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EGR3 Polymorphism Is a Potential Susceptibility Factor of Schizophrenia Risk in a Chinese Population

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Objective: The purpose of this study was to evaluate the association between the single nucleotide polymorphisms (SNPs) (*EGR3* rs1996147; *EGR4* rs3813226, rs6747506; *ERBB3* rs2292238; and *ERBB4* rs707284, rs7560730) and the risk of schizophrenia (SZ) in a Chinese population.
Materials and Methods: We conducted a case–control study, including 248 patients with SZ and 236 healthy controls matched for age and sex. The Mass-array platform was used to detect all the genotypes of the SNPs.
Results: The results revealed that the *EGR3* rs1996147 AA genotype was associated with borderline decreased SZ risk (AA *vs.* GG: adjusted OR = 0.43, 95% CI: 0.18–1.02, $p = 0.06$). However, no significant correlation was found between the other SNPs and overall SZ risk. Subgroup analysis also failed to show any significant association between all SNPs and the risk of SZ.
Conclusion: In summary, this study revealed that the *EGR3* rs1996147 AA genotype was associated with a borderline risk for SZ.

Keywords: schizophrenia, polymorphism, single nucleotide polymorphisms, genotypes

Introduction

Schizophrenia (SZ) is a common, devastating, and heritable brain disorder, affecting approximately 1% of the global population (Zhang et al., 2018). Clinically, it often manifests as a syndrome with various causes and symptoms, including delusions, hallucinations, emotional problems, and cognitive impairment (Rund, 2018). In China, SZ typically onsets during early adulthood, with around 80% of cases occurring between ages 16 and 25 years (Wang et al., 2021). To date, the etiology and pathogenesis of SZ remain unclear (Chen et al., 2020). According to a genetic epidemiological study (Khavari and Cairns, 2020), the heritability of SZ is around 80%, suggesting an association between genetic factors and the pathogenesis of SZ.

Over the past few decades, single nucleotide polymorphisms (SNPs) in several candidate genes, including *EGR3* (He et al., 2024), *EGR4 (*Hu et al., 2023*)*, *ERBB3* (Zhang et al., 2018), and *ERBB4* (Feng et al., 2017), have been found to be closely related to SZ. As vital transcription regulators, the early growth response (*EGR*) protein family plays a major role in coordinating gene expression, laying the foundation for neural plasticity. The family consists of *EGR1* (also known as *NGFI-A*, *krox24*, *zif268*), *EGR2* (also known as *Krox-20*), *EGR3* (also known as *PILOT*), and *EGR4* (also known as *NGFI-C*) (Cheng et al., 2012). *EGR3* is one of the members of the family, controlled by calcineurin (also known as protein phosphatase 2B).

Calcineurin regulates glutamatergic and dopaminergic signaling by dephosphorylation (Li et al., 2011) and participates in the pathology of SZ (Kim et al., 2010). *EGR4*, localized at chromosome 2p12.2, is commonly expressed in the central nervous system and appears to be a critical gene involved in the early stages of meiosis (Sung et al., 2017). Moreover, *EGR3* and *EGR4* have been shown to interact with the specific nuclear mediator NF-kappaB, which is related to SZ and could regulate the expression of cytokines (Wieland et al., 2005).

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