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Association of FKBP5 gene variants with depression susceptibility: a comprehensive meta-analysis

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Review question / Objective: **We perform this comprehensive meta-analysis to combine data from case-control and cohort studies, and to produce a reliable estimate of the association between FKBP5 variants and depression susceptibility.**
Condition being studied: **Depression have affected 350 million people in communities across the world and have represented the third leading contributor to the global disease burden. Although depression is a complex problem, the exact pathological mechanism is still unclear. Previous studies report that genetic factors play a vital role in conferring vulnerability to depression. The dysfunctional and dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity and glucocorticoid receptor (GR) signaling pathway has been one of the possible biological mechanisms of depression. Given the regulatory role of FKBP5 in HPA axis activity and GR signaling pathway, many genetic studies have investigated the associations between the single nucleotide polymorphisms (SNPs) of FKBP5 and depression. Several studies involving German and Polish cohorts have demonstrated FKBP5 polymorphisms is associated with an increased risk of depression. However, other studies cannot find a significant association of FKBP5 variants with depression in Spanish, German, Italian and Swedish populations, even though a number of SNPs in FKBP5 have been reported. The inconsistent results might be related to the relatively small sample size of prior studies and population heterogeneity between ethnicities. Therefore, we performed this meta-analysis to combine data from different studies, and to produce a reliable estimates of the association between FKBP5 variants.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 August 2020 and was last updated on 21 August 2020 (registration number INPLASY202080086).

INTRODUCTION

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Condition being studied: Depression have affected 350 million people in communities across the world and have represented the third leading contributor to the global disease burden. Although depression is a complex problem, the exact pathological mechanism is still unclear. Previous studies report that genetic factors play a vital role in conferring vulnerability to depression. The dysfunctional and dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity and glucocorticoid receptor (GR) signaling pathway has been one of the possible biological mechanisms of depression. Given the regulatory role of FKBP5 in HPA axis activity and GR signaling pathway, many genetic studies have investigated the associations between the single nucleotide polymorphisms (SNPs) of FKBP5 and depression. Several studies involving German and Polish cohorts have demonstrated FKBP5 polymorphisms is associated with an increased risk of depression. However, other studies cannot find a significant association of FKBP5 variants with depression in Spanish, German, Italian and Swedish populations, even though a number of SNPs in FKBP5 have been reported. The inconsistent results might be related to the relatively small sample size of prior studies and population heterogeneity between ethnicities. Therefore, we performed this meta-analysis to combine data from different studies, and to produce a reliable estimates of the association between FKBP5 variants.

METHODS

Participant or population: Patients with depression and heathy controls or controls without any mental disorder.

Intervention: NA.

Comparator: NA.

Study designs to be included: Case-control and cohort studies.

Eligibility criteria: All the eligible studies were required to meet the following criteria: 1) studies investigating at least one FKBP5 SNP; 2) the studies contained sufficient published data to estimate an odds ratio (OR) and a 95% confidence interval (CI); 3) genotype frequencies in the controls were in Hardy-Weinberg equilibrium (HWE); 4) the studies were independent studies; 5) the studies provided all available data that can be extracted; 6) studies presenting non-original data, such as reviews, editorials, opinion papers, or letters to the editor, were excluded; 7) studies using nonhuman subjects or specimens were excluded; 8) studies with no extractable numerical data were excluded.

Information sources: An electronic search was conducted on PubMed (http://www.ncbi.nlm.nih.gov), EMBASE (http://www.elsevier.com/online-tools/embase), SCOPUS (https://www.scopus.com), the Cochrane library (https://www.cochranelibrary.com), and the China National Knowledge Infrastructure (http://cnki.net/) for articles published prior to August 1, 2020.

Main outcome(s): Depression susceptibility.

Quality assessment / Risk of bias analysis: Two reviewers independently assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We resolved disagreements by discussion, and we assessed the risk of bias according to the following parts: (1) selection bias; (2) performance bias; (3) detection bias; (4) attrition bias; (5) reporting bias; and (6) other bias.

Strategy of data synthesis: Chi-square test was used to test the HWE of genotype frequencies in controls, when it was not reported. Cochran's chi-square-based Q statistic was calculated to estimate the heterogeneity among studies, and a $P \leq 0.10$ was considered statistically significant for the Q statistic test. The inconsistency index (I2) was applied to quantify the heterogeneity, and an I2-value of 0-25% indicated no to low observed heterogeneity with larger values representing increased

heterogeneity. If heterogeneity existed among the studies, a random-effects model was used to combine the odds ratio (OR) with 95% confidence interval (CI); otherwise, a fixed-effects model was used. The significance of the pooled OR was determined by the Z test, with a P<0.05 considered statistically significant. Moreover, the allelic contrast genetic model, codominant model, dominant model and recessive model were evaluated. Publication bias were evaluated by visual inspection of a funnel plot and Egger's test. Egger's linear regression test was used to assess asymmetry, and a P<0.05 was set as the level of significance. Sensitivity analyses were performed by sequentially removing each study and recalculated the pooled OR and 95% CI, and the potential heterogeneity among ethnicities was also considered.

Subgroup analysis: Subgroup analyses by study population are also performed separately in Caucasian and Asian, and only FKBP5 gene polymorphisms reported in at least 3 studies are incorporated in subgroup analyses.

Sensibility analysis: We perform sensitivity analyses to explore the source of the heterogeneity which might influence the findings.

Country(ies) involved: Sweden, Germany, US, Poland, Italy, Japan, China, Korea, Ireland.

Keywords: FKBP5, depression, polymorphism.

Contributions of each author:

Author 1 - Beifang Fan - Author 1 drafted the manuscript.

Author 2 - Jianping Ma - Author 2 provided statistical expertise and extracted the information.

Author 3 - Huimin Zhang - Author 3 contributed to the development of the selection criteria, and the risk of bias assessment strategy.

Author 4 - Yuhua Liao - Author 4 read, provided feedback and approved the final manuscript.

Author 5 - Wanxin Wang - Author 5 read, provided feedback and approved the final manuscript.

Author 6 - Sheng Zhang - Author 6 read, provided feedback and approved the final manuscript.

Author 7 - Ciyong Lu - Author 7 helped revise the final manuscript.

Author 8 - Lan Guo - Author 8 provided statistical expertise, extracted the information, and drafted the manuscript.