117/1 | 0.00 | 0.02 | 0.01714 | 153/3360/134 | 3 |
| MF GO:00153  | primary active transmembrane transporter activity | 3/57 | 125/1 | 0.00 | 0.03 | 0.02008 | 4514/10060/683 | 3 |
| MF GO:00995  | protein-coupled neurotransmitter receptor activity | 2/57 | 41/1 | 0.00 | 0.03 | 0.02008 | 153/3360 | 2 |
| MF GO:00020  | protease binding | 3/57 | 128/1 | 0.00 | 0.03 | 0.02084 | 3630/7124/6261 | 3 |
| MF GO:00154  | potassium channel regulator | 2/57 | 52/1 | 0.01 | 0.04 | 0.03071 | 154/10060 | 2 |
## Table S10 KEGG pathway enrichment

| ID     | Description                               | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | geneID          | Count |
|--------|-------------------------------------------|-----------|---------|--------|----------|--------|-----------------|-------|
| hsa04022 | eGMP-PKG signaling pathway                | 18/5      | 167     | 1.9    | 3.75E-16 | 2.72E-16 | 4879/3764/148/154/1 | 18    |
| hsa04261 | Adrenergic signaling in cardiomyocytes    | 15/5      | 150     | 6.9    | 6.66E-13 | 4.83E-13 | 148/154/153/146/147/152/1 | 15    |
| hsa04020 | Calcium signaling pathway                 | 15/5      | 201     | 5.4    | 3.50E-11 | 2.54E-11 | 148/154/153/146/147/152/1 | 15    |
| hsa05020 | Prion disease                             | 15/5      | 273     | 4.5    | 2.21E-09 | 1.61E-09 | 1349/4512/4513/4514/185/6331/6330/6324/801/136/775/776/779/781 | 15    |
| hsa04930 | Type II diabetes mellitus                 | 8/50      | 46/3     | 2.6    | 1.02E-08 | 7.37E-08 | 3630/6833/775/776/777/778/779/780/7124/6261/5290/639/0/6391/6389 | 8     |
| hsa04260 | Cardiac muscle contraction                | 9/50      | 87/3     | 2.2    | 7.23E-08 | 5.24E-08 | 1349/4512/4513/4514/185/6331/6330/6324/801/136/775/776/779/781 | 9     |
| hsa05010 | Alzheimer disease                         | 15/5      | 369     | 3.1    | 8.60E-08 | 6.24E-08 | 1349/4512/4513/4514/185/6331/6330/6324/801/136/775/776/779/781 | 15    |
| hsa04270 | Vascular smooth muscle contraction        | 10/5      | 135     | 7.1    | 1.63E-07 | 1.18E-07 | 4879/148/146/147/148/3630/801/136/775/776/777/783/779/781 | 10    |
| hsa04924 | Renin secretion                           | 8/50      | 69/3     | 7.5    | 1.63E-07 | 1.18E-07 | 154/153/185/801/134/185/775/776/777 | 8     |
| hsa04932 | Non-alcoholic fatty liver disease         | 10/5      | 150     | 1.9    | 3.81E-07 | 2.76E-07 | 1349/4512/4513/4514/185/6331/6330/6324/801/136/775/776/777/781 | 10    |
| hsa04080 | Neuroactive ligand-receptor               | 13/5      | 341     | 9.3    | 1.64E-06 | 1.19E-06 | 148/154/150/153/146/147/152/185/151/336 | 13    |
| Pathway                                  | Start Coord. | End Coord. | Score | FDR   | DAVID ID          |
|------------------------------------------|--------------|------------|-------|-------|-------------------|
| r interaction                            | 73           | 80         | 0/134/136/5340 |      |                   |
| cAMP signaling pathway                   | 0            | 80         | 4/775/776/779/5290/2 | 033 |                   |
| Dilated cardiomyopathy                   | 7/50         | 96/216     | 153/775/776/783/779/7124/781 | 7   |                   |
| Huntington disease                       | 11/5         | 306/80     | 1349/4512/4513/4514/5290/2033 | 11  |                   |
| Aldosterone-regulated sodium reabsorption| 5/50         | 37/102     | 6337/6340/6338/3630/5290 | 5   |                   |
| Arrhythmogenic right ventricular cardiomyopathy | 6/50    | 77/807     | 88/775/776/783/779/73/81 | 6   |                   |
| Thermogenesis                            | 9/50         | 231/80     | 1349/4512/4513/4514/5290/2033 | 9   |                   |
| Insulin secretion                        | 6/50         | 86/133     | 3630/6833/775/776/3/767/779 | 6   |                   |
| Oxidative phosphorylation                | 7/50         | 133/80     | 1349/4512/4513/4514/5290/2033 | 7   |                   |
| Hypertrophic cardiomyopathy              | 6/50         | 90/173     | 775/776/783/779/712/4/781 | 6   |                   |
| Parkinson disease                        | 9/50         | 249/173    | 1349/4512/4513/4514/5290/2033 | 9   |                   |
| Salivary secretion                       | 6/50         | 93/216     | 148/154/153/146/147/801/775/776/783/779/6261/781 | 6   |                   |
| Regulation of lipolysis in adipocytes    | 5/50         | 56/133     | 154/153/3630/134/52/3630/134/52/3630/134/52/3630/134/52 | 5   |                   |
| Oxytocin signaling pathway               | 7/50         | 154/80     | 801/775/776/783/779/6261/781 | 7   |                   |
| GnRH                                     | 5/50         | 64/154     | 775/776/3767/779/52 | 5   |                   |
| Pathway                                      | P-value | q-value | Log2 Fold Change | Genes (Accession) |
|----------------------------------------------|---------|---------|------------------|-------------------|
| Aldosterone synthesis and secretion          | 98/3    | 0.002   | 0.001            | 185/801/775/776/779 |
| MAPK signaling pathway                       | 241/3   | 0.002   | 0.001            | 3630/775/776/783/77 |
| Cholinergic synapse                          | 341/3   | 0.003   | 0.001            | 775/776/779/74/529 |
| Cortisol synthesis and secretion             | 65/3    | 0.004   | 0.001            | 185/775/776/779 |
| Serotonergic synapse                         | 115/3   | 0.004   | 0.001            | 3360/775/776/779/77 |
| Growth hormone synthesis, secretion and action | 119/3   | 0.004   | 0.001            | 775/776/779/529/20 |
| Citrate cycle (TCA cycle)                    | 30/3    | 0.004   | 0.001            | 6390/6391/6389 |
| Amyotrophic lateral sclerosis                | 364/3   | 0.009   | 0.006            | 1349/4512/4513/4514 |
| Taste transduction                           | 86/3    | 0.010   | 0.007            | 6337/6340/6338/775 |
| GABAergic synapse                            | 89/3    | 0.011   | 0.008            | 775/776/779/774 |
| GnRH signaling pathway                       | 93/3    | 0.013   | 0.009            | 801/775/776/779 |
| Circadian entrainment                       | 97/3    | 0.015   | 0.011            | 801/775/776/6261 |
| Influenza A                                  | 171/3   | 0.020   | 0.014            | 291/7124/5290/5340/5 |
| AMPK                                         | 120/3   | 0.031   | 0.022            | 5468/148/3630/5290 |
| Pathway Description                                                                 | ID   | Start | End   | FDR  | q-value | P-value | p | p | p | p |
|-----------------------------------------------------------------------------------|------|-------|-------|------|---------|---------|---|---|---|---|
| Long-term potentiation signaling pathway                                           | hsa04720 | 3/50  | 67/73 | 0.0  | 0.039   | 0.028   | 801/775/2033 | 3 |
| Amphetamine addiction                                                             | hsa05031 | 3/50  | 69/73 | 0.0  | 0.040   | 0.029   | 801/775/776  | 3 |
| Dopaminergic synapse                                                              | hsa04728 | 4/50  | 132/73| 0.0  | 0.040   | 0.029   | 801/775/776/774 | 4 |
| Retrograde endocannabinoid signaling                                              | hsa04723 | 4/50  | 148/73| 0.0  | 0.058   | 0.042   | 775/776/779/774 | 4 |
| Cushing syndrome                                                                  | hsa04934 | 4/50  | 155/73| 0.0  | 0.066   | 0.048   | 185/775/776/779 | 4 |
| Cellular senescence                                                               | hsa04218 | 4/50  | 156/73| 0.0  | 0.066   | 0.048   | 801/291/776/5290 | 4 |
| Longevity regulating pathway                                                      | hsa04211 | 3/50  | 89/807| 0.0  | 0.073   | 0.053   | 5468/3630/5290 | 3 |
| Prostate cancer                                                                   | hsa05215 | 3/50  | 97/807| 0.0  | 0.090   | 0.065   | 3630/5290/2033 | 3 |
| AGE-RAGE signaling pathway in diabetic complications                              | hsa04933 | 3/50  | 100/80 | 0.0  | 0.095   | 0.069   | 185/7124/5290 | 3 |
| C-type lectin receptor signaling pathway                                          | hsa04625 | 3/50  | 104/80 | 0.0  | 0.103   | 0.075   | 801/7124/5290 | 3 |
| Type 1 diabetes mellitus                                                           | hsa04940 | 2/50  | 43/807| 0.0  | 0.109   | 0.079   | 3630/7124 | 2 |
| Insulin resistance                                                                | hsa04931 | 3/50  | 108/80 | 0.0  | 0.109   | 0.079   | 3630/7124/5290 | 3 |
| HIF-1 signaling pathway                                                            | hsa04066 | 3/50  | 109/80 | 0.0  | 0.110   | 0.079   | 3630/5290/2033 | 3 |
| ID      | Name                                      | Enrichment | Log2 Fold Change | p-value | FDR   | Combined p-value | Combined FDR |
|---------|-------------------------------------------|------------|------------------|---------|-------|------------------|--------------|
| hsa02010 | ABC transporters                          | 2/50       | 0.0              | 0.0     | 0.083 | 10060/6833       | 2            |
| hsa04973 | Carbohydrate digestion and absorption     | 2/50       | 0.0              | 0.0     | 0.088 | 776/5290        | 2            |
| hsa01200 | Carbon metabolism                         | 3/50       | 0.0              | 0.0     | 0.092 | 6390/6391/6389   | 3            |
| hsa04071 | Sphingolipid signaling pathway            | 3/50       | 0.0              | 0.0     | 0.121 | 134/7124/5290    | 3            |
| hsa04015 | Rap1 signaling pathway                    | 4/50       | 0.0              | 0.0     | 0.099 | 3630/801/136/5290| 4            |
| hsa04380 | Osteoclast differentiation                | 3/50       | 0.0              | 0.0     | 0.107 | 5468/7124/5290   | 3            |
| hsa05166 | Human T-cell leukemia virus 1 infection   | 4/50       | 0.0              | 0.0     | 0.109 | 291/7124/5290/2033| 4            |
| hsa04068 | FoxO signaling pathway                    | 3/50       | 0.0              | 0.0     | 0.109 | 3630/5290/2033   | 3            |
| hsa04371 | Apelin signaling pathway                  | 3/50       | 0.0              | 0.0     | 0.1187| 185/801/6261     | 3            |
| hsa04910 | Insulin signaling pathway                 | 3/50       | 0.0              | 0.0     | 0.1187| 3630/801/5290    | 3            |
| hsa05418 | Fluid shear stress and atherosclerosis    | 3/50       | 0.0              | 0.0     | 0.121 | 801/7124/5290    | 3            |
| hsa04213 | Longevity regulating pathway - multiple species | 2/50 | 0.0        | 0.0     | 0.122 | 3630/5290       | 2            |
| hsa05017 | Spinocerebellar ataxia                    | 3/50       | 0.0              | 0.0     | 0.125 | 291/6261/5290    | 3            |
| hsa04072 | Phospholipase                            | 3/50       | 0.0              | 0.0     | 0.134 | 185/3630/5290    | 3            |
| Pathway Description                          | Start | End    | % Change | p Value | FDR | Rank |
|---------------------------------------------|-------|--------|----------|---------|-----|------|
| D signaling pathway                         |       |        |          |         |     |      |
| Fc epsilon RI signaling pathway             | 80    |       |          |         |     |      |
| Renal cell carcinoma signaling pathway      | 50    |       |          |         |     |      |
| Prolactin signaling pathway                 | 50    |       |          |         |     |      |
| mTOR signaling pathway                      | 50    |       |          |         |     |      |
| Glioma signaling pathway                    | 50    |       |          |         |     |      |
| Hepatitis B signaling pathway               | 50    |       |          |         |     |      |
| Pertussis signaling pathway                 | 50    |       |          |         |     |      |
| Tuberculosis signaling pathway              | 50    |       |          |         |     |      |
| Morphine addiction                         | 50    |       |          |         |     |      |
| TGF-beta signaling pathway                  | 50    |       |          |         |     |      |
| Kaposi sarcoma-associated herpesvirus infection | 50   |       |          |         |     |      |
| Phosphatidylinositol signaling system       | 50    |       |          |         |     |      |
| Inflammatory mediator regulation of         | 50    |       |          |         |     |      |
| Gene ID   | Description                           | DEG Mean | Fold Change | p-Value | Adjusted p-Value |
|----------|---------------------------------------|----------|-------------|---------|-----------------|
| hsa04914 | TRP channels                          | 2/50     | 100         | 0.1     | 0.303           | 0.220           | 3630/5290       | 2      |
|          | Progesterone-mediating oocyte maturation | /80     | 271         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04916 | Melanogenesis                         | 2/50     | 101         | 0.1     | 0.303           | 0.220           | 801/2033       | 2      |
|          |                                       | /80     | 291         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa05142 | Chagas disease                        | 2/50     | 102         | 0.1     | 0.303           | 0.220           | 7124/5290      | 2      |
|          |                                       | /80     | 312         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa05146 | Amoebiasis                            | 2/50     | 102         | 0.1     | 0.303           | 0.220           | 7124/5290      | 2      |
|          |                                       | /80     | 312         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04614 | Renin-angiotensin system               | 1/50     | 23/         | 0.1     | 0.303           | 0.220           | 185             | 1      |
|          |                                       |         | 807         | 333     | 981             | 0.504           |                      |       |
|          |                                       | 3        | 981         | 0.3     | 0.03            |                      |                   |
| hsa04620 | Toll-like receptor signaling pathway   | 2/50     | 104         | 0.1     | 0.303           | 0.220           | 7124/5290      | 2      |
|          |                                       | /80     | 354         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04660 | T cell receptor signaling pathway      | 2/50     | 104         | 0.1     | 0.303           | 0.220           | 7124/5290      | 2      |
|          |                                       | /80     | 354         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04977 | Vitamin digestion and absorption      | 1/50     | 24/         | 0.1     | 0.307           | 0.223           | 10560          | 1      |
|          |                                       |         | 807         | 387     | 704             | 205             |                      |       |
|          |                                       | 3        | 981         | 0.3     | 0.03            |                      |                   |
| hsa04922 | Glucagon signaling pathway             | 2/50     | 107         | 0.1     | 0.310           | 0.225           | 801/2033       | 2      |
|          |                                       | /80     | 417         | 595     | 302             |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa05170 | Human immunodeficiency virus 1 infection | 3/50    | 212         | 0.1     | 0.310           | 0.225           | 801/7124/5290  | 3      |
|          |                                       | /80     | 432         | 595     | 302             |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04950 | Maturity onset diabetes of the young   | 1/50     | 26/         | 0.1     | 0.320           | 0.232           | 3630           | 1      |
|          |                                       |         | 807         | 493     | 324             | 36              |                      |       |
|          |                                       | 3        | 981         | 0.3     | 0.03            |                      |                   |
| hsa04668 | TNF signaling pathway                 | 2/50     | 112         | 0.1     | 0.323           | 0.234           | 7124/5290      | 2      |
|          |                                       | /80     | 525         | 45      | 627             |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04724 | Glutamatergic synapse                 | 2/50     | 114         | 0.1     | 0.329           | 0.238           | 775/776        | 2      |
|          |                                       | /80     | 568         | 117     | 665             |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| hsa04744 | Phototransduction                     | 1/50     | 28/         | 0.1     | 0.331           | 0.240           | 801            | 1      |
|          |                                       |         | 801         | 981     | 0.504           |                      |                   |
|          |                                       | 73       | 981         | 0.3     | 0.03            |                      |                   |
| Gene Symbol | Pathway Description                          | P | FDR | p-value | FDR-adjusted p-value | Log2 Fold Change | p-value | FDR |
|-------------|---------------------------------------------|----|-----|---------|----------------------|------------------|---------|-----|
| hsa05163    | Human cytomegalovirus infection             | 3  | 13  | 0.241   | 0.001                | 0.333            | 0.241   | 3   |
|             |                                             | 801/7124/5290 | 3   |         |                      |                  |         |     |
| hsa04722    | Neurotrophin signaling pathway              | 2  | 64  | 0.247   | 0.001                | 0.340            | 0.247   | 2   |
|             |                                             | 801/5290 | 2   |         |                      |                  |         |     |
| hsa04919    | Thyroid hormone signaling pathway           | 2  | 099 | 0.248   | 0.001                | 0.248            | 0.248   | 2   |
|             |                                             | 5290/2033 | 2   |         |                      |                  |         |     |
| hsa04014    | Ras signaling pathway                       | 3  | 79  | 0.248   | 0.001                | 0.342            | 0.248   | 3   |
|             |                                             | 3630/801/5290 | 3   |         |                      |                  |         |     |
| hsa01523    | Antifolate resistance                       | 1  | 81  | 0.155   | 0.001                | 0.342            | 0.248   | 1   |
|             |                                             | 7124 | 1   |         |                      |                  |         |     |
| hsa05310    | Asthma                                      | 1  | 81  | 0.155   | 0.001                | 0.342            | 0.248   | 1   |
|             |                                             | 7124 | 1   |         |                      |                  |         |     |
| hsa04114    | Oocyte meiosis                              | 2  | 94  | 0.265   | 0.001                | 0.366            | 0.265   | 2   |
|             |                                             | 3630/801 | 2   |         |                      |                  |         |     |
| hsa05135    | Yersinia infection                          | 2  | 41  | 0.266   | 0.001                | 0.367            | 0.266   | 2   |
|             |                                             | 7124/5290 | 2   |         |                      |                  |         |     |
| hsa04650    | Natural killer cell mediated cytotoxicity   | 2  | 91  | 0.266   | 0.001                | 0.368            | 0.266   | 2   |
|             |                                             | 7124/5290 | 2   |         |                      |                  |         |     |
| hsa05143    | African trypanosomias                        | 1  | 74  | 0.273   | 0.001                | 0.376            | 0.273   | 1   |
|             |                                             | 7124 | 1   |         |                      |                  |         |     |
| hsa05216    | Thyroid cancer                              | 1  | 74  | 0.273   | 0.001                | 0.376            | 0.273   | 1   |
|             |                                             | 5468 | 1   |         |                      |                  |         |     |
| hsa04210    | Apoptosis                                   | 2  | 94  | 0.273   | 0.001                | 0.376            | 0.273   | 2   |
|             |                                             | 7124/5290 | 2   |         |                      |                  |         |     |
| hsa04140    | Autophagy - animal                          | 2  | 64  | 0.273   | 0.001                | 0.376            | 0.273   | 2   |
|             |                                             | 3630/5290 | 2   |         |                      |                  |         |     |
| hsa04915    | Estrogen signaling                          | 2  | 15  | 0.273   | 0.001                | 0.376            | 0.273   | 2   |
|             |                                             | 801/5290 | 2   |         |                      |                  |         |     |

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| Pathway                                      | # Datasets | p-values | q-values | q-values corrected | Significance |
|----------------------------------------------|------------|----------|----------|--------------------|--------------|
| Allograft rejection                          | 1/50       | 0.2      | 0.376    | 0.273              | 1            |
| Nicotine addiction                           | 1/50       | 0.2      | 0.390    | 0.283              | 1            |
| Graft-versus-host disease                    | 1/50       | 0.2      | 0.403    | 0.292              | 1            |
| Hepatitis C                                  | 2/50       | 0.2      | 0.441    | 0.320              | 2            |
| Ribosome                                     | 2/50       | 0.2      | 0.441    | 0.320              | 2            |
| Necroptosis                                  | 2/50       | 0.2      | 0.441    | 0.320              | 2            |
| JAK-STAT signaling pathway                  | 2/50       | 0.2      | 0.449    | 0.325              | 2            |
| Malaria                                      | 1/50       | 0.2      | 0.449    | 0.325              | 1            |
| Ovarian steroidogenensis                     | 1/50       | 0.2      | 0.453    | 0.328              | 1            |
| Notch signaling pathway                      | 1/50       | 0.2      | 0.464    | 0.336              | 1            |
| Pyrimidine metabolism                        | 1/50       | 0.2      | 0.481    | 0.348              | 1            |
| Glutathione metabolism                       | 1/50       | 0.2      | 0.481    | 0.348              | 1            |
| Legionellosis                                | 1/50       | 0.2      | 0.481    | 0.348              | 1            |
| Endometrial cancer                           | 1/50       | 0.3      | 0.484    | 0.3511             | 1            |
| VEGF                                         | 1/50       | 0.3      | 0.486    | 0.353              | 1            |
| ID       | Pathway                                      | Nodes | Isomorphism | Fold Change | p-Value | q-Value |
|----------|----------------------------------------------|-------|-------------|-------------|---------|---------|
| hsa04730 | Long-term depression                         | 807   | 1           | 1           | 6261    | 0.355   |
| hsa05034 | Alcoholism                                   | 187   | 0.3         | 0.497       | 801/136 | 2       |
| hsa05321 | Inflammatory bowel disease                   | 807   | 0.3         | 0.497       | 7124    | 1       |
| hsa05165 | Human papillomavirus infection               | 331   | 0.3         | 0.497       | 7124/5290/2033 | 3       |
| hsa05221 | Acute myeloid leukemia                       | 807   | 0.3         | 0.497       | 5290    | 1       |
| hsa05223 | Non-small cell lung cancer                   | 807   | 0.3         | 0.497       | 5290    | 1       |
| hsa04920 | Adipocytokine signaling pathway              | 807   | 0.3         | 0.497       | 7124    | 1       |
| hsa04622 | RIG-I-like receptor signaling pathway        | 807   | 0.3         | 0.497       | 7124    | 1       |
| hsa05230 | Central carbon metabolism in cancer          | 807   | 0.3         | 0.497       | 5290    | 1       |
| hsa05169 | Epstein-Barr virus infection                 | 202   | 0.3         | 0.497       | 7124/5290 | 2       |
| hsa04520 | Adherens junction                            | 807   | 0.3         | 0.497       | 2033    | 1       |
| hsa05203 | Viral carcinogenesis                         | 204   | 0.3         | 0.497       | 5290/2033 | 2       |
| hsa05218 | Melanoma                                     | 807   | 0.3         | 0.497       | 5290    | 1       |
| hsa05205 | Proteoglycans                                | 205   | 0.3         | 0.497       | 7124/5290 | 2       |
| Pathway                          | Type | ID   | Tissue | p-value | LogFC | FDR  | 104 |
|---------------------------------|------|------|--------|---------|-------|------|-----|
| Inositol phosphate metabolism   |      | hsa00562 | 1/50   | 73/80   | 0.3   | 0.497| 0.360| 5290| 1   |
| Platinum drug resistance        |      | hsa01524 | 1/50   | 73/80   | 0.3   | 0.497| 0.360| 5290| 1   |
| p53 signaling pathway           |      | hsa04115 | 1/50   | 73/80   | 0.3   | 0.497| 0.360| 50484| 1   |
| Bacterial invasion of epithelial cells |      | hsa05100 | 1/50   | 73/80   | 0.3   | 0.497| 0.360| 5290| 1   |
| Gastric acid secretion          |      | hsa04971 | 1/50   | 76/80   | 0.3   | 0.497| 0.360| 801  | 1   |
| Pancreatic cancer               |      | hsa05212 | 1/50   | 76/80   | 0.3   | 0.497| 0.360| 5290| 1   |
| Chronic myeloid leukemia        |      | hsa05220 | 1/50   | 76/80   | 0.3   | 0.497| 0.360| 5290| 1   |
| PPAR signaling pathway          |      | hsa03320 | 1/50   | 77/80   | 0.3   | 0.497| 0.360| 5468| 1   |
| Leishmaniasis                   |      | hsa05140 | 1/50   | 77/80   | 0.3   | 0.497| 0.360| 7124| 1   |
| Salmonella infection            |      | hsa05132 | 2/50   | 213/80  | 0.3   | 0.497| 0.360| 7124/5290| 2 |
| Regulation of actin cytoskeleton|      | hsa04810 | 2/50   | 214/80  | 0.3   | 0.497| 0.360| 3630/5290| 2 |
| Antigen processing and presentation |      | hsa04612 | 1/50   | 78/80   | 0.3   | 0.497| 0.360| 7124| 1   |
| Synaptic vesicle cycle          |      | hsa04721 | 1/50   | 78/80   | 0.3   | 0.497| 0.360| 774  | 1   |
| Drug metabolism -               |      | hsa00983 | 1/50   | 79/80   | 0.3   | 0.497| 0.360| 50484| 1   |
| ID        | Pathway                                      | Gene     | Fold Change | p-Value | Adjusted p-Value | Score | q-value | q-value adj |
|-----------|----------------------------------------------|----------|-------------|---------|------------------|-------|---------|-------------|
| hsa01521 | EGFR tyrosine kinase inhibitor resistance    | 1/50     | 0.3         | 0.497   | 0.360            | 5290  | 1       |
| hsa04662 | B cell receptor signaling pathway            | 1/50     | 0.4         | 0.508   | 0.369            | 5290  | 1       |
| hsa04012 | ErbB signaling pathway                       | 1/50     | 0.4         | 0.516   | 0.374            | 5290  | 1       |
| hsa04610 | Complement and coagulation cascades          | 1/50     | 0.4         | 0.516   | 0.374            | 5340  | 1       |
| hsa05210 | Colorectal cancer                            | 1/50     | 0.4         | 0.517   | 0.375            | 5290  | 1       |
| hsa04540 | Gap junction                                 | 1/50     | 0.4         | 0.523   | 0.379            | 153   | 1       |
| hsa05235 | PD-L1 expression and PD-L1 checkpoint pathway in cancer | 1/50 | 0.4         | 0.524   | 0.380            | 5290  | 1       |
| hsa05222 | Small cell lung cancer                       | 1/50     | 0.4         | 0.529   | 0.384            | 5290  | 1       |
| hsa04666 | Fc gamma R-mediated phagocytosis             | 1/50     | 0.4         | 0.529   | 0.384            | 5290  | 1       |
| hsa05323 | Rheumatoid arthritis                         | 1/50     | 0.4         | 0.529   | 0.384            | 7124  | 1       |
| hsa04657 | IL-17 signaling pathway                      | 1/50     | 0.4         | 0.529   | 0.384            | 7124  | 1       |
| hsa05131 | Shigellosis                                  | 2/50     | 0.4         | 0.529   | 0.384            | 7124  | 2       |

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| HSA      | Description                                      | P-transformed | FDR (FDR) | P-value | Fold Change |
|---------|--------------------------------------------------|--------------|-----------|---------|-------------|
| hsa05150 | Staphylococcus aureus infection                  | 1/50         | 0.4       | 0.534   | 0.387       | 5340        | 1 |
| hsa01522 | Endocrine resistance                             | 1/50         | 0.4       | 0.535   | 0.388       | 5290        | 1 |
| hsa05231 | Choline metabolism in cancer                    | 1/50         | 0.4       | 0.536   | 0.389       | 5124        | 1 |
| hsa04640 | Hematopoietic cell lineage                      | 1/50         | 0.4       | 0.537   | 0.389       | 5124        | 1 |
| hsa04061 | Viral protein interaction with cytokine and cytokine receptor | 1/50         | 0.4       | 0.537   | 0.389       | 5124        | 1 |
| hsa04064 | NF-kappa B signaling pathway                    | 1/50         | 0.4       | 0.549   | 0.398       | 7124        | 1 |
| hsa05145 | Toxoplasmosis                                   | 1/50         | 0.5       | 0.575   | 0.417       | 7124        | 1 |
| hsa04670 | Leukocyte transendothelial migration            | 1/50         | 0.5       | 0.578   | 0.419       | 5290        | 1 |
| hsa04110 | Cell cycle                                      | 1/50         | 0.5       | 0.605   | 0.439       | 2033        | 1 |
| hsa04611 | Platelet activation                             | 1/50         | 0.5       | 0.605   | 0.439       | 5290        | 1 |
| hsa04926 | Relaxin signaling pathway                       | 1/50         | 0.5       | 0.617   | 0.448       | 5290        | 1 |
| hsa00230 | Purine metabolism                              | 1/50         | 0.5       | 0.617   | 0.448       | 50484       | 1 |
| hsa05322 | Systemic lupus erythematosus                    | 1/50         | 0.5       | 0.632   | 0.458       | 7124        | 1 |
| hsa05206 | MicroRNAs in cancer                             | 2/50         | 0.5       | 0.633   | 0.459       | 5290/2033   | 2 |

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| Gene ID  | Description                                                                 | Score 1 | Score 2 | Score 3 | Score 4 | Score 5 | Score 6 |
|---------|------------------------------------------------------------------------------|---------|---------|---------|---------|---------|---------|
| hsa05162 | Measles                                                                      | 1/50    | 139     | 0.5     | 0.634   | 0.459   | 5290    |
|         |                                                                              | /102    | 814     | 0.5     | 0.057   | 0.938   | /139    |
|         |                                                                              | 73      | 93      |         |         |         |         |
| hsa04550 | Signaling pathways regulating pluripotency of stem cells                    | 1/50    | 143     | 0.5     | 0.641   | 0.465   | 5290    |
|         |                                                                              | /102    | 919     | 0.5     | 0.828   | 0.575   | /139    |
|         |                                                                              | 73      | 45      |         |         |         |         |
| hsa05224 | Breast cancer                                                                | 1/50    | 147     | 0.6     | 0.649   | 0.470   | 5290    |
|         |                                                                              | /102    | 237     | 0.6     | 0.949   |         | /139    |
|         |                                                                              | 73      | 42      |         |         |         |         |
| hsa05226 | Gastric cancer                                                               | 1/50    | 149     | 0.6     | 0.650   | 0.472   | 5290    |
|         |                                                                              | /102    | 995     | 0.6     | 0.224   |         | /139    |
|         |                                                                              | 73      | 46      |         |         |         |         |
| hsa04310 | Wnt signaling pathway                                                        | 1/50    | 160     | 0.6     | 0.675   | 0.490   | 2033    |
|         |                                                                              | /102    | 591     | 0.6     | 0.066   |         | /139    |
|         |                                                                              | 73      | 86      |         |         |         |         |
| hsa04530 | Tight junction                                                               | 1/50    | 162     | 0.6     | 0.676   | 0.490   | 776     |
|         |                                                                              | /102    | 774     | 0.6     | 0.924   |         | /139    |
|         |                                                                              | 73      | 02      |         |         |         |         |
| hsa04151 | PI3K-Akt signaling pathway                                                   | 2/50    | 354     | 0.6     | 0.683   | 0.495   | 3630/5290 |
|         |                                                                              | /102    | 588     | 0.6     | 0.867   |         | /139    |
|         |                                                                              | 73      | 25      |         |         |         |         |
| hsa05225 | Hepatocellular carcinoma                                                   | 1/50    | 168     | 0.6     | 0.683   | 0.495   | 5290    |
|         |                                                                              | /102    | 588     | 0.6     | 0.867   |         | /139    |
|         |                                                                              | 73      | 11      |         |         |         |         |
| hsa04360 | Axon guidance                                                                | 1/50    | 181     | 0.6     | 0.704   | 0.5113  | 5290    |
|         |                                                                              | /102    | 873     | 0.6     | 0.07    |         | /139    |
|         |                                                                              | 73      | 08      |         |         |         |         |
| hsa04621 | NOD-like receptor signaling pathway                                           | 1/50    | 181     | 0.6     | 0.704   | 0.5113  | 7124    |
|         |                                                                              | /102    | 873     | 0.6     | 0.07    |         | /139    |
|         |                                                                              | 73      | 08      |         |         |         |         |
| hsa04062 | Chemokine signaling pathway                                                 | 1/50    | 192     | 0.7     | 0.717   | 0.520   | 5290    |
|         |                                                                              | /102    | 748     | 0.7     | 0.646   |         | /139    |
|         |                                                                              | 73      | 76      |         |         |         |         |
| hsa05202 | Transcriptional misregulation in cancer                                      | 1/50    | 192     | 0.7     | 0.717   | 0.520   | 5468    |
|         |                                                                              | /102    | 748     | 0.7     | 0.646   |         | /139    |
|         |                                                                              | 73      | 76      |         |         |         |         |
| hsa05130 | Pathogenic Escherichia coli infection                                        | 1/50    | 193     | 0.7     | 0.717   | 0.520   | 7124    |
|         |                                                                              | /102    | 748     | 0.7     | 0.646   |         | /139    |
|         |                                                                              | 73      | 73      |         |         |         |         |
| hsa04510 | Focal                                                                         | 1/50    | 201     | 0.7     | 0.728   | 0.528   | 5290    |
|         |                                                                              | /102    | 748     | 0.7     | 0.646   |         | /139    |
|         |                                                                              | 73      | 73      |         |         |         |         |
Supplementary File S5

S5.1 Experimental method of pharmacodynamics of PRP for treating arrhythmia zebrafish

The pharmacodynamics experiments were carried out from three aspects: Cardiovascular morphological observation, sinus venosus - bulbus arteriosus (SV-BA) distance measurement and Acridine orange (AO) staining for apoptosis evaluation.

S5.2 Experimental results of pharmacodynamics of PRP for treating arrhythmia zebrafish

The original data of cardiac congestion area of zebrafish in each group and the data analysis results were shown in Table S11, Table S11-1, Table S11-2. The original data of SV-BA distance measurement of zebrafish in each group and the data analysis results were shown in Table S12, Table S12-1, Table S12-2. The original data of average fluorescence density of zebrafish in each group and the data analysis results were shown in Table S13, Table S13-1, Table S13-2.

Table S11 Original data of congestion area of zebrafish in each group

|       | Control | Model | Positive | PRP-H | PRP-M | PRP-L |
|-------|---------|-------|----------|-------|-------|-------|
| 1     | 4547    | 31067 | 5357     | 6086  | 7340  | 14687 |
| 2     | 4921    | 32411 | 5904     | 6900  | 7905  | 15902 |
| 3     | 3408    | 30998 | 5187     | 6599  | 7470  | 14600 |
| 4     | 5175    | 29975 | 5824     | 7085  | 8024  | 19562 |
| 5     | 3721    | 27546 | 5431     | 7132  | 8321  | 16771 |
| 6     | 4025    | 29980 | 6078     | 6134  | 7856  | 13952 |
| Means | 4299.5  | 30329.5 | 5630.167 | 6656  | 7819.333 | 15912.333 |
| SD    | 695.529 | 1632.123 | 353.212 | 462.771 | 361.673 | 2055.434 |
| Means ±  | 4299.5 | 30329.5 | 5630.167 | 6656 | 7819.333 | 15912.333 |
| SD      | ±695.529 | ±1632.123 | ±353.212 | ±462.771 | ±361.673 | ±2055.434 |

**Table S11-1** Homogeneity of variance results

| expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|-------------------------------|-----|-----|--------------|
|                     | 3.457                         | 5   | 30  | 0.014<0.05   |

**Table S11-2** Multiple comparison results

| Tamhane | (I) Grouping | (J) Grouping | The mean difference (I-J) | standard error | significance |
|---------|--------------|--------------|---------------------------|----------------|--------------|
| 1       | 1            | 2            | -26030.000*               | 724.291        | 0            |
|         | 3            | 1            | -1330.667                 | 318.465        | 0.053        |
|         | 4            | 1            | -2356.500*                | 341.057        | 0.001        |
|         | 5            | 1            | -3519.833*                | 320.044        | 0            |
|         | 6            | 1            | -11612.833*               | 885.868        | 0            |
| 2       | 1            | 3            | 26030.000*                | 724.291        | 0            |
|         | 3            | 2            | 24699.333*                | 681.736        | 0            |
|         | 4            | 2            | 23673.500*                | 692.578        | 0            |
|         | 5            | 2            | 22510.167*                | 682.475        | 0            |
|         | 6            | 2            | 14417.167*                | 1071.497       | 0            |
| 3       | 1            | 2            | 1330.667                  | 318.465        | 0.053        |
|         | 2            | 1            | -24699.333*               | 681.736        | 0            |
|         | 3            | 1            | -1025.833*                | 237.668        | 0.026        |
|         | 4            | 1            | 1318.167*                 | 206.384        | 0            |
|         | 5            | 1            | -10282.167*               | 851.427        | 0.001        |
| 4       | 1            | 3            | 2356.500*                 | 341.057        | 0.001        |
|         | 2            | 3            | -23673.500*               | 692.578        | 0            |
|         | 3            | 3            | 1025.833*                 | 237.668        | 0.026        |
|         | 5            | 3            | -1163.333*                | 239.779        | 0.012        |
|         | 6            | 3            | -9256.333*                | 860.132        | 0.001        |
| 5       | 1            | 2            | 3519.833*                 | 320.044        | 0            |
|         | 2            | 2            | -22510.167*               | 682.475        | 0            |
|         | 3            | 2            | 2189.167*                 | 206.384        | 0            |
|         | 4            | 2            | 1163.333*                 | 239.779        | 0.012        |
|         | 6            | 2            | -8093.000*                | 852.019        | 0.002        |
| 6       | 1            | 3            | 11612.833*                | 885.868        | 0            |
|         | 2            | 3            | -14417.167*               | 1071.497       | 0            |
|         | 3            | 3            | 10282.167*                | 851.427        | 0.001        |
|         | 4            | 3            | 9256.333*                 | 860.132        | 0.001        |
|         | 5            | 3            | 8093.000*                 | 852.019        | 0.002        |

**Table S12** Original data of SV-BA interval of zebrafish in each group

| Control | Model  | Positive | PRP-H | PRP-M | PRP-L |
|---------|--------|----------|-------|-------|-------|
| 1       | 139.98 | 218.26   | 149.74| 156.47| 167.26| 187.23|
|    | 141.25 | 219.89 | 152.37 | 160.32 | 160.57 | 184.76 |
|----|--------|--------|--------|--------|--------|--------|
| 3  | 138.27 | 214.32 | 150.86 | 163.45 | 161.59 | 190.14 |
| 4  | 140.25 | 220.57 | 158.4  | 157.81 | 170.68 | 187.35 |
| 5  | 143.22 | 226.73 | 154.31 | 164.94 | 169.96 | 179.4  |
| 6  | 140.77 | 234.2  | 150.72 | 159.74 | 158.2  | 180.69 |

**Means** 140.623 222.328 152.733 160.455 164.71 184.928

**SD** 1.628 7.072 3.202 3.24 5.272 4.168

Means ± SD 140.623 ±1.628 222.328 ±7.072 152.733 ±3.202 160.455 ±3.24 164.71 ±5.272 184.928 ±4.168

### Table S12-1 Homogeneity of variance results

| Expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|-----------------------------|-----|-----|--------------|
|                     |                             | 3.074 | 5 | 0.023<0.05 |

### Table S12-2 Multiple comparison results

| (I) Grouping | (J) Grouping | The mean difference (I-J) | standard error | significance |
|--------------|--------------|--------------------------|----------------|--------------|
| Tamhane      |              |                          |                |              |
| 1            | 2            | -81.705*                 | 2.962          | 0            |
| 3            | 4            | -12.110*                 | 1.466          | 0.001        |
| 4            | 5            | -19.832*                 | 1.48           | 0            |
| 5            | 6            | -24.087*                 | 2.252          | 0.001        |
| 6            |              | -44.305*                 | 1.827          | 0            |
| 2            | 1            | 81.705*                  | 2.962          | 0            |
| 3            | 4            | 69.595*                  | 3.169          | 0            |
| 4            | 5            | 61.873*                  | 3.176          | 0            |
| 5            | 6            | 57.618*                  | 3.601          | 0            |
| 6            |              | 37.400*                  | 3.351          | 0            |
| 3            | 1            | 12.110*                  | 1.466          | 0.001        |
| 2            | 4            | -69.595*                 | 3.169          | 0            |
| 4            | 5            | -7.722*                  | 1.86           | 0.029        |
| 5            | 6            | -11.977*                 | 2.518          | 0.02         |
| 6            |              | -32.195*                 | 2.146          | 0            |
| 4            | 1            | 19.832*                  | 1.48           | 0            |
| 2            | 3            | -61.873*                 | 3.176          | 0            |
| 3            | 5            | 7.722*                   | 1.86           | 0.029        |
| 5            | 6            | -4.255                   | 2.526          | 0.874        |
| 6            |              | -24.473*                 | 2.155          | 0            |
| 5            | 1            | 24.087*                  | 2.252          | 0.001        |
| 2            | 4            | -57.618*                 | 3.601          | 0            |
| 3            | 5            | 11.977*                  | 2.518          | 0.02         |
| 4            | 6            | 4.255                    | 2.526          | 0.874        |
| 5            |              | -20.218*                 | 2.744          | 0            |
| 6            | 1            | 44.305*                  | 1.827          | 0            |
| 2            |              | -37.405*                 | 3.351          | 0            |
Table S13 Original data of average fluorescence density of zebrafish in each group

|       | Control  | Model    | Positive | PRP-H | PRP-M | PRP-L |
|-------|----------|----------|----------|-------|-------|-------|
| 1     | 0.119    | 0.178    | 0.123    | 0.134 | 0.139 | 0.154 |
| 2     | 0.121    | 0.192    | 0.125    | 0.137 | 0.14  | 0.157 |
| 3     | 0.115    | 0.173    | 0.121    | 0.1311| 0.143 | 0.151 |
| 4     | 0.132    | 0.182    | 0.12     | 0.142 | 0.145 | 0.158 |
| 5     | 0.126    | 0.179    | 0.126    | 0.13  | 0.14  | 0.15  |
| 6     | 0.108    | 0.186    | 0.125    | 0.142 | 0.141 | 0.162 |
| Means | 0.12     | 0.182    | 0.123    | 0.136 | 0.141 | 0.155 |
| SD    | 0.008    | 0.007    | 0.002    | 0.005 | 0.002 | 0.005 |
| Means | ±0.008   | ±0.007   | ±0.002   | ±0.005| ±0.002|       |

Table S13-1 Homogeneity of variance results

| Expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|-------------------------------|-----|-----|--------------|
|                     |                               | 2.080 | 5 | 30 | 0.096>0.05 |

Table S13-2 Multiple comparison results

| (I) Grouping | (J) Grouping | The mean difference (I-J) | standard error | significance |
|--------------|--------------|---------------------------|----------------|--------------|
| LSD          | 1            | 2                         | -.061*         | 0.003         | 0            |
|              | 3            | -.003                     | 0.003          | 0.316         |
|              | 4            | -.016*                    | 0.003          | 0             |
|              | 5            | -.021*                    | 0.003          | 0             |
|              | 6            | -.035*                    | 0.003          | 0             |
|              | 2            | 1                         | .061*          | 0.003         | 0            |
|              | 3            | .058*                     | 0.003          | 0             |
|              | 4            | .046*                     | 0.003          | 0             |
|              | 5            | .040*                     | 0.003          | 0             |
|              | 6            | .026*                     | 0.003          | 0             |
|              | 3            | 1                         | 0.003          | 0.003         | 0.316        |
|              | 2            | -.058*                    | 0.003          | 0             |
|              | 4            | -.013*                    | 0.003          | 0             |
|              | 5            | -.018*                    | 0.003          | 0             |
|              | 6            | -.032*                    | 0.003          | 0             |
|              | 4            | 1                         | .016*          | 0.003         | 0             |
|              | 2            | -.046*                    | 0.003          | 0             |
|              | 3            | .013*                     | 0.003          | 0             |
|              | 5            | -.005                     | 0.003          | 0.097         |
|              | 6            | -.019*                    | 0.003          | 0             |
S6.1 Quantitative Reverse Transcriptase Polymerase Chain Reaction Analysis (qRT-PCR analysis) and Quantitative determination of adenosine and cGMP metabolites

After treatment at 96 hpf, zebrafish embryos were randomly selected (n=30 each group) for qRT-PCR analysis. Thirty milligrams of zebrafish embryos were homogenized in TRIzol reagent to extract total RNA. The extracted RNA was used as a template, and cDNA was synthesized by reverse transcription with appropriate primers according to the instructions of the Servicebio® RT First Strand cDNA Synthesis kit. qRT-PCR was performed in an ABI 7900HT FastReal-Time PCR system. The primer sequences were as follows: TTCTGACCCAAAGTTCCATCCT (forward) and CTCAAACTGGCAGGTGACGAT (reverse). Levels of the ADORA1 mRNAs were normalized to the GAPDH mRNA and determined using the 2-ΔΔCt method, and all reactions were performed in triplicate.

Adenosine and cGMP metabolite markers were quantitated by comparing to the areas of the peaks for the external standards.

S6.2 PRP rescues metabolite profiles from the ADORA1-mediated cGMP-PKG signalling pathway

By quantifying the levels of adenosine and cGMP in embryo samples using LC-MS in multiple reaction monitoring (MRM) mode, the results were shown in Table S14, Table S14-1, Table S14-2 and Table S15, Table S15-1, Table S15-2. ADORA1 expression was determined using qRT-PCR assays to examine how the PRP treatment influenced barium chloride induced arrhythmia in zebrafish embryos, the results were shown in Table S16,
Table S16-1, Table S16-2.

Table S14 Original data of adenosine of in each group

|       | Control | Model | Positive | PRP-H | PRP-M | PRP-L |
|-------|---------|-------|----------|-------|-------|-------|
| 1     | 3686    | 1154  | 2616     | 2236  | 2116  | 1832  |
| 2     | 3474    | 1236  | 2384     | 1934  | 2127  | 1833  |
| 3     | 2482    | 1168  | 2498     | 1973  | 1504  | 1487  |
| 4     | 3368    | 1012  | 2332     | 2097  | 1983  | 1558  |
| 5     | 3293    | 1233  | 2483     | 2191  | 2075  | 1498  |
| 6     | 3097    | 1317  | 2117     | 2089  | 2065  | 1882  |

Means 3233.333 1186.667 2405 2086.667 1978.333 1681.667
SD 416.56 103.432 172.028 117.92 237.875 185.773

Means ± 3233.333± 1186.667± 2405± 2086.667± 1978.333± 1681.667±
SD 416.56 103.432 172.028 117.92 237.875 185.773

Table S14-1 Homogeneity of variance results

| Expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|------------------------------|-----|-----|--------------|
| 1.979               | 5                            | 30  |     | 0.111>0.05   |

Table S14-2 Multiple comparison results

(1) Grouping (J) Grouping The mean difference (I-J) standard error significance

|       |       | The mean difference (I-J) | standard error |
|-------|-------|---------------------------|----------------|
| LSD   | 1     | 2046.667*                 | 133.086        | 0              |
|       | 3     | 828.333*                  | 133.086        | 0              |
|       | 4     | 1146.667*                 | 133.086        | 0              |
|       | 5     | 1255.000*                 | 133.086        | 0              |
|       | 6     | 1551.667*                 | 133.086        | 0              |

|       | 2     | -2046.667*                | 133.086        | 0              |
|       | 3     | -1218.333*                | 133.086        | 0              |
|       | 4     | -900.000*                 | 133.086        | 0              |
|       | 5     | -791.667*                 | 133.086        | 0              |
|       | 6     | -495.000*                 | 133.086        | 0.001          |

|       | 3     | -828.333*                 | 133.086        | 0              |
|       | 2     | 1218.333*                 | 133.086        | 0              |
|       | 4     | 318.333*                  | 133.086        | 0.023          |
|       | 5     | 426.667*                  | 133.086        | 0.003          |
|       | 6     | 723.333*                  | 133.086        | 0              |

|       | 4     | -1146.667*                | 133.086        | 0              |
|       | 2     | 900.000*                  | 133.086        | 0              |
|       | 3     | -318.333*                 | 133.086        | 0.023          |
|       | 5     | 108.333*                  | 133.086        | 0.422          |
|       | 6     | 405.000*                  | 133.086        | 0.005          |

|       | 5     | -1255.000*                | 133.086        | 0              |
|       | 2     | 791.667*                  | 133.086        | 0              |
| Table S15 | Original data of cGMP of in each group |
|-----------------|-----------------------------------|
|               | Control | Model | Positive | PRP-H | PRP-M | PRP-L |
| 1              | 59280   | 11820 | 46560    | 39330 | 27340 | 24350 |
| 2              | 84000   | 11050 | 50220    | 37710 | 30680 | 21630 |
| 3              | 87420   | 11280 | 50840    | 38870 | 29500 | 20480 |
| 4              | 91930   | 12310 | 51080    | 39520 | 30460 | 19670 |
| 5              | 94870   | 12490 | 50250    | 40390 | 31420 | 19920 |
| 6              | 97500   | 11550 | 51050    | 37780 | 33600 | 20050 |
| Mea ns         | 85833.33 | 11750 | 50000    | 38933.33 | 30500 | 21016.67 |
| SD             | 13898.92 | 568.683 | 1727.368 | 1044.426 | 2072.486 | 1773.467 |
| Mea ns ±       | 85833.33±13 | 11750±568 | 50000±172 | 38933.33±10 | 30500±207 | 21016.667±17 |
| SD             | 898.92 | .683       | 7.368    | 44.426    | 2.486 | 73.467 |

### Table S15-1 Homogeneity of variance results

| Expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|-------------------------------|-----|-----|--------------|
|                     | 4.765                         | 5   | 30  | 0.003<0.05   |

### Table S15-2 Multiple comparison results

| (I) Grouping | (J) Grouping | The mean difference (I-J) | standard error | significance |
|--------------|--------------|----------------------------|----------------|--------------|
| Tamhane      | 1            | 74083.333*                | 5678.958      | 0.001        |
|              | 3            | 35833.333*                | 5717.864      | 0.02         |
|              | 4            | 46900.000*                | 5690.208      | 0.006        |
|              | 5            | 55333.333*                | 5736.944      | 0.002        |
|              | 6            | 64816.667*                | 5720.215      | 0.001        |
|              | 2            | -74083.333*               | 5678.958      | 0.001        |
|              | 3            | -38250.000*               | 742.428       | 0            |
|              | 4            | -27183.333*               | 485.494       | 0            |
|              | 5            | -18750.000*               | 877.363       | 0            |
|              | 6            | -9266.667*                | 760.327       | 0            |
|              | 1            | -35833.333*               | 5717.864      | 0.02         |
|              | 2            | 38250.000*                | 742.428       | 0            |
|              | 4            | 11066.667*                | 824.078       | 0            |
Table S16 Original data of qRT-PCR of zebrafish in each group

|   | Control | Model | Positive | PRP-H | PRP-M | PRP-L |
|---|---------|-------|----------|-------|-------|-------|
| 1 | 2.15    | 0.558 | 1.394    | 1.169 | 1.269 | 0.886 |
| 2 | 1.808   | 0.323 | 1.513    | 1.235 | 1.176 | 0.891 |
| 3 | 1.985   | 0.21  | 1.68     | 1.544 | 0.659 | 0.999 |
| Means | 1.981 | 0.364 | 1.529    | 1.316 | 1.035 | 0.925 |
| SD  | 0.171   | 0.178 | 0.144    | 0.2   | 0.329 | 0.064 |
| Means ± | 1.981 | ±0.171 | ±0.144 | ±0.200 | ±0.329 | ±0.064 |

Table S16-1 Homogeneity of variance results

| Expression quantity | Levene statistical magnitude | df1 | df2 | significance |
|---------------------|------------------------------|-----|-----|--------------|
|                     |                              | 5   | 30  | 0.15>0.05    |

Table S16-2 Multiple comparison results

| (I) Grouping | (J) Grouping | The mean difference (I-J) | standard error | significance |
|--------------|--------------|----------------------------|----------------|--------------|
| LSD          | 1            | 2                          | 1.620*         | 0.161        | 0            |
|              | 3            | 4                          | .457*          | 0.161        | 0.015        |
|              | 4            | 5                          | .667*          | 0.161        | 0.001        |
|              | 5            | 6                          | .947*          | 0.161        | 0            |
|              | 6            | 1                          | 1.057*         | 0.161        | 0            |

| 2            | 1            | -1.620*                    | 0.161          | 0            |
| 3            | 4            | -1.163*                    | 0.161          | 0            |
| 4            | 5            | -.953*                     | 0.161          | 0            |
| 5            | 6            | -.673*                     | 0.161          | 0.001        |
| 6            | 3            | -.563*                     | 0.161          | 0.004        |
|   |   |   |   |   |
|---|---|---|---|---|
| 3 | 1 | -0.457* | 0.161 | 0.015 |
| 2 | 1.163* | 0.161 | 0 |
| 4 | 0.21 | 0.161 | 0.217 |
| 5 | 0.490* | 0.161 | 0.01 |
| 6 | 0.600* | 0.161 | 0.003 |
| 4 | 1 | -0.667* | 0.161 | 0.001 |
| 2 | 0.953* | 0.161 | 0 |
| 3 | -0.21 | 0.161 | 0.217 |
| 5 | 0.28 | 0.161 | 0.108 |
| 6 | 0.390* | 0.161 | 0.032 |
| 5 | 1 | -0.947* | 0.161 | 0 |
| 2 | 0.673* | 0.161 | 0.001 |
| 3 | -0.490* | 0.161 | 0.01 |
| 4 | -0.28 | 0.161 | 0.108 |
| 6 | 0.11 | 0.161 | 0.507 |
| 6 | 1 | -1.057* | 0.161 | 0 |
| 2 | 0.563* | 0.161 | 0.004 |
| 3 | -0.600* | 0.161 | 0.003 |
| 4 | -0.390* | 0.161 | 0.032 |
| 5 | -0.11 | 0.161 | 0.507 |