Association between Genetic Variations in the Arachidonic Acid Cascade and Major Depressive Disorder: A Case-control Study in Taiwan

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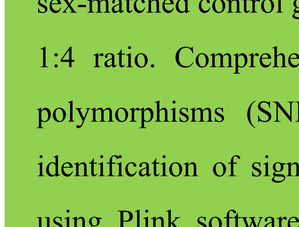

ABSTRACT

Background: Major depressive disorder (MDD) is a significant contributor to global morbidity and mortality. Dysregulation in polyunsaturated fatty acids (PUFAs) metabolism has been observed in patients with MDD and other psychiatric disorders, with elevated levels of arachidonic acid (AA) specifically reported in MDD patients. The genetic link between AA cascade and MDD has not been previously investigated. Therefore, this study aims to explore the association between genetic polymorphisms in AA cascade and MDD.

Methods: The study cohort included 317 patients with MDD (case group), compared to a sex-matched control group comprising 1,268 participants from the Taiwan Biobank (TWB) at a 1:4 ratio. Comprehensive full-model tests were conducted to evaluate single nucleotide polymorphisms (SNPs) across all candidate genes within the AA cascade. Upon the identification of significant SNPs, 5,000 genome-wide max(T) permutations were executed using Plink software. Subsequently, a predictive model was developed employing logistic regression using body mass index, education status and marital status as covariates.

Results: A total of 59 genes and 720 SNPs were analyzed. We identified 10 SNPs significantly associated with MDD within the AA cascade in our cohort. These include one SNP in paraoxonase 3 (PON3) (rs11768074), one in gamma-glutamyltransferase 1 (GGT1) (rs2330795), two in prostaglandin-endoperoxide synthase 1 (PTGS1) (rs4273915 and rs6478565), and six in ATP binding cassette subfamily C member 1 (ABCC1) (rs9635480, rs12921924, rs12924212, rs11075289, rs11075290, and rs11075291). The associations were statistically significant under the dominant inheritance model, with adjustments for marital status, education level, and body mass index as covariates.

Conclusion: Our findings offer genetic evidence supporting the involvement of AA in MDD among the Taiwanese population.

Introduction

- Major depressive disorder (MDD) is a significant contributor to global morbidity and mortality.
- The exact cause of MDD remains a mystery
  - Pathological: Monoamine hypothesis, brain-derived neurotrophic factor hypothesis, inflammation (Su et al., 2008)
  - Genetic: genetic polymorphisms.
  - Social and environmental: Mental stress, social nonconformity, withdrawal and other forms of diminished communication, bullying, bereavement of a close relative, and addictive drug abuse (Nabeshima & Kim, 2013).
- Dysregulation in polyunsaturated fatty acids (PUFAs) is increasingly recognized to play a role in MDD and other psychiatric disorders (Chang et al., 2018; Lin et al., 2012; Messamore et al., 2017; Satogami et al., 2019).
  - MDD patients have elevated levels of arachidonic acid (AA) and decreased levels of omega-3 PUFAs compared with healthy control (Lotrich et al., 2012; Su et al., 2023).
  - AA is metabolized into proinflammatory eicosanoids, such as prostaglandins, and its elevation may induce inflammation, which is increasingly recognized as a key factor in MDD pathophysiology (Miller et al., 2016; Su et al., 2012).
  - Patients with MDD exhibit elevated levels of interleukin-1β and tumour necrosis factor-α which positively correlated with depression severity (Das et al. 2021)
- The genetic link between AA cascade and MDD has not been extensively investigated.

Methods

Study design:

- Case-control study involving MDD patients (case, n = 327) and control (healthy individuals, n = 1268).

Participants:

- Case: Adult patients with MDD based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and with Hamilton Depression Rating Scale (HAM-D) score of >18.
- Controls: Sex-matched healthy controls to cases (4:1) ratio by using the data from Taiwan Biobank.

Exclusion criteria

- Psychiatric disorders (such as bipolar disorders and schizophrenia). suicidal ideations, and substance use disorder.

Candidate gene selection

- We utilized established pathways in Reactome (https://reactome.org/ accessed on 2 June 2024) for the selection of candidate genes.
- The entry “Arachidonic acid metabolism” (R-HSA-2142753).
- We found 59 genes, which were included in our study.

Genotyping Genomic

- DNA from the patients was extracted from the buffy coat using QIAamp DNA Blood Mini Kit (Qiagen, Crawley, UK).

Statistical analysis

- Plink v1.90b6.24 to investigate the association between MDD and the candidate genes.
- There were two steps in our analyses:
  - Full-model association test: Case-control association analysis using allelic, dominant, and recessive models was applied to identify the significant SNPs among all candidate SNPs.
  - Logistics regression: The best model obtained in the first step was considered as the mode of inheritance, and marital status, education level, and body mass index (BMI) were used as covariates

Results

Table 1. Significant SNPs and results from full-model association test and logistics regression

S/N	Gene	SNP	Empirical p-value	p-value	Odds ratio	Minor Allele	Major Allele	MAF in cases	MAF in controls
1	*PON3*	rs11768074	0.0043	0.0042	1.60	A	G	0.0868	0.0560
2	*GGT1*	rs2330795	0.0028	0.0031	1.31	A	G	0.4228	0.3585
3	*PTGS1*	rs4273915	0.0070	0.0065	1.57	C	G	0.0852	0.0560
		rs6478565	0.0070	0.0064	1.57	G	A	0.0852	0.0559
4	*ABCC1*	rs9635480	0.0004	0.0003	0.72	G	A	0.3429	0.4210
		rs12921924	0.0004	0.0005	0.72	T	G	0.3438	0.4198
		rs12924212	0.0003	0.0001	0.70	G	A	0.3434	0.4261
		rs11075289	0.0004	0.0005	0.72	C	T	0.3549	0.4316
		rs11075290	0.0007	0.0010	0.74	T	C	0.3576	0.4296
		rs11075291	0.0003	0.0002	0.71	A	G	0.3556	0.4362

Abbreviations: ABCC1: ATP binding cassette subfamily C member 1, GGT1: gamma-glutamyltransferase 1, MAF: Minor allele frequency, PON3: paraoxonase 3, PTGS1: prostaglandin-endoperoxide synthase 1, SNP: single nucleotide polymorphism. Empirical p-value means the p-values obtained with the permutation technique. p-value means the p-values obtained in the original chi-squared test.

Discussion

- This is the first study providing genetic evidence of the involvement of AA in MDD among the Taiwanese population.
- Ten (10) SNPs in 4 genes (GGT1, PON3, PTGS1, ABCC1) in the AA cascade are associated with MDD.
- GGT1 encodes for GGT1 enzyme, involved in the metabolism of glutathione, an important antioxidant in the body, further supporting the role of oxidative stress in MDD.
- PON3 encodes for the PON3 enzyme, a member of the paraoxonase family of enzymes, known for their primary roles in preventing oxidative stress and lipid peroxidation.
- *PTGS1* encodes for PTGS1 enzyme, responsible for the formation of pro-inflammatory eicosanoids from AA. Proinflammatory eicosanoids such as prostaglandins trigger inflammatory reactions, leading to inflammation, a key pathophysiological mechanism in MDD (Su 2015).
- *ABCC1* encodes for multidrug resistance-associated protein 1 (MRP1).
- MRP1 is primarily involved in the efflux of various substrates, including antidepressants across the BBB.
- Polymorphisms in the *MRP1* gene are associated with response to antidepressants, such as citalopram (Lee et al., 2010)

Conclusion

- Our findings offer comprehensive genetic evidence supporting the involvement of AA in MDD.
- SNPs in *GGT1* (rs2330795), *PON3* (rs11768074), *PTGS1* (rs4273915 and rs6478565), *ABCC1* (rs9635480, rs12921924, rs12924212, rs11075289, rs11075290, and rs11075291) are associated with MDD.
- Genotyping individuals for these SNPs could facilitate earlier diagnosis of MDD, potentially improving treatment outcomes.