Integrative Analysis Revealed Common Genes, Brain Cell-Type and Pathways Between Stiripentol Targets and Risk Genes of Dravet Syndrome and Epilepsy

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Abstract

Stiripentol is an anti-epileptic drug used for treating Dravet syndrome and epilepsy. To explore common molecular mechanism between antiepileptic effect of stiripentol and genetic etiology of Dravet syndrome and epilepsy, we retrieved target genes of stiripentol through DrugBank database, as well as risk genes of Dravet syndrome and epilepsy from related database and literature research. Then we performed genetic overlap analysis, Expression Weighted Cell type Enrichment (EWCE) analysis based on single-cell RNA-seq data of brain, as well as pathway enrichment analysis. A total of 23, 19 and 118 genes were retrieved for stiripentol targets, risk genes of Dravet syndrome and epilepsy respectively. For stiripentol targets and risk genes of Dravet syndrome, three genes (GABRA1, GABRB3 and GABRG2) were overlapped with P-value of $1.265 \times 10^{-6}$; hippocampal CA1 pyramidal cells and interneurons were common brain cell types that were significantly enriched by EWCE; and 10 common pathways were identified. For stiripentol targets and risk genes of epilepsy, five genes (GABRA1, GABRA2, GABRB2, GABRB3, and GABRG2) were overlapped with P-value of $1.963 \times 10^{-7}$; hippocampal CA1 pyramidal cells and interneurons were also common brain cell types that were significantly enriched and 22 common pathways were identified. Our results revealed that stiripentol might exert its anti-epileptic effect by regulating GABA_A receptors on hippocampal CA1 pyramidal cells and interneurons.

Introduction

Stiripentol is an antiepileptic drug with a unique structure, which is currently approved in Europe, Japan, and Canada in combination with clobazam and sodium valproate for treating refractory seizures associated with Dravet syndrome. For Dravet syndrome, the evidence for its efficacy is the strongest. Mostly, adding stiripentol to clobazam and sodium valproate can reduce the frequency and severity of seizures. The small case series also shows the benefits of malignant migratory partial seizures in infancy, super-refractory status epilepticus, and stubborn focal epilepsy, although these diseases require larger prospective studies[1,2].

Epilepsy is a collective term for a group of syndromes caused by abnormal discharges of the nervous system, and can cause varying degrees of damage to behavior, cognition, and memory. Previous studies have shown that epilepsy genetic factors play a major role in the pathogenesis of epilepsy. During these decades, genetic association studies, genome wide association studies, as well as researches using next generation sequencing technology have identified several genetic variations of genes such as sodium channel, potassium channel and GABA_A receptor that were clearly related to a variety of epileptic phenotypes[3]. Similarly, Dravet syndrome is a case in epileptic encephalopathy caused by genetic variation. Dravet syndrome is a severe myoclonic epilepsy characterized by the onset of prolonged febrile and afebrile seizures in infancy, and behavioral, cognitive, and movement disorders appear after approximately 2 years old. Most cases are currently deemed to be caused by pathogenic variants in the sodium channel gene SCN1A, but numerous other genes have also been implicated[4]. Genes that have been recorded to cause DS-like phenotypes include SCN2A, SCN8A, SCN9A, SCN1B, PCDH19, GABRA1, GABRG2, STXBP1, HCN1, CHD2, and KCNA2[5].

As hundreds of risk genes have been identified in both epilepsy and Dravet syndrome, their regulating roles on brain cells were worthy of being explored. As gene expression is heterogeneous among various cell types in brain tissue, a more accurate understanding of transcriptome in a single cell is essential to clarify their role in cellular function and to understand how gene expression promotes beneficial or harmful states[6]. Emerging advances using single-cell RNA sequencing (scRNA-seq) in the central nervous system (CNS) have already begun to provide
exciting molecular insights into the complexity of the brain by identifying novel cellular subtypes based on transcriptional profiles as well as possible disease-relevant mechanisms[7]. By applying knowledge of the cellular taxonomy of the brain from single-cell RNA sequencing, previous researchers have evaluated whether the genomic loci implicated in schizophrenia map onto specific brain cell types[8].

For stiripentol, the molecular and cellular mechanisms of its antiepileptic effect are still not fully understood, therefore, in our research, we explore the molecular mechanism and cellular location of the target genes of stiripentol from a multi-omics perspective and investigate common molecular mechanism between antiepileptic effect of stiripentol and genetic etiology of Dravet syndrome and epilepsy. Our analysis may provide insights for molecular mechanism of anti-epileptic of stiripentol on Dravet syndrome and epilepsy.

Materials And Methods

Identification of stiripentol targets

DrugBank (https://go.drugbank.com/) is a web-based database containing comprehensive molecular information about drugs, their mechanisms of action, interactions and their targets[9]. To obtain target genes of stiripentol, we searched DrugBank database (Version 5.0) with the searching term “stiripentol”, and all types of targets listed with supported publications in stiripentol were collected.

Identification of risk genes of Dravet syndrome and epilepsy

As stiripentol is used for treatment of both Dravet syndrome and epilepsy, we retrieved risk genes of Dravet syndrome and epilepsy respectively. Genes with convincing evidences from both comprehensive literature search and disease-gene related databases (OMIM Database (https://omim.org)[12], DisGeNET Database (http://www.disgenet.org) [13] and MalaCards Database (http://www.malacards.org/) [14]) were considered as risk genes. Therefore, we retrieved Dravet syndrome risk genes from genetic studies or reviews with convincing evidences [5,10,11]; meanwhile, we obtained risk genes of epilepsy identified by both common variants and rare variants, of which common variants are extracted from the largest genome-wide association study currently[15], which included 15,212 individuals with epilepsy and 29,677 controls and identified 16 genome-wide significant loci with P-value<5.0×10⁻⁸. Rare variants were identified by exome-sequencing under the largest sample size with 1165 cases and 3877 controls and their mapped genes were considered as monogenic epilepsy genes[15,16]. These genes also were confirmed by other literature retrieval, DisGeNET database[13] and MalaCards database [14].

Genetic overlap of stiripentol targets with risk genes of Dravet syndrome and epilepsy

To investigate whether there was genetic overlap between stiripentol targets and risk gene of Dravet syndrome and epilepsy, we analyzed the overlap genes between the stiripentol targets and Dravet syndrome genes, and the overlap genes between the stiripentol targets and epilepsy genes, then Fisher’s exact test were performed through R language, using whole human genome (~20,000 genes) as background. P-value < 0.05 was considered as a statistical significance.

Expression Weighted Cell type Enrichment analysis of stiripentol targets, risk genes of Dravet syndrome and epilepsy
To explore whether target genes of stiripentol, risk genes of Dravet syndrome and epilepsy could map on specific brain cell types, we implemented Expression Weighted Cell type Enrichment (EWCE) method, which used single-cell transcriptome dataset to calculate whether the average expression levels of input gene list was significantly stronger than that in randomly generated gene list with the same size as input in each annotated cell type \[17\]. Moreover, we utilized a superset of brain scRNA-seq data from the Karolinska Institutet (KI), which included a total of 9,970 cells annotated with 24 cell types from mouse brain regions of neocortex, hippocampus, hypothalamus, striatum and midbrain, as well as samples enriched for oligodendrocytes, dopaminergic neurons and cortical parvalbuminergic interneurons\[8,18-20\]. Taking into account the existence of species differences, we validated the results in another human single-nucleus RNA sequencing dataset from the Allen Institute for Brain Science (AIBS), which included a total of 4,401 cells with 6 cell types from human mid-temporal cortex\[8\]. Since we used the mouse single-cell transcriptome sequencing data set as the background gene set, we first converted the human stiripentol target genes into mouse gene form, then we perform EWCE to calculate that significance of expression enrichment for stiripentol target genes in each brain cell type with 100,000 permutations and P-value <0.05 and false discovery rate (FDR) <0.2 was considered as significance. R Package EWCE was used to perform the analysis and ggplot2 was used to generate graphs \[21\]. Then common brain cell-type between stiripentol targets and risk genes of Dravet syndrome and epilepsy were obtained.

**Pathway enrichment analysis of stiripentol targets, Dravet syndrome and epilepsy**

We used DAVID (https://david.ncifcrf.gov/) to perform functional enrichment analysis for stiripentol targets, risk genes of Dravet syndrome and epilepsy \[22\], in which GO functional annotation and KEGG annotation were used and Hypergeometric test was performed, with false discovery rate (FDR) < 0.05 as significance. Then common pathways between stiripentol targets and risk genes of Dravet syndrome and epilepsy were obtained.

**Results**

**Identification of stiripentol targets**

After searching in DrugBank, we retrieved a total of 23 target genes for stiripentol, of which 16 were GABA<sub>A</sub> receptor subunits, 2 were lactate dehydrogenase and 5 were Cytochrome P450. The targets of stiripentol were shown in Table 1.

**Identification of risk genes of Dravet syndrome and Epilepsy**

Through literature and database searches, risk genes of Dravet syndrome and epilepsy were obtained, and the results are listed in Supplementary Table 1 and Supplementary Table 2. A total of 19 Dravet syndrome risk genes and 118 epilepsy risk genes have been summarized.

**Genetic overlap of stiripentol targets with risk genes of Dravet syndrome and epilepsy**

Among 23 target genes of stiripentol, there are 3 overlapping genes of GABA<sub>A</sub> receptor subunits between the targets of stiripentol and risk genes of Dravet syndrome, which were \textit{GABRA1}, \textit{GABRB3} and \textit{GABRG2} genes and its Fisher's exact test P-value was \(1.265 \times 10^{-6}\); meanwhile, there were 5 genes of GABA<sub>A</sub> receptor subunits (\textit{GABRA1}, \textit{GABRA2}, \textit{GABRB2}, \textit{GABRB3}, and \textit{GABRG2}) overlapped with 118 risk genes of epilepsy. By Fisher's exact test, the total overlap P-value achieved \(1.963 \times 10^{-7}\).
Common brain cell-type enrichment between stiripentol targets and risk genes of Dravet syndrome and epilepsy

To evaluated whether expressions of stiripentol targets and risk genes of Dravet syndrome and epilepsy were significantly enriched in specific brain cell types, we performed EWCE in mouse brain scRNA-seq of Karolinska Institute (KI) dataset and human brain scRNA-seq of the Allen Institute for Brain Science (AIBS) dataset [8,18-20]. For KI dataset, among 24 cell types, stiripentol target genes, risk genes of Dravet syndrome and epilepsy were significantly enriched in six, three and five brain cell types respectively, with P-value < 0.05 and FDR < 0.2 (Figure1, Supplementary Table 3). Among these significant cell types, hippocampal CA1 pyramidal cells, interneurons, and somatosensory pyramidal cells were common brain cell types that were enriched for stiripentol target genes, risk genes of Dravet syndrome and epilepsy. Besides, striatal medium spiny neurons were also common in stiripentol target genes and risk genes of epilepsy. For AIBS dataset, among 6 cell types, stiripentol target genes, risk genes of Dravet syndrome and epilepsy were all significantly enriched in interneurons (GABAergic) and pyramidal neurons (Glutamatergic), with P-value < 0.05 and FDR < 0.2 (Figure2, Supplementary Table 4).

Common pathways between stiripentol targets and risk genes of Dravet syndrome and epilepsy

By pathway enrichment analysis of target genes of stiripentol, risk genes of Dravet syndrome and epilepsy, a total of 44, 23 and 87 pathways were significantly enriched respectively (Supplementary Table 5-7). Among these pathways, we identified 10 significantly pathways that were common between stiripentol targets and risk genes of Dravet syndrome, which were involved in cellular response to histamine, GABA_A receptor complex, plasma membrane, chloride channel complex, GABA_A receptor activity and extracellular ligand-gated ion channel activity for GO terms, as well as nicotine addiction, GABAergic synapse, morphine addiction and retrograde endocannabinoid signaling for KEGG. Meanwhile, we identified 22 significantly pathways that were common between stiripentol targets and risk genes of epilepsy, which were involved in gamma-aminobutyric acid signaling pathway, ion transmembrane transport, cellular response to histamine, GABAergic synaptic transmission for GO terms, as well as nicotine addiction, GABAergic synapse, morphine addiction, retrograde endocannabinoid signaling and neuroactive ligand-receptor interaction for KEGG (Table2, Supplementary Table 8).

Discussion

Stiripentol, as a novel antiepileptic drug, it was originally used in Dravet syndrome[23]. When stiripentol was used in combination with valproic acid and clobazam, it could significantly reduce the frequency of seizures and the incidence of status epilepticus in patients with Dravet syndrome, and protect the brain nerve injury of the patients[24]. Meanwhile, stiripentol also has efficacy in refractory focal seizures, particularly when combined with carbamazepine, and in super-refractory status epilepticus[2]. However, there is still a lack of research on the antiepileptic mechanism of stiripentol, we carried out an integrated analysis based on bioinformatics methods for providing a better idea for the study of the antiepileptic mechanism of stiripentol.

In our research, we have identified the target genes of stiripentol and the risk genes of Dravet syndrome and epilepsy through literature search and database search. Next, we used the hypergeometric distribution test method to determine the significant overlap between the stiripentol targets and the Dravet risk gene or the epilepsy risk gene. As a result, we observed 5 target genes (GABRA1, GABRA2, GABRB2, GABRB3, and GABRG2) were significantly overlapped with 118 epilepsy risk genes, and 3 target genes (GABRA1, GABRB3 and GABRG2) were significantly overlapped with 19 Dravet syndrome risk genes. Our results suggested stiripentol might exert its anticonvulsant effect by regulating these genes. For epilepsy, previous studies have reported that SNPs on
 were involved in risk of epilepsy. Meanwhile, for rare variants, it was also reported that mutations in GABRA1, GABRA6, GABRB3, GABRG2, and GABRD could cause various forms of epilepsy[28,29]. For Dravet syndrome, GABRA1[30], GABRB3[10], GABRG2[31] gene mutations occupy an important role in its genomic variation. It is the genomic variation of GABA_A receptor caused by various causes that leads to the dysfunction of the GABA_A receptor so that it can not be bind well with GABA ligand and reduce the inhibitory effect. As an agonist of the GABA_A receptor, stiripentol strengthens the inhibitory effect of GABA and plays an antiepileptic mechanism. Quilichini et al also proved this point that stiripentol can increase GABA_A receptor-mediated signal transduction by patch-clamp methodology, which is mainly achieved by increasing the frequency of micro-inhibitory postsynaptic current and prolonging decay-time constant[32].

Brain cell types enrichment analysis from two independent scRNA-seq data of brain cells both demonstrated hippocampal CA1 pyramidal cells and interneurons were common brain cell-type enriched by target genes of stiripentol, risk genes of Dravet syndrome and epilepsy. Increasing evidence showed that epilepsy was due to an imbalance between neuronal excitation and inhibition [33]. The normal function of the cerebral cortex depends on two types of neurons: a) excitatory, pyramidal neurons, using glutamate as their neurotransmitter; b) inhibitory local-circuit interneurons, using GABA as a neurotransmitter[34]. Excitatory pyramidal cells mainly releasing glutamate and inhibitory interneurons mainly releasing GABA work together to maintain the excitability of nerve cells[35]. In our research, by analyzing Dravet syndrome susceptibility genes and epilepsy susceptibility genes, we found that they were both enriched in interneurons and pyramidal cells, which supported that the imbalance of excitation and inhibition played an important role in the pathogenesis of epilepsy from a genetic perspective. In a case-control study, spontaneous excitatory postsynaptic currents(sEPSCs) was found in 42% and 62% of hippocampal CA1 pyramidal cells in the control group and kainate-induced epilepsy group respectively, and the frequency of sEPSCs in the kainate-induced epilepsy group was significantly higher than that in the control group[36]. These findings strongly proved that there was a significant correlation between abnormal discharges of pyramidal neurons in the CA1 region and epilepsy. Of course, interneurons also play an important role in the pathogenesis of epilepsy[37]. As hippocampal CA1 pyramidal cells and interneurons were also significantly enriched by target genes of stiripentol, our results indicated that stiripentol may exert its antiepileptic effect by acting on interneurons or hippocampal CA1 pyramidal cells.

Pathway enrichment analysis also identified that GABA_A receptor activity and multi-substance addiction related pathways were common pathways between stiripentol targets and risk genes of Dravet syndrome and epilepsy. Previous experimental studies have also proved that the GABA_A receptor is linked to nicotine addiction and alcohol addiction, which may involve the mechanism of reward and punishment[38]. GABA_A receptors are heteromeric GABA-gated chloride channels. The transmembrane ion channel is opened pursuant to a stimulus generated by GABA, which allows an influx of chloride ions. This results in a decrease of the depolarizing effects of excitatory input, depressing excitability[39]. Therefore, we imply that stiripentol might exert its antiepileptic mechanism mainly by heightening the inhibitory effect of GABA. Previous study reported that the relative expression levels of two inhibitory neurotransmitter receptors GABRA1 and GABRA2 in CA1 neurons were markedly higher than those in CA3 neurons[40]. The pyramidal cells in the CA1 region of the hippocampus receive 92% of the GABAergic input into the dendrites. GABAergic input mainly comes from local interneurons, which promote the formation of cell aggregates by regulating the activity of pyramidal cells. Local GABAergic interneurons control the firing frequency of pyramidal cells, adjust their spike timing, and synchronize their activities[41]. Based on previous research results and our results, we speculate that the target genes of stiripentol may still function mainly by acting on
pyramidal cells in the hippocampal CA1 area, and this effect may be maintained mainly by binding to GABA_A receptors.

In our study, we explored common molecular mechanism between antiepileptic effect of stiripentol and genetic etiology of Dravet syndrome and epilepsy by systematic data collection and integrative analysis. However, there are still some limitations of our analysis. First, since the number of cells taken in the single-cell data sets accounts for only a small portion of the whole brain tissue, they may not represent all types of brain cells. Second, our results are obtained from public databases based on bioinformatics, which might only reveal underlying mechanisms with currently existing information and needs further experimental validation.

**Conclusions**

Based on our analysis, we identified there were common genes, brain cell-type and pathways between target genes of stiripentol and genetic basis of epilepsy, indicating antiepileptic mechanism of stiripentol may be achieved by acting on the GABA_A receptors in the pyramidal cells of the CA1 region and interneurons.

**Declarations**

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**Author Contributions** The work presented here was carried out in collaboration among all authors. Jing-jun Zhang and Lei Gao conceived and designed the work and helped to coordinate support and funding. Yu-qin Lv analyzed all experimental steps and wrote the manuscript. Yu-zhuang Jiao, Yan-hua Wang and Na Wang rechecked all experimental steps. All authors reviewed and approved the final manuscript.

**Data Availability** Not applicable.

**Compliance with Ethical Standards**

**Disclosure of Potential Conflicts of Interest** The authors declare that they have no potential conflicts of interests.

**Consent to Participate** Not applicable

**Consent for Publication** Not applicable

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Tables

Table1. stiripentol target genes from DrugBank database
| Target  | Gene Name                                                                 | Types of target |
|---------|---------------------------------------------------------------------------|-----------------|
| GABRA1  | Gamma-aminobutyric acid receptor subunit alpha-1                          | Target          |
| GABRA2  | Gamma-aminobutyric acid receptor subunit alpha-2                          | Target          |
| GABRA3  | Gamma-aminobutyric acid receptor subunit alpha-3                          | Target          |
| GABRA4  | Gamma-aminobutyric acid receptor subunit alpha-4                          | Target          |
| GABRA5  | Gamma-aminobutyric acid receptor subunit alpha-5                          | Target          |
| GABRA6  | Gamma-aminobutyric acid receptor subunit alpha-6                          | Target          |
| GABRB1  | Gamma-aminobutyric acid receptor subunit beta-1                           | Target          |
| GABRB2  | Gamma-aminobutyric acid receptor subunit beta-3                           | Target          |
| GABRB3  | Gamma-aminobutyric acid receptor subunit beta-3                           | Target          |
| GABRD   | Gamma-aminobutyric acid receptor subunit delta                             | Target          |
| GABRE   | Gamma-aminobutyric acid receptor subunit epsilon                          | Target          |
| GABRG1  | Gamma-aminobutyric acid receptor subunit gamma-1                          | Target          |
| GABRG2  | Gamma-aminobutyric acid receptor subunit gamma-2                          | Target          |
| GABRG3  | Gamma-aminobutyric acid receptor subunit gamma-3                          | Target          |
| GABRP   | Gamma-aminobutyric acid receptor subunit pi                              | Target          |
| GABRQ   | Gamma-aminobutyric acid receptor subunit theta                            | Target          |
| LDHA    | L-lactate dehydrogenase A chain                                           | Target          |
| LDHB    | L-lactate dehydrogenase B chain                                           | Target          |
| CYP2C19 | Cytochrome P450 2C19                                                      | Enzyme          |
| CYP2D6  | Cytochrome P450 2D6                                                       | Enzyme          |
| CYP3A4  | Cytochrome P450 3A4                                                       | Enzyme          |
| CYP1A2  | Cytochrome P450 1A2                                                       | Enzyme          |
| CYP2C9  | Cytochrome P450 2C9                                                       | Enzyme          |

Table 2: Common pathways between stiripentol targets and risk genes of Dravet syndrome and epilepsy
| Category       | Term                                                                 | stiripentol targets | risk genes of Dravet syndrome | risk genes of epilepsy |
|---------------|----------------------------------------------------------------------|---------------------|------------------------------|------------------------|
|               |                                                                      | P-value             | P-value                      | P-value                |
|               |                                                                      | FDR                 | FDR                          | FDR                    |
| GOTERM_BP_DIRECT | G0:0007214~gamma-aminobutyric acid signaling pathway               | 8.39E-22            | 1.44E-05                     | 2.10E-03               |
|               |                                                                      | 9.11E-19            | 6.08E-04                     | 1.19E-03               |
| GOTERM_BP_DIRECT | G0:0034220~ion transmembrane transport                            | 5.57E-16            | 1.95E-06                     | 1.10E-03               |
|               |                                                                      | 6.00E-13            | 1.18E-04                     | 2.82E-05               |
| GOTERM_BP_DIRECT | G0:0071420~cellular response to histamine                        | 1.54E-10            | 2.69E-05                     | 5.17E-16               |
|               |                                                                      | 1.67E-07            | 5.46E-04                     | 2.74E-04               |
| GOTERM_BP_DIRECT | G0:0006810~transport                                               | 2.50E-10            | 1.75E-05                     | 5.46E-04               |
|               |                                                                      | 2.71E-07            | 7.07E-04                     | 1.01E-03               |
| GOTERM_BP_DIRECT | G0:0006811~ion transport                                           | 2.05E-05            | 2.05E-07                     | 2.82E-05               |
|               |                                                                      | 2.23E-02            | 1.10E-03                     | 1.01E-03               |
| GOTERM_BP_DIRECT | G0:0051932~synaptic transmission, GABAergic                      | 3.43E-05            | 1.92E-40                     | 3.72E-02               |
|               |                                                                      | 3.72E-02            | 1.66E-37                     | 1.24E-04               |
| GOTERM_CC_DIRECT | G0:1902711~GABA-A receptor complex                                 | 1.92E-40            | 1.24E-04                     | 4.45E-06               |
|               |                                                                      | 1.66E-37            | 2.48E-03                     | 9.35E-05               |
| GOTERM_CC_DIRECT | G0:0034707~chloride channel complex                                | 4.29E-35            | 4.29E-35                     | 2.65E-04               |
|               |                                                                      | 3.72E-32            | 3.72E-04                     | 2.78E-03               |
| G0:0045211~postsynaptic membrane                              | 8.61E-25            | 8.61E-25                     | 8.96E-10               |
|               |                                                                      | 7.45E-22            | 1.50E-07                     | 4.27E-07               |
| GOTERM_CC_DIRECT | G0:0030054~cell junction                                          | 1.19E-19            | 1.19E-19                     | 5.09E-09               |
|               |                                                                      | 1.03E-16            | 5.09E-09                     | 4.27E-07               |
| GOTERM_CC_DIRECT | G0:0045202~synapse                                                | 2.30E-11            | 2.30E-11                     | 2.07E-05               |
|               |                                                                      | 1.99E-08            | 2.07E-05                     | 3.86E-04               |
| GOTERM_CC_DIRECT | G0:0005887~integral component of plasma membrane                  | 2.10E-06            | 2.10E-06                     | 2.15E-04               |
|               |                                                                      | 1.82E-03            | 2.15E-04                     | 2.41E-03               |
| GOTERM_CC_DIRECT | G0:0016021~integral component of membrane                          | 1.99E-05            | 1.99E-05                     | 4.93E-05               |
|               |                                                                      | 1.72E-02            | 4.93E-05                     | 6.91E-04               |
| GOTERM_CC_DIRECT | G0:0005886~plasma membrane                                         | 4.38E-05            | 4.38E-05                     | 2.57E-07               |
|               |                                                                      | 3.79E-02            | 2.57E-07                     | 7.21E-06               |
| GOTERM_MF_DIRECT | G0:0004890~GABA-A receptor activity                               | 3.37E-43            | 3.37E-43                     | 6.36E-06               |
|               |                                                                      | 3.22E-40            | 3.22E-40                     | 4.55E-04               |
| GOTERM_MF_DIRECT | G0:0005230~extracellular ligand-gated ion channel activity         | 8.97E-38            | 8.97E-38                     | 1.63E-09               |
|               |                                                                      | 8.56E-35            | 8.56E-35                     | 3.63E-07               |
| GOTERM_MF_DIRECT | G0:0022851~GABA-gated chloride ion channel activity                | 1.08E-11            | 1.08E-11                     | 4.23E-04               |
|               |                                                                      | 1.03E-08            | 1.03E-08                     | 1.16E-02               |
| KEGG_PATHWAY  | hsa05033:Nicotine addiction                                        | 2.43E-30            | 2.43E-30                     | 2.43E-04               |
|               |                                                                      | 1.90E-27            | 1.90E-27                     | 1.16E-02               |
|               |                                                                      | 6.80E-04            | 8.84E-04                     | 8.87E-12               |
