Genetic overlap between type 2 diabetes and major depressive disorder identified by bioinformatics analysis

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ABSTRACT

Our study investigated the shared genetic etiology underlying type 2 diabetes (T2D) and major depressive disorder (MDD) by analyzing large-scale genome wide association studies statistics. A total of 496 shared SNPs associated with both T2D and MDD were identified at \( p \)-value \( \leq 1.0 \times 10^{-07} \). Functional enrichment analysis showed that the enriched pathways pertained to immune responses (Fc gamma R-mediated phagocytosis, T cell and B cell receptors signaling), cell signaling (MAPK, Wnt signaling), lipid metabolism, and cancer associated pathways. The findings will have potential implications for future interventional studies of the two diseases.

INTRODUCTION

Type 2 diabetes (T2D) and depression are prevalent chronic diseases and have been serious public health burdens around the world. The comorbidity between T2D and depression is proven by a series of epidemiological evidence [1-3]. Many studies indicate that the associations between T2D and depression are bidirectional and the presence of T2D increases the risk of depression, and vice versa [4-6].

Despite improved understanding of shared origins of T2D and depression has been gained in recent years [7-10], more effort is needed to identify the shared genetic etiology underlying the two diseases. A wealth of large-scale genome wide association studies (GWAS) about T2D and major depressive disorder (MDD) have been produced in the past few years. These GWAS data provide opportunity to investigate the shared genetic etiology of the two diseases. In this study, we performed a bioinformatics analysis on single nucleotide polymorphisms (SNPs) for T2D and MDD on the basis of GWAS meta-analysis data. The overlapped SNPs for T2D and MDD were identified and functional enrichment analysis was then performed. The findings will benefit future mechanistic and interventional studies for both diseases.

RESULTS

During the identification of SNPs that are associated with MDD or T2D on the basis of independent DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) or Psychiatric Genomics Consortium meta-GWAS statistics, multiple GWAS genetic association \( p \)-values ranging from \( 1.0 \times 10^{-10} \) to \( 1.0 \times 10^{-06} \) were set as cutoff criteria. The results were shown in Table 1. It can be seen that when setting at \( p \)-value of \( 1.0 \times 10^{-06} \) as cutoff criteria, the number of identified SNPs is comparable. With improved \( p \)-values, the number of identified SNPs associated with T2D is significantly larger than MDD as shown in Table 1. Using \( p \)-value threshold at \( 1.0 \times 10^{-10} \), we identified 2496 and 64 SNPs associated with T2D and MDD, respectively (Table 1).

Through overlapping the identified SNPs associated with T2D or MDD, we obtained the number of overlapped SNPs associated with both diseases with different \( p \)-values as cutoff criteria. As shown in Table 1, when setting the threshold at \( p \)-value \( \leq 1.0 \times 10^{-09} \) and \( \leq 1.0 \times 10^{-08} \), there were 1 and 10 overlapped SNPs between T2D and MDD, respectively. When setting the threshold at \( p \)-value \( \leq 1.0 \times 10^{-07} \), 496 SNPs were identified to be associated with both diseases, which was significantly larger than random chance (overlapped \( p \)-value of \( 5.32 \times 10^{-08} \) and odds ratio = 1.08).

Among the overlapped 496 SNPs, there were 216 SNPs with annotated genes. The functional enrichment
Table 1: Number of SNPs associated with T2D or MDD and overlapped SNPs associated with both diseases with different p-values as cutoff criteria

| P-value threshold | Number of SNPs | Number of overlapped SNPs |
|-------------------|----------------|--------------------------|
|                   | T2D       | MDD         |                     |
| 1.0E-10           | 2496      | 64          | 0                    |
| 1.0E-09           | 4445      | 505         | 1                    |
| 1.0E-08           | 11280     | 3943        | 10                   |
| 1.0E-07           | 42271     | 27410       | 496                  |
| 1.0E-06           | 127905    | 123041      | 3966                 |

**DISCUSSION**

Based on the available meta-GWAS statistic for T2D and MDD, we performed a bioinformatics analysis to explore the shared genetic etiology underlying the two diseases. When setting the threshold at \( p \)-value \( \leq 1.0E-07 \), 496 overlapped SNPs were identified to be associated with both T2D and MDD. Further functional enrichment analysis observed 61 KEGG pathways, including immune responses (Fc gamma R-mediated phagocytosis, T cell and B cell receptors signaling), cell signaling (MAPK, Wnt signaling), lipid metabolism, as well as several cancer associated pathways.

The findings gained supports from previous studies. First, abnormality in the immune and inflammation systems has been reported to be involved in the pathogenesis of both T2D and MDD [11-15]. Several pathways, including Fc gamma R-mediated phagocytosis, T cell and B cell receptors signaling, have been observed (Table 2). Oxidative stress caused by excessive reactive oxygen species (ROS) contribute to the pathogenesis of T2D and MDD. As crucial secondary messengers in signal transduction, ROS may also exert significant effect on inflammatory pathways through MAPK activation [16, 17]. Wnt signal has also been implicated in the development of both T2D and MDD [18-20] In addition, several cancer associated pathways have been found, which may arise from the epidemiologically observed close relationships between diabetes or depression and many types of cancer [21-23].

There are some limitations in our study. First, the functional enrichment analysis of the shared genes of T2D and MDD is based on the accuracy and completeness of KEGG database. Thus, some genes possessing impacts on both diseases but not annotated in KEGG databases are not included. Second, although we employed two most comprehensive large-scale meta-GWAS statistics for T2D and MDD respectively, other GWAS not considered may potentially affect the results.

In summary, through bioinformatics analysis of two most comprehensive large-scale meta-GWAS statistic of T2D and MDD, we identified the overlapped SNPs and performed functional enrichment pathway of the annotated genes. The findings tentatively support the disease concordance between T2D and MDD indicated by epidemiological studies, and also have potential implications for future therapeutic strategies for the two diseases.

**MATERIALS AND METHODS**

The identification of SNPs associated with T2D risk was based on the meta-GWAS statistics from the DIAGRAM consortium study, which was generated from a meta-analysis study covering 34,840 cases and 114,981 controls, overwhelmingly of European descent [24]. These T2D statistics provide more than 2 million SNPs on the basis of the calculation using HapMap project. The identification of SNPs associated with MDD was based on the meta-GWAS statistics from the Psychiatric Genomics Consortium study, the largest and most comprehensively genome-wide analysis of MDD yet conducted [25]. This study investigated more than 1.2 million autosomal and X chromosome SNPs in 18759 independent and unrelated subjects of recent European ancestry (9240 MDD cases and 9519 controls) in the MDD discovery phase. In the MDD replication phase, this study also evaluated 554 SNPs in independent 6,783 MDD cases and 50,695 controls [25].
### Table 2: Overlapped pathways identified in T2D and MDD.

| Term                                         | Total pathway size | Number of genes modulated by overlapped sNPs | Benjamini-corrected $p$-value | Genes                      |
|----------------------------------------------|--------------------|---------------------------------------------|------------------------------|-----------------------------|
| ECM-receptor interaction                     | 2                  | 2                                           | 1.36E-05                     | HSPG2, COL4A2               |
| Glycerolipid metabolism                      | 8                  | 3                                           | 5.46E-05                     | PPAP2B, DGKB, LIPC          |
| Glycerophospholipid metabolism               | 8                  | 3                                           | 5.46E-05                     | PPAP2B, DGKB, ACHE          |
| Ether lipid metabolism                        | 2                  | 1                                           | 1.36E-05                     | PPAP2B                      |
| Sphingolipid metabolism                      | 2                  | 1                                           | 1.36E-05                     | PPAP2B                      |
| Fe gamma R-mediated phagocytosis             | 3                  | 2                                           | 2.05E-05                     | PPAP2B, DNM3                |
| Cytokine-cytokine receptor interaction       | 4                  | 4                                           | 2.73E-05                     | LEPR, TGBF2, IL2RA, CCL11   |
| Neuroactive ligand-receptor interaction      | 6                  | 6                                           | 4.09E-05                     | LEPR, PTGER3, GABRB1, GRM8, LPAR2, GRIK1 |
| Jak-STAT signaling pathway                   | 3                  | 3                                           | 2.05E-05                     | LEPR, SPRED2, IL2RA         |
| Adipocytokine signaling pathway              | 2                  | 2                                           | 1.36E-05                     | LEPR, PPARGC1A              |
| Calcium signaling pathway                    | 5                  | 4                                           | 3.41E-05                     | PTGER3, SLC8A1, CACNA1C, ITPR2 |
| Cell adhesion molecules                      | 3                  | 2                                           | 2.05E-05                     | NEGR1, CNTN1                |
| Wnt signaling pathway                        | 7                  | 6                                           | 4.77E-05                     | VANGL1, PRICKLE2, CTBP2, SMAD3, IGF1, FGF14, NFATC2 |
| Dorso-ventral axis formation                 | 2                  | 2                                           | 1.36E-05                     | NOTCH2, EV6                 |
| Notch signaling pathway                      | 2                  | 2                                           | 1.36E-05                     | NOTCH2, CTBP2               |
| Endocytosis                                  | 4                  | 4                                           | 2.73E-05                     | DNMT3, IL2RA, USP8, GIT1    |
| MAPK signaling pathway                       | 6                  | 6                                           | 4.09E-05                     | TGFB2, MRAS, MAP4K2, CACNA1C, FGF14, NFATC2 |
| Cell cycle                                   | 5                  | 3                                           | 3.41E-05                     | TGFB2, E2F3, SMAD3          |
| TGF-beta signaling pathway                   | 3                  | 2                                           | 2.05E-05                     | TGFB2, SMAD3                |
| Pathways in cancer                           | 11                 | 9                                           | 7.5E-05                      | TGFB2, PPARG, E2F3, CTBP2, IGF1, FGF14, COL4A2, SMAD3, DCC |
| Colorectal cancer                            | 4                  | 3                                           | 2.73E-05                     | TGFB2, SMAD3, DCC           |
| Pancreatic cancer                            | 5                  | 3                                           | 3.41E-05                     | TGFB2, E2F3, SMAD3          |
| Chronic myeloid leukemia                     | 6                  | 4                                           | 4.09E-05                     | TGFB2, E2F3, CTBP2, SMAD3   |
| Hypertrophic cardiomyopathy                  | 7                  | 6                                           | 4.77E-05                     | TGFB2, SLC8A1, TTN, ACTB, CACNA1C, IGF1 |
| Dilated cardiomyopathy                       | 7                  | 6                                           | 4.77E-05                     | TGFB2, SLC8A1, TTN, ACTB, CACNA1C, IGF1 |
| O-Glycan biosynthesis                        | 2                  | 2                                           | 1.36E-05                     | GALNT2, C1GALT1             |
| Cardiac muscle contraction                   | 3                  | 2                                           | 2.05E-05                     | SLC8A1, CACNA1C             |
| Arrhythmogenic right ventricular cardiomyopathy | 5                 | 4                                           | 3.41E-05                     | SLC8A1, ACTB, CACNA1C, PKP2 |
| Ubiquitin mediated proteolysis               | 2                  | 2                                           | 1.36E-05                     | FANCL, UBE2R2               |
| PPAR signaling pathway                       | 2                  | 2                                           | 1.36E-05                     | PPARG, EHHAHD               |
| Huntington's disease                         | 5                  | 4                                           | 3.41E-05                     | PPARG, DNAH1, PPARGC1A, CREB5 |
| Valine, leucine and isoleucine biosynthesis  | 2                  | 2                                           | 1.36E-05                     | LARS2, EHHAHD               |
| Aminoacyl-tRNA biosynthesis                  | 2                  | 2                                           | 1.36E-05                     | LARS2, CARS                 |
| Axon guidance                                | 6                  | 6                                           | 4.09E-05                     | ROBO2, UNC5C, ABLIM1, NFATC3, DCC, NFATC2 |
| Tight junction                               | 3                  | 3                                           | 2.05E-05                     | MRAS, ACTB, SYMPK           |
| Regulation of actin cytoskeleton             | 4                  | 4                                           | 2.73E-05                     | MRAS, ACTB, FGF14, GIT1     |
| Insulin signaling pathway                    | 2                  | 2                                           | 1.36E-05                     | PPARGC1A, GCK               |
To identify SNPs significantly associated with diseases, multiple cutoff p-value criteria were employed. SNPs identified by GWAS were compared to identify overlapped SNPs between T2D and MDD. As we know, for a given complex diseases, such as T2D and MDD, individual genetic variants may interpret only a very small amount of genetic risk. Thus, with the aim to more comprehensively identify SNPs with small effect sizes, a “relaxed” cutoff genetic association p-value of 1.0E-07 was employed as a criterion for identifying SNPs that are associated with risk for both T2D and MDD.

The location and mapped genes of each shared SNPs for T2D and MDD were obtained via the Single-Nucleotide Polymorphism database (dbSNP) at the National Center for Biotechnology Information (NCBI). Functional enrichment analysis of obtained genes was performed by the DAVID v6.7 [26] to perform KEGG pathway and GO term enrichment analysis. The significance of pathway was calculated by statistical method of hypergeometric distribution, and P-value of 0.05 was set as the threshold of significance. Significant pathways and GO terms identified in enrichment analysis were compared between T2D and MDD to investigate shared pathways of these two disorders.

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**CONFLICTS OF INTEREST**

The authors declared no potential conflicts of interest.

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