Brain Tissue Matters in the Study of FKBP5 Gene Expression Activities in Schizophrenia – A Meta-Analysis

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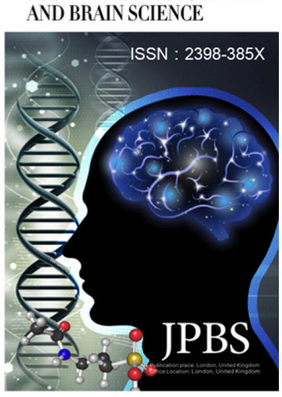

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ABSTRACT

Background: Gene FKBP5 has been linked to stress and cognition symptoms of schizophrenia (SCZ). However, few studies have reported changes in direct expression of FKBP5 in the brain of SCZ patients.

Method: Here we performed a systematic review and a meta-analysis to explore gene expression activity of FKBP5 in brain tissue in the SCZ. Ten RNA expression datasets were acquired from Gene Expression Omnibus, including 543 samples (269 SCZ cases and 274 controls). Both fixed-effect and random-effects models were employed for meta-analysis. Multiple linear regression (MLR) was employed to study the impact of three factors (Case Control Ratio, Female Male Ratio of Cases, Tissue and Country) on SCZ.

Results: FKBP5 presented no significant log fold change (LFC) in SCZ (LFC = 0.064; *p-value* = 0.30). MLR models showed that Case Control Ratio, Female Male Ratio of Cases and Country were not significant factors for the expression fold change of FKBP5 (*p-values* > 0.39) in regards to SCZ and that tissue was a wake impact factor (*p-value* < 0.11). Literature based pathway analysis showed that tissues from this study were not linked to stress or cognition related functions.

Conclusion: Gene expression levels of FKBP5 vary within different brain regions, and this needs to be take into consideration when studied in relation to SCZ.

Keywords: Schizophrenia; RNA expression data; Random model; Multiple linear regression model

1 INTRODUCTION

Schizophrenia (SCZ) is a chronic and severe mental disorder characterized by abnormal social behavior and failure to understand reality. In 2013, there were an estimated 23.6 million cases globally [1], and male patients usually present earlier onset age than that of female patients [2]. Although the etiology of SCZ remains unclear, the greatest risk factor for developing SCZ is having a first-degree relative with the disease. This means that if one parent is affected, the risk that a child will have SCZ is about 13 %, and if both parents are affected, the risk is nearly 50 % [3]. The risk rises to more than 40 % in monozygotic twins of affected parents [4, 5]. Thus, both family and twin studies suggest that SCZ is a highly heritable neuropsychiatric disorder.

Moreover, genetic risk factors are believed to be involved in the development of SCZ pathogenesis [6]. Data from brain regions at the gene expression level were employed in efforts to identify SCZ genetic determinants [7-14]. Recently, a targeted single-nucleotide polymorphism (SNP) study suggested that polymorphisms of FKBP5 (rs9296158, rs3800373, rs9296158, rs3800373, rs9470080 and rs737054) are associated with schizophrenia [15]. Previous gene expression studies also suggested that FKBP5 may be linked to stress and cognition symptoms of SCZ [16-18]. These studies revealed possible relationships between FKBP5 and SCZ. However, no direct linkage has yet been determined between FKBP5 and the pathogenesis of SCZ.

Considering the fact that SCZ is a mental health disease that is directly linked to physical and functional mutations within brain tissues, we performed a meta-analysis using gene expression data collected from brain tissues of both SCZ patients and healthy controls. The aim of this study was to explore the expression activity of FKBP5 in different brain regions in the case of SCZ. Moreover, we utilized multiple linear regression (MLR) to test the influence of several clinical factors on the FKBP5-SCZ relation.

2 METHODS AND MATERIALS

2.1 Data selection

A systematic search was conducted using Illumine BaseSpace Correlation Engine (http://www.illumina.com) and a public functional genomics database--Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). Fifty-six studies were initially examined based on the keyword “schizophrenia”. Further filter criteria included: 1) The data organism is Homo sapien; 2) The data type is RNA expression by array or by sequencing; 3) The study design is limited to SCZ vs. healthy control cases; 4) The sample site is the brain region. In total, 14 studies satisfied the selection criteria. After closer review, only 10 out of the 14 studies included the gene FKBP5 and were included in this meta-analysis [7-14], as shown in Table 1. More parameters of the data were provided in Appendix 1. There were 543 samples in total, including 269 SCZ cases and 274 controls. To note, although there is no date limitation in this systematical review, the age of data (current year - collection date) identified was from 0 to 13 years (2004 to 2017).

Table 1. Ten studies satisfied the selection criteria.

Study Name	GEO ID	Sample Organism	Data Type	Tissue Name	N Cases	N Controls	Country
Iwamoto *et al.* 2004 [7]	GSE12654	Homo sapiens	RNA expression	prefrontal cortex	13	15	Japan
Iwamoto *et al.* 2005 [8]	GSE12649	Homo sapiens	RNA expression	prefrontal cortex	35	34	Japan
Maycox *et al.* 2009 [9]	GSE17612	Homo sapiens	RNA expression	brain anterior prefrontal cortex	28	23	United Kingdom

Narayan *et al.* 2008 [10]	GSE21138	Homo sapiens	RNA expression	prefrontal cortex	30	29	USA
Barnes *et al.* 2011 [11]	GSE21935	Homo sapiens	RNA expression	superior temporal cortex	23	19	United Kingdom
Durrenberger *et al.* 2012 [12]	GSE26927	Homo sapiens	RNA expression	Entorhinal cortex	10	10	United Kingdom
Pietersen *et al.* 2012	GSE37981	Homo sapiens	RNA expression	the superior temporal cortex	9	9	USA
Pietersen *et al.* 2013	GSE46509	Homo sapiens	RNA expression	the superior temporal cortex	8	8	USA
Lanz *et al.* 2015 [13]	GSE53987	Homo sapiens	RNA expression	Pre-frontal cortex, striatum and hippocampus	48	55	USA
Arion *et al.* 2017 [14]	GSE87610	Homo sapiens	RNA expression	dorsolateral prefrontal cortex	65	72	USA

2.2 Meta-analysis models

Both fixed-effect model and random-effects model were employed to study the effect size of gene FKBP5 in a case vs. control expression comparison. The expression log fold change (LFC) was used as an index of effect size. Results from both models were reported and compared. The heterogeneity of the meta-analysis was analyzed to study the variance within and between different studies.

2.3 Multiple linear regression analysis

A MLR model was employed to study the possible influence of four factors on the gene expression changes of FKBP5 in SCZ: Case Control Ratio, Female Male Ratio of Cases, Tissue and Country. The regression analysis was conducted using function “regress()” in Matlab. P-values and 95 % confidence intervals (CI) were reported for each of the three factors.

3 RESULTS

3.1 Meta-analysis results

The effect sizes and related statistics from the ten studies and the meta-analysis results for gene FKBP5 are presented in Table 2. We noted that the weights from the random-effects model and the fixed-effect model were the same (See Table 2, columns “Weight_Fixed” and “Weight_Random”). This was due to the fact that the between study variance Tau-squared, , was calculated as 0, indicating no significant between-study variance. The total variance, Q, was 1.47, with the expected variance df (under the assumption that all studies have the same effect size) of 9. This led to a p-value of 0.9974 for the hypothesis that Q was from within-study variances only. Therefore, the following analyses will focus on results from the fixed-effect model.

The effect size (LFC) from the meta-analysis was 0.064 (95 % CI: [-0.18, 0.30], p = 0.30). These results suggested that FKBP5 presented no significant gene expression fold change in SCZ.

Table 2. The effects of two models for FKBP5.

Study Name	Effect Size	Lower Limit of 95% CI	Upper Limit of 95% CI	Z_Value	pValue (one tailed)	pValue (two tailed)	Weight _Fixed	Weight _Random
Arion *et al.* 2017 [14]	0.01	-0.36	0.38	0.06	0.48	0.95	28.38	28.38
Lanz *et al.* 2015 [13]	0.42	-1.99	2.83	0.34	0.37	0.73	0.66	0.66
Pietersen *et al.* 2012	-0.95	-3.74	1.85	-0.66	0.75	0.51	0.49	0.49
Pietersen *et al.* 2013	0.81	-1.63	3.26	0.65	0.26	0.52	0.64	0.64
Durrenberger *et al.* 2012 [12]	-0.30	-1.73	1.14	-0.40	0.66	0.69	1.88	1.88
Barnes *et al.* 2011 [11]	-0.12	-3.46	3.21	-0.07	0.53	0.94	0.35	0.35
Maycox *et al.* 2009 [9]	0.22	-2.60	3.04	0.15	0.44	0.88	0.48	0.48
Narayan *et al.* 2008 [10]	0.17	-1.47	1.80	0.20	0.42	0.84	1.44	1.44
Iwamoto *et al.* 2005 [8]	0.07	-0.43	0.58	0.28	0.39	0.78	14.89	14.89
Iwamoto *et al.* 2004 [7]	0.16	-0.31	0.64	0.66	0.25	0.51	17.04	17.04
Fixed Model	0.06	-0.18	0.30	0.52	0.30	0.60		
Random Model	0.06	-0.18	0.30	0.52	0.30	0.60		

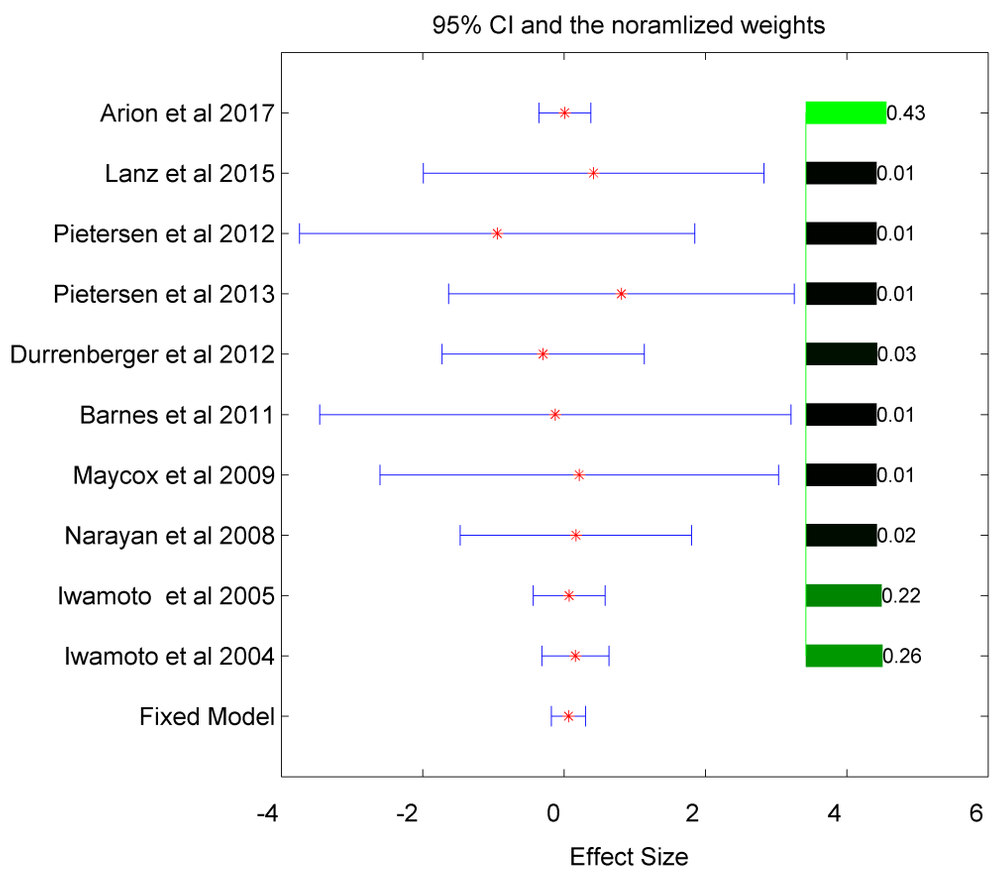

Fig. 1 The effect size, 95 %CI and weights for gene FKBP5. The results are from meta-analysis using a fixed-effect model.

3.2 MLR analysis results

As shown in Table 3, results from the MLR models showed that Case / Control Ratio, Female / Male Ratio of Cases, and Country were not significant factors for expression fold change of FKBP5 (*p-value* > 0.39).

Table 3. Multiple linear regression analysis results.

	Constant	Case / Control Ratio	Female / Male Ratio in Case	Country	Tissue
Beta	0.30	0.02	-0.72	0.14	0.22
LowLimit	-31.82	-23.49	-5.75	-3.95	-0.3
UpLimit	32.43	23.54	4.31	4.23	0.79
p-value	0.50	0.50	0.82	0.39	0.07

However, it should be noted that tissue type seemed to be a significant impact factor for the expression LCF of FKBP5 (*p-value* < 0.07), as shown Fig. 2. In this study, expression data were sampled from five different tissues, including “entorhinal cortex”, “anterior prefrontal cortex”, “dorsolateral prefrontal cortex”, “prefrontal cortex”, and “superior temporal cortex”. It turned out that expressions of FKBP5 demonstrated both within and between brain region differences, as shown in Fig. 2.

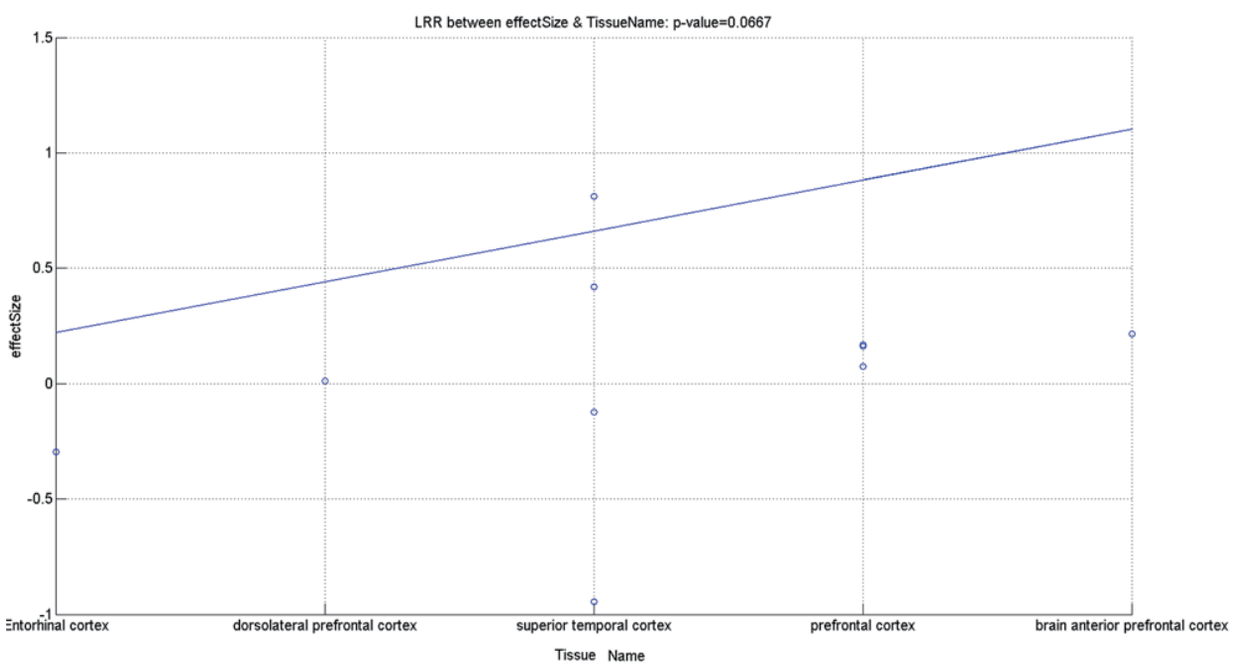

Fig. 2 The linear regression relation between expression fold change of FKBP5 in the case of SCZ and sample tissues.

4 DISCUSSION

This study conducted an RNA expression data based meta-analysis to explore gene expression activities of FKBP5 in the case of SCZ. Both a fixed-effect model and a random-effects model were employed, and heterogeneity analysis was conducted. Furthermore, MLR analysis was performed to study the influence of 4 factors on effect size of FKBP5 in SCZ: Case / Control Ratio, Female / Male Ratio in Cases, Tissue, and Country.

Ten studies passed our screen criteria and were employed within this study, including 543 samples from humans (269 SCZ cases and 274 controls), as shown in Table 1. These ten expression datasets were acquired from “entorhinal cortex”, “anterior prefrontal cortex”, “dorsolateral prefrontal cortex”, “prefrontal cortex”, and “superior temporal cortex”. Using these data for a meta-analysis, no significant fold change was observed for FKBP5 (*p-value* = 0.30).

Previous studies suggested that FKBP5 could play a role in regulating symptoms related to SCZ, including stress and cognition [15-18]. For instance, Schmidt *et al.* found that FKBP5 deletion prevented stress-induced decline in the prefrontal cortical [16]. Also, Wei *et al.* found that exposure to chronic mild stress led to markedly upregulated FKBP5 protein expression in the prefrontal cortex [19]. Although exposure to stress may increase the risk of SCZ development [15], no evidence thus far supports stress as a direct cause of SCZ. Therefore, when studying the FKBP5-SCZ relationship, related clinical measures (e.g., stress cores and cognition ability score) should be integrated.

Another possible explanation of the wake fold change of FKBP5 from the results of this meta-

analysis was that, the expression data were acquired from brain regions that are not significantly related to stress and cognition. For example, the prefrontal cortex is mainly related to attention and memory [20], the entorhinal cortex is mainly associated with neuron information processing [21], and the superior temporal cortex is mainly related to auditory processing and social cognition processes [22, 23]. Furthermore, results from MLR analysis showed that brain tissue was an influential factor for expression activity of FKBP5 (*p-value* < 0.07; see Fig. 2). Therefore, more data from different brain regions should be employed for the further study of the possible linkage between FKBP5 and SCZ pathogenesis.

5 CONCLUSION

Results of this meta-analysis revealed no significant expression change of FKBP5 in the case of SCZ. However, expression levels of FKBP5 could vary within different brain tissues, which is worthy of further study.

CONFLICT OF INTERESTS

Authors claim no conflict of interests.

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