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ORIGINAL PAPER

Network Analysis of Depression-Related Transcriptomic Profiles

Xiao Miao[1,2] · Bin Fan[1] · Rongqun Li[3] · Shaoping Zhang[2] · Honghuang Lin[4] · for the Alzheimer's Disease Neuroimaging Initiative

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Abstract

Major depressive disorder is a common debilitating disorder that is associated with increased morbidity and mortality. However, the molecular mechanism underlying depression remains largely unknown. The current study investigated the association of depression with blood gene expression using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Depression was measured by the geriatric depression scale, and the blood gene expression was measured by the Affymetrix Human Genome U219 Array. Linear regression was used to test the association between gene expression and depression, and the model was adjusted for age and sex. A total of 671 participants were included in our study (mean age 75 ± 8 years, 43.2% women). We found three genes were associated with depression, including *COL1A2* ($P = 8.9 \times 10^{-8}$), *RNF150* ($P = 1.4 \times 10^{-7}$) and *CTGF* ($P = 8.3 \times 10^{-7}$). An interaction network was built, and the pathway analysis indicated that many depression-related genes were involved in the neurotrophin signaling pathway ($P = 2.1 \times 10^{-7}$). Future studies are necessary to validate our findings and further investigate potential mechanism of depression.

Keywords Depression · Interaction network · Gene expression

Introduction

Major depressive disorder (MDD) is a common debilitating disorder with a lifetime prevalence rate of 6–30% (Waraich et al. 2004; Kessler et al. 2005; Wilhelm et al. 2003). The disease could seriously affect the quality of life (Wells et al. 1989) and result in numerous days lost from work (Broadhead et al. 1990; Lopez and Murray 1998; Craddock and Forty 2006). It is also associated with an increased mortality (Berglund and Nilsson 1987) and suicide rate (Cavanagh et al. 2003). The disease causes $43.7 billion in US alone (Greenberg et al. 1993). Therefore, a better understanding of depression is essential to the prevention and the treatment of the disease.

Xiao Miao and Bin Fan have contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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✉ Xiao Miao
0000002623@shutcm.edu.cn

✉ Honghuang Lin
hhlin@bu.edu

[1] Department of Dermatology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, 1200 Cailun Road, Pudong, Shanghai 201210, China

[2] Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

[3] College of Basic Medical Science, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

[4] Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, 72 East Concord Street, B-616, Boston, MA 02118, USA

Despite of high prevalence, the etiology of the disease is still poorly understood. The disease has been observed with high familial aggregation (Sullivan et al. 2000; Kendler et al. 2005) and women have twice of risk than men (Weissman et al. 1993; Kendler et al. 1993). An affected sibling would increase the risk of MDD by threefold to ninefold (Farmer et al. 2000; Sullivan et al. 2000). Family and twin studies estimated a heritability of depression ranging from 17 to 75% (McGuffin et al. 1996; Craddock and Forty 2006; Sullivan et al. 2000). However, genome-wide association studies and candidate gene association studies only found a handful candidate genetic loci (Lopez-Leon et al. 2008; Boomsma et al. 2008; Muglia et al. 2010; Sullivan et al. 2009; Shi et al. 2011; Shyn et al. 2011; Lewis et al. 2010). Another reason might due to the interplay between genetic and environmental factors in the development of depression. Given that gene expression is regulated by both genetic and environmental factors, it is of interest to examine the association of gene expression with depression.

The objective of this study is to perform transcriptome-wide association study and identify gene expression associated with depression. We further built a gene interaction network to investigate potential gene regulation underlying depression.

Materials and Methods

Study Samples

Participants were enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal study of Alzheimer's disease launched in 2003 (Petersen et al. 2010). More than 1500 participants have been recruited and followed up regularly. The primary goal of ADNI is to test whether serial magnetic resonance imaging, positron emission tomography, clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. All participants provided written consent, and the institutional review boards of all participating approved the study protocol.

Measurement of Depression

The Geriatric Depression Scale (GDS) is a quantitative measure of symptoms of depression in the elderly (Marc et al. 2008). Participants were asked to answer "Yes" or "No" to 15 questions. Each question had a score of 1. The total score was used as the measurement of depression. A higher score represents a higher possibility of depression. The current study was restricted to tests that were performed within 6 months when the blood was collected for gene expression profiling. All the data were obtained from the ADNI database (adni.loni.usc.edu).

Gene Expression Profiling

Details about gene expression profiling in ADNI have been described previously (Saykin et al. 2015). In brief, the whole blood samples were collected using Qiagen PAXgene tubes (Germantown, MD, USA). Total RNA was extracted using Qiagen QIAcube according to the manufacturer's protocol. The RNA expression was profiled by Affymetrix Human Genome U219 Array (Affymetrix Inc, Santa Clara, CA) at the Bristol-Myers Squibb laboratories. Stringent quality controls were performed. Sixty-four samples were excluded from further processing because of inferior quality. The raw signal was processed using Robust Multi-chip Average (RMA), and the expression of 49,386 transcripts was summarized. Additional quality checks were performed to verify sample identity and sex match. Samples of non-European ancestry were excluded. Five pairs of samples were found as first-degree relatives and thus only one sample in each pair was kept.

Statistical Analyses

The association of gene expression with GDS was assessed by linear regression, whereas gene expression was treated as the outcome, and GDS was treated as the predictor. The model was adjusted for age and sex. Bonferroni correction was used to account for multiple testing, and the significance cutoff was defined as $P < 0.05/N$, where N is the total number of genes. The analyses were performed using R software package version 3.4.2 (https://www.r-project.org/).

Construction of GDS-Related Interaction Network

A dense module searching strategy (Jia et al. 2011) was employed to construct a depression-related interaction network. Gene interactions were obtained from the PINA database v2.0 (Cowley et al. 2012). Any interactions involved in a non-human gene were excluded. A score was assigned to each gene to indicate its association with GDS. The score was equivalent to the absolute value of Wald test statistic from the association test. Seed genes were defined as those that were significantly associated with GDS. For each of the seed genes, a module was created that initially contained only the gene itself. The overall score (Ideker et al. 2002) of the module is defined as $Z_{\mathrm{m}} = \frac{\sum g_i}{\sqrt{k}}$, where k is the number of genes in the module, and g_i is the score of the gene i. Neighboring genes were then sequentially added if (1) it interacts directly with at least one gene already in the module; (2) it could increase the overall score of the module. The

searching of neighboring genes continued until no more significant genes could be added. We repeated such process for each of the seed genes and merged all the resulting modules together to build an interaction subnetwork. Potential function of the subnetwork was assessed by the enrichment analysis using WebGestalt (Wang et al. 2013). Gene sets with false discovery rate less than 5% were considered as significant (Miao et al. 2018).

Identification of Key Drivers of the Network

Some genes in the network are connected to more GDS-related genes than expected from a randomly selected gene set with an equal number of genes. These genes were defined as key drivers, and they were pivotal to the structure of the network. In order to identify key drivers, for each gene in the network, we calculated the association of its neighboring genes with GDS. The Kolmogorov–Smirnov test was used to assess the deviation of the associations from random distribution. Bonferroni adjustment was used to correct for multiple testing.

Results

The clinical characteristics of study participants are shown in Table 1. A total of 671 participants who had gene expression profiles and GDS measures were included. Most of participants were old (mean age 75 ± 8 years), and 43.2% were women. The distribution of GDS among all participants is shown in Supplemental Fig. 1. The majority had GDS scores less than 5. Only four participants had GDS scores higher than 10.

Table 1 Clinical characteristics of participants

Characteristics	(n = 671)
Women, n (%)	290 (43.2%)
Age, years	75 ± 8
Education, number of school years	16 ± 3
APOE e4 carrier, n (%)	269 (40.1%)
Cognitive status	
Clinical normal (%)	236 (35.2%)
Mild cognitive impairment (%)	394 (58.7%)
Alzheimer's disease (%)	41 (6.1%)
Marriage status	
Married (%)	517 (77.0%)
Widowed (%)	77 (11.5%)
Divorced (%)	59 (8.8%)
Never married (%)	16 (2.4%)
NA (%)	2 (0.3%)

Association of Gene Expression with GDS

Figure 1 is the volcano plot showing the association of 49,386 genes with GDS. After correction for multiple testing, three genes reached the Bonferroni significance ($P < 1.0 \times 10^{-6}$), including *COL1A2* ($P = 8.9 \times 10^{-8}$), *RNF150* ($P = 1.4 \times 10^{-7}$) and *CTGF* ($P = 8.3 \times 10^{-7}$). Table 2 shows the association of these genes with GDS. All of them had positive beta values, suggesting the increased expression was associated with increased GDS scores. We also examined the expression of these genes in brain and blood tissues using data from the GTEx database (GTEx Consortium 2015). As shown in Supplemental Fig. 2, all of them tended to express higher in brain than in blood.

In our sensitivity analysis, we additionally adjusted the model for psychiatric and neurologic medications. As shown in Supplemental Table 1, the association of three

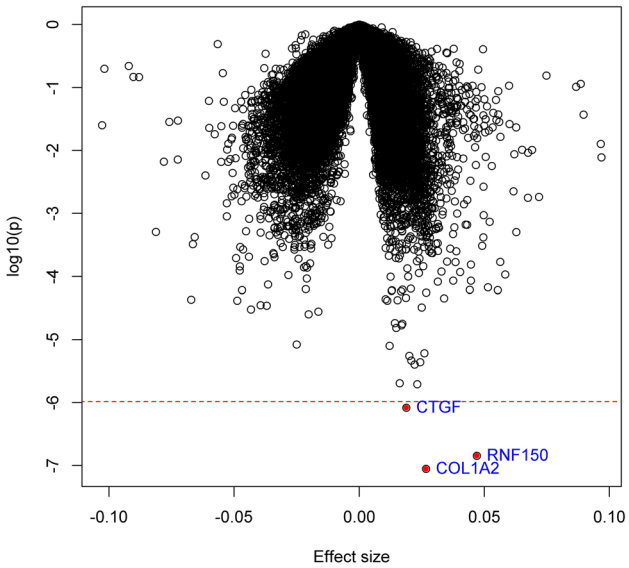

Fig. 1 Volcano plot of genes associated with GDS. Each dot represents one gene. The x-axis represents the beta estimation (β) of each gene, whereas the y-axis represents the $\log_{10}(P)$. Positive effects represent that genes were positively associated with GDS, whereas negative effects represent that the genes were negatively associated with GDS. The red dash line represents the significant cutoff ($P < 1.0 \times 10^{-6}$). Three genes that reached significance cutoff were highlighted

Table 2 Genes significantly associated with GDS ($P < 0.05/48{,}157 = 1.0 \times 10^{-6}$)

Affymetrix ID	Gene	Beta	SE	P value
11715353_s_at	COL1A2	0.027	0.005	8.9E−08
11730677_a_at	RNF150	0.047	0.009	1.4E−07
11715440_a_at	CTGF	0.019	0.004	8.3E−07

SE standard error

genes remained significant although slightly attenuated. Similar pattern was also observed for the adjustment of adverse events.

GDS-Related Interaction Network

Many GDS-related genes could interact with each other to form a complex interaction network. We thus built an interaction network by integrating known gene interactions. As shown in Fig. 2, the subnetwork is comprised of 88 nodes and 122 edges, whereas each node represents one gene, and each edge represents the interaction between two genes. We further performed pathway analysis to examine potential function of the interaction network. Table 3 shows the top enriched biologic pathways. Neurotrophin signaling pathway was one of the top pathways enriched with GDS-related genes ($P = 2.1 \times 10^{-7}$).

Key Drivers of Depression-Related Network

We also performed key driver analysis by examining the structure of the depression-related network. These genes could be potential targets for further functional characterization. The most significant key driver was *SMAD3*. The gene was only moderately associated with GDS ($P = 1.6 \times 10^{-3}$) but did not reach the transcriptome-wide significance cutoff. However, it was connected with ten other genes, many of which were associated with GDS, which was much higher than what would be expected from the random distribution ($P = 7.8 \times 10^{-8}$ by the Kolmogorov–Smirnov test), suggesting that *SMAD3* might be involved in the regulation of depression-related genes.

Discussion

Depression is a complex condition, and the etiology is still poorly understood. Our current study aims to examine the association of blood gene expression with GDS, which is a

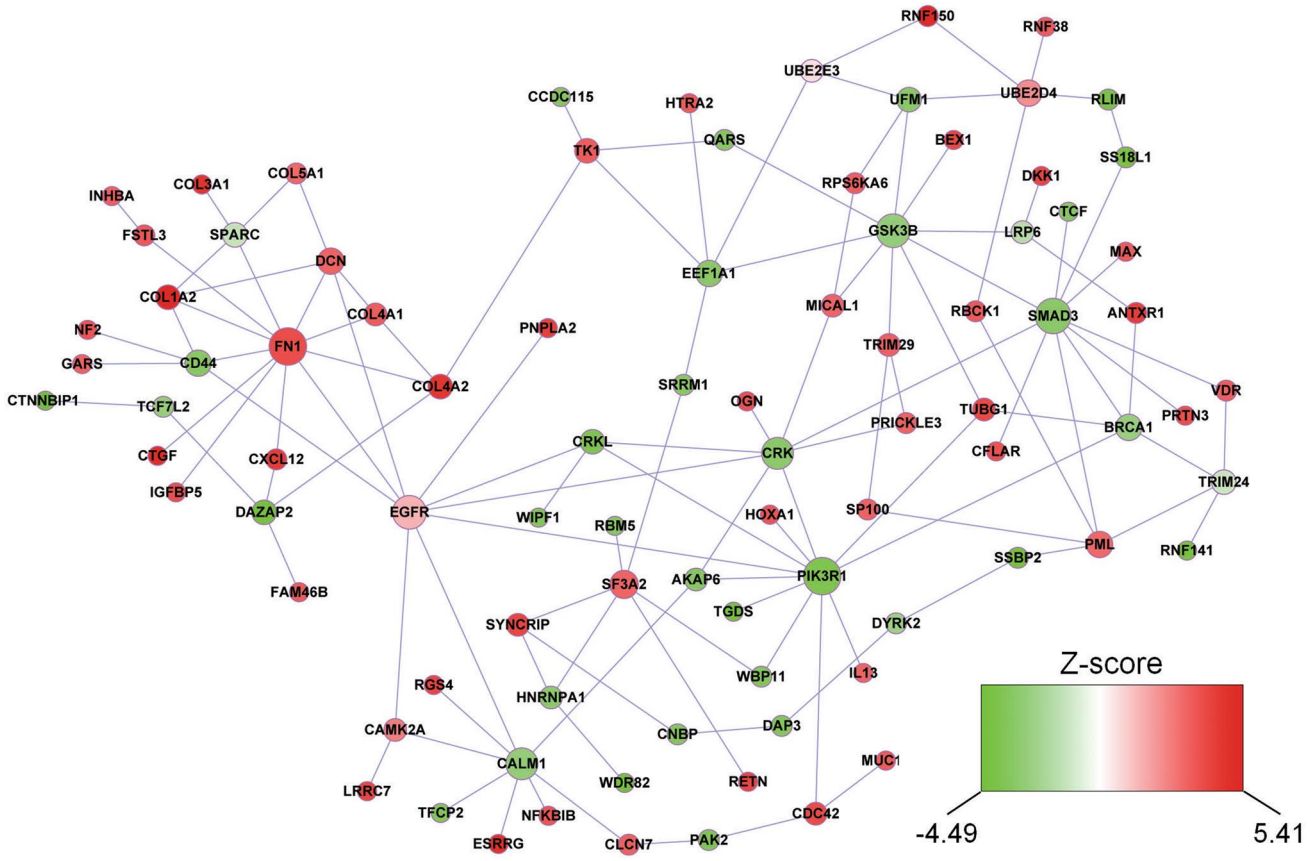

Fig. 2 Gene interaction network associated with depression derived from protein–protein interaction. Each node represents one gene, whereas each edge represents the interaction between two genes. The nodes were colored to represent their association with depression: red color represents genes that were positively associated with depression, whereas green color represents genes that were negatively associated with depression. The node size is proportional to the number of edges that the node connects to

Table 3 Top 10 biological pathways enriched with genes associated with GDS

KEGG pathway	#Genes in pathway	Ratio of enrichment	*P* value	False discovery rate	GDS-related genes in the pathway
Focal adhesion	203	7.27	2.0*E*−07	3.1*E*−05	COL1A2, COL4A1, COL4A2, CRK, CRKL, EGFR, FN1, GSK3B, PAK2, PIK3R1, CDC42
Neurotrophin signaling pathway	121	9.98	2.1*E*−07	3.1*E*−05	CRK, CRKL, RPS6KA6, GSK3B, NFKBIB, PIK3R1, CALM1, CAMK2A, CDC42
AGE-RAGE signaling pathway in diabetic complications	101	10.63	6.5*E*−07	5.4*E*−05	COL1A2, COL3A1, COL4A1, COL4A2, FN1, SMAD3, PIK3R1, CDC42
Pathways in cancer	397	4.73	7.2*E*−07	5.4*E*−05	COL4A1, COL4A2, CRK, CRKL, EGFR, FN1, GSK3B, SMAD3, MAX, PIK3R1, PML, CXCL12, TCF7L2, CDC42
ErbB signaling pathway	88	10.68	3.4*E*−06	2.0*E*−04	CRK, CRKL, EGFR, GSK3B, PAK2, PIK3R1, CAMK2A
Wnt signaling pathway	143	6.57	8.1*E*−05	3.9*E*−03	DKK1, GSK3B, LRP6, SMAD3, CTNNBIP1, TCF7L2, CAMK2A
Amoebiasis	100	8.05	8.9*E*−05	3.9*E*−03	COL1A2, COL3A1, COL4A1, COL4A2, FN1, PIK3R1
Shigellosis	65	10.32	1.1*E*−04	4.2*E*−03	CRK, CRKL, NFKBIB, CD44, CDC42
Renal cell carcinoma	67	10.02	1.3*E*−04	4.3*E*−03	CRK, CRKL, PAK2, PIK3R1, CDC42
Bacterial invasion of epithelial cells	78	8.60	2.6*E*−04	8.0*E*−03	CRK, CRKL, FN1, PIK3R1, CDC42

quantitative measure of depression. We found three genes were significantly associated with GDS. A gene interaction network was also built to investigate potential molecular interactions related to depression.

The most significant GDS-related gene was *COL1A2*, which encodes type I collagen. Collagens are widely found in multiple tissues in the body, which provide key support for the body shape and thus function. Mutations in collagen were associated with fragile cerebral arteries (Pope et al. 1991). Another gene associated with GDS was *RNF150* that encodes a ring finger protein. Genetic variants within *RNF150* were associated with increased risk of chronic obstructive pulmonary disease (Ding et al. 2015). A third GDS-related gene was *CTGF*. It encodes the connective tissue growth factor that is involved in cell proliferation and migration. Genetic mutations in *CTGF* were associated with a variety of diseases including cancer (Chu et al. 2008; Jacobson and Cunningham 2012), pulmonary hypertension (Bryant et al. 2016) and systemic sclerosis (Fonseca et al. 2007; Granel et al. 2010).

An earlier genome-wide association study of major depression disorder (Wray et al. 2012) found that a genetic variant (rs17400379) was associated with major depressive disorder although did not reach genome-wide significance. The SNP, located within 5 kb downstream of *SGCE*, was associated with *SGCE* expression in tibial nerve ($P = 2.4e-13$)(GTEx Consortium 2015). Interestingly, the expression of *SGCE* in blood was also associated with GDS in our current study ($P < 0.05$). *SGCE* is a maternally imprinted gene that encodes the epsilon-sarcoglycan protein. Studies have found that mutations in *SCGE* were associated with myoclonus dystonia syndrome, a young-onset movement disorder (Peall et al. 2014; Zimprich et al. 2001; Schule et al. 2004). Another SNP rs3732293 was also associated with major depressive disorder (Wray et al. 2012). The SNP was associated with the expression of *MOGS* in cerebellum. The expression of *MOGS* in blood was also associated with GDS in our current study ($P < 0.05$).

We acknowledge several limitations of our study. Less than 1000 samples were included, so the statistical power to detect genes with small effects is limited. The analysis was also restricted on relatively old participants of European ancestry, and the generalization of our findings to other ethnicity/age groups is unknown. Although ADNI is a longitudinal study with multiple measures of clinical and imaging phenotypes, gene expression was only measured from blood drawn in a single visit. It is thus unclear whether the increased expression of these genes caused depression or vice versa. No causality between gene expression and depression could be inferred. The network analysis provides some insights into the interactions between GDS-related genes. It, however, cannot infer causality either. Therefore, our findings should be considered as exploratory for hypothesis generating. Future studies with larger sample sizes and functional investigations are necessary to validate our findings and further investigate molecular mechanisms underlying depression.

In conclusion, we identified three genes that were significantly associated with depression. Our study suggests that neurotrophin signaling pathway might be one of pathways

involved in the regulation of depression interaction network. Future studies would be needed to validate our findings and identify potential therapeutic targets for depression.

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Author contributions XM and HL initiated the study and drafted the manuscript. BF, RL, SZ and BZ performed the analyses and critically reviewed the manuscript. All authors approve the final version of the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interests.

Ethical Approval The institutional review boards of all sites participating in the ADNI provided review and approval of the ADNI data collection protocol. All participants provided written consent.

References

Berglund, M., & Nilsson, K. (1987). Mortality in severe depression. A prospective study including 103 suicides. *Acta Psychiatrica Scandinavica, 76*(4), 372–380.

Boomsma, D. I., Willemsen, G., Sullivan, P. F., Heutink, P., Meijer, P., Sondervan, D., et al. (2008). Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *European Journal of Human Genetics, 16*(3), 335–342. https://doi.org/10.1038/sj.ejhg.5201979.

Broadhead, W. E., Blazer, D. G., George, L. K., & Tse, C. K. (1990). Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA, 264*(19), 2524–2528.

Bryant, A. J., Carrick, R. P., McConaha, M. E., Jones, B. R., Shay, S. D., Moore, C. S., et al. (2016). Endothelial HIF signaling regulates pulmonary fibrosis-associated pulmonary hypertension. *American Journal of Physiology Lung Cellular and Molecular Physiology, 310*(3), L249–L262. https://doi.org/10.1152/ajplung.00258.2015.

Cavanagh, J. T., Carson, A. J., Sharpe, M., & Lawrie, S. M. (2003). Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine, 33*(3), 395–405.

Chu, C. Y., Chang, C. C., Prakash, E., & Kuo, M. L. (2008). Connective tissue growth factor (CTGF) and cancer progression. *Journal of Biomedicine Science, 15*(6), 675–685. https://doi.org/10.1007/s11373-008-9264-9.

Cowley, M. J., Pinese, M., Kassahn, K. S., Waddell, N., Pearson, J. V., Grimmond, S. M., et al. (2012). PINA v2.0: mining interactome modules. [Research Support, Non-U.S. Gov't]. Nucleic Acids Research. 40(Database issue), D862–D865. https://doi.org/10.1093/nar/gkr967.

Craddock, N., & Forty, L. (2006). Genetics of affective (mood) disorders. *European Journal of Human Genetics, 14*(6), 660–668. https://doi.org/10.1038/sj.ejhg.5201549.

Ding, Y., Niu, H., Yang, H., Sun, P., Chen, Y., Duan, M., et al. (2015). EGLN2 and RNF150 genetic variants are associated with chronic obstructive pulmonary disease risk in the Chinese population. *International Journal of Chronic Obstructive Pulmonary Disease, 10*, 145–151. https://doi.org/10.2147/COPD.S73031.

Farmer, A., Harris, T., Redman, K., Sadler, S., Mahmood, A., & McGuffin, P. (2000). Cardiff depression study. A sib-pair study of life events and familiality in major depression. *The British Journal of Psychiatry, 176*, 150–155.

Fonseca, C., Lindahl, G. E., Ponticos, M., Sestini, P., Renzoni, E. A., Holmes, A. M., et al. (2007). A polymorphism in the CTGF promoter region associated with systemic sclerosis. *New England Journal of Medicine, 357*(12), 1210–1220. https://doi.org/10.1056/NEJMoa067655.

Granel, B., Argiro, L., Hachulla, E., Fajardy, I., Weiller, P. J., Durand, J. M., et al. (2010). Association between a CTGF gene polymorphism and systemic sclerosis in a French population. *The Journal of Rheumatology, 37*(2), 351–358. https://doi.org/10.3899/jrheum.090290.

Greenberg, P. E., Stiglin, L. E., Finkelstein, S. N., & Berndt, E. R. (1993). The economic burden of depression in 1990. *The Journal of Clinical Psychiatry, 54*(11), 405–418.

GTEx Consortium. (2015). Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science, 348*(6235), 648–660. https://doi.org/10.1126/science.1262110.

Ideker, T., Ozier, O., Schwikowski, B., & Siegel, A. F. (2002). Discovering regulatory and signalling circuits in molecular interaction networks. *Bioinformatics, 18*(Suppl 1), S233–S240.

Jacobson, A., & Cunningham, J. L. (2012). Connective tissue growth factor in tumor pathogenesis. Fibrogenesis Tissue Repair. 5(Suppl 1), S8. https://doi.org/10.1186/1755-1536-5-S1-S8.

Jia, P., Zheng, S., Long, J., Zheng, W., & Zhao, Z. (2011). dmGWAS: dense module searching for genome-wide association studies in protein-protein interaction networks. *Bioinformatics, 27*(1), 95–102.

Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2005). Age at onset and familial risk for major depression in a Swedish national twin sample. *Psychological Medicine, 35*(11), 1573–1579. https://doi.org/10.1017/S0033291705005714.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Archives of General Psychiatry, 50*(11), 863–870.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593.

Lewis, C. M., Ng, M. Y., Butler, A. W., Cohen-Woods, S., Uher, R., Pirlo, K., et al. (2010). Genome-wide association study of major recurrent depression in the U.K. population. *American Journal of Psychiatry, 167*(8), 949–957. https://doi.org/10.1176/appi.ajp.2010.09091380.

Lopez, A. D., & Murray, C. C. (1998). The global burden of disease, 1990–2020. *Nature Medicine, 4*(11), 1241–1243. https://doi.org/10.1038/3218.

Lopez-Leon, S., Janssens, A. C., Gonzalez-Zuloeta Ladd, A. M., Del-Favero, J., Claes, S. J., Oostra, B. A., et al. (2008). Meta-analyses of genetic studies on major depressive disorder. *Molecular Psychiatry, 13*(8), 772–785. https://doi.org/10.1038/sj.mp.4002088.

Marc, L. G., Raue, P. J., & Bruce, M. L. (2008). Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population. *The American Journal of Geriatric Psychiatry, 16*(11), 914–921. https://doi.org/10.1097/JGP.0b013e318186bd67.

McGuffin, P., Katz, R., Watkins, S., & Rutherford, J. (1996). A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry, 53*(2), 129–136.

Miao, X., Chen, X., Xie, Z., & Lin, H. (2018). Tissue-specific network analysis of genetic variants associated with coronary artery disease. *Scientific Reports, 8*(1), 11492. https://doi.org/10.1038/s41598-018-29904-7.

Muglia, P., Tozzi, F., Galwey, N. W., Francks, C., Upmanyu, R., Kong, X. Q., et al. (2010). Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Molecular Psychiatry, 15*(6), 589–601. https://doi.org/10.1038/mp.2008.131.

Peall, K. J., Kurian, M. A., Wardle, M., Waite, A. J., Hedderly, T., Lin, J. P., et al. (2014). SGCE and myoclonus dystonia: motor characteristics, diagnostic criteria and clinical predictors of genotype. *Journal of Neurology, 261*(12), 2296–2304. https://doi.org/10.1007/s00415-014-7488-3.

Petersen, R. C., Aisen, P. S., Beckett, L. A., Donohue, M. C., Gamst, A. C., Harvey, D. J., et al. (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology, 74*(3), 201–209. https://doi.org/10.1212/WNL.0b013e3181cb3e25.

Pope, F. M., Kendall, B. E., Slapak, G. I., Kapoor, R., McDonald, W. I., Compston, D. A., et al. (1991). Type III collagen mutations cause fragile cerebral arteries. *British Journal of Neurosurgery, 5*(6), 551–574.

Saykin, A. J., Shen, L., Yao, X., Kim, S., Nho, K., Risacher, S. L., et al. (2015). Genetic studies of quantitative MCI and AD phenotypes in ADNI: Progress, opportunities, and plans. *Alzheimers Dementia, 11*(7), 792–814. https://doi.org/10.1016/j.jalz.2015.05.009.

Schule, B., Kock, N., Svetel, M., Dragasevic, N., Hedrich, K., De Carvalho Aguiar, P., et al. (2004). Genetic heterogeneity in ten families with myoclonus-dystonia. *Journal of Neurology Neurosurgery and Psychiatry, 75*(8), 1181–1185. https://doi.org/10.1136/jnnp.2003.027177.

Shi, J., Potash, J. B., Knowles, J. A., Weissman, M. M., Coryell, W., Scheftner, W. A., et al. (2011). Genome-wide association study of recurrent early-onset major depressive disorder. *Molecular Psychiatry, 16*(2), 193–201. https://doi.org/10.1038/mp.2009.124.

Shyn, S. I., Shi, J., Kraft, J. B., Potash, J. B., Knowles, J. A., Weissman, M. M., et al. (2011). Novel loci for major depression identified by genome-wide association study of Sequenced Treatment Alternatives to Relieve Depression and meta-analysis of three studies. *Molecular Psychiatry, 16*(2), 202–215. https://doi.org/10.1038/mp.2009.125.

Sullivan, P. F., de Geus, E. J., Willemsen, G., James, M. R., Smit, J. H., Zandbelt, T., et al. (2009). Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. *Molecular Psychiatry, 14*(4), 359–375. https://doi.org/10.1038/mp.2008.125.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry, 157*(10), 1552–1562. https://doi.org/10.1176/appi.ajp.157.10.1552.

Wang, J., Duncan, D., Shi, Z., & Zhang, B. (2013). WEB-based GEne SeT AnaLysis Toolkit (WebGestalt): update 2013. *Nucleic Acids Research, 41*(Web Server issue), W77–W83. https://doi.org/10.1093/nar/gkt439.

Waraich, P., Goldner, E. M., Somers, J. M., & Hsu, L. (2004). Prevalence and incidence studies of mood disorders: a systematic review of the literature. *Canadian Journal of Psychiatry, 49*(2), 124–138. https://doi.org/10.1177/070674370404900208.

Weissman, M. M., Bland, R., Joyce, P. R., Newman, S., Wells, J. E., & Wittchen, H. U. (1993). Sex differences in rates of depression: cross-national perspectives. *Journal of Affective Disorders, 29*(2–3), 77–84.

Wells, K. B., Stewart, A., Hays, R. D., Burnam, M. A., Rogers, W., Daniels, M., et al. (1989). The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA, 262*(7), 914–919.

Wilhelm, K., Mitchell, P., Slade, T., Brownhill, S., & Andrews, G. (2003). Prevalence and correlates of DSM-IV major depression in an Australian national survey. *Journal of Affective Disorders, 75*(2), 155–162.

Wray, N. R., Pergadia, M. L., Blackwood, D. H., Penninx, B. W., Gordon, S. D., Nyholt, D. R., et al. (2012). Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. *Molecular Psychiatry, 17*(1), 36–48. https://doi.org/10.1038/mp.2010.109.

Zimprich, A., Grabowski, M., Asmus, F., Naumann, M., Berg, D., Bertram, M., et al. (2001). Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nature Genetics, 29*(1), 66–69. https://doi.org/10.1038/ng709.