Schizophrenia is not associated with the ERBB3 gene in a Han Chinese population sample: Results from case-control and family-based studies

Dawei Li¹#, Guang He¹#, Yifeng Xu³, Yun Duan⁴, Niufan Gu³, Xingwang Li¹², Yongyong Shi¹², Wei Qin¹², Guoyin Feng³ and Lin He¹²⁴

¹Bio-X Center, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, Shanghai, China.
²Institutes of Biomedical Sciences, Fudan University, Shanghai, China.
³Shanghai Institute of Mental Health, Shanghai, China.
⁴Institute for Nutritional Sciences, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, Shanghai, China.

Abstract

ERBB3 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 3), encoding a receptor of neuregulin-1 (NRG1), has been considered a functional candidate gene for schizophrenia susceptibility. In order to investigate a relationship between ERBB3 gene and schizophrenia in the Chinese population, case-control and family-based studies were carried out in 470 cases matched by controls, and in 532 family trios. Our results failed to show any evidence of significant association between the ERBB3 rs2292238 polymorphism and schizophrenia.

Key words: schizophrenia, ERBB3 gene.

Received: June 4, 2009; Accepted: July 7, 2009.

Evidence of association between the NRG1 (Neuregulin-1) gene and schizophrenia has been documented (Li et al., 2006). The association of schizophrenia and single-nucleotide polymorphisms (SNPs) of ERBB4 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 4), encoding one of the receptors for NRG1 has been shown, thus suggesting that NRG1-ERBB signaling is involved in the pathogenesis of schizophrenia (Benzel et al., 2007). ERBB3 is another NRG1 receptor, and its mRNA has been reported to be down-regulated in brains from schizophrenic patients (Hakak et al., 2001; Tkachev et al., 2003). These findings made ERBB3 a functional candidate gene for susceptibility to schizophrenia. However, studies in samples from the Japanese population did not reveal any association between ERBB3 polymorphisms and schizophrenia (Kana-zawa et al., 2007; Watanabe et al., 2007).

In order to investigate the relationship between the ERBB3 gene and schizophrenia in the Chinese population, we carried out case-control and family-based studies of the ERBB3 rs2292238 polymorphism, using samples consisting of 470 cases matched by controls and 532 family trios composed each one by normal parents and a single affected offspring, all of Han Chinese origin. The patients (mean duration of illness: five years) were interviewed and diagnosed according to the DSM-IV, by two independent psychiatrists. The case sample included 250 patients from northern and 220 from southern China; 227 (48.3%) were males and 243 (51.7%) females, with an overall mean age of 32.5 years (sd = 11.0). The controls consisted of 334 subjects from northern and 136 from southern China; 227 (48.3%) were males and 243 (51.7%) females, with an overall mean age of 32.5 years (sd = 9.5). The family trios were composed respectively by 170, 191, and 171 nuclear families from Shanghai, Anhui and Changchun; among the 532 probands, 260 (48.9%) were males and 272 (51.1%) females. A standard informed consent for the genetic analysis, reviewed and approved by the Shanghai Ethical Committee of Human Genetics, was obtained from all subjects.

Genomic DNA was extracted from peripheral whole blood using a modified phenol-chloroform method (Gao et al., 2001). Real-time quantitative PCR with allele-specific amplification was performed through two PCR reactions for each sample, carried out in a total volume of 5 μL containing 10 ng genomic DNA, 2.5 μL Taqman® Universal PCR Master Mix (Applied Biosystems), 0.2 μM allele-specific primer, 0.2 μM common primer and 0.2x SYBR® Green I (Molecular Probes) on an ABI PRISM 7900 Se-
sequence Detection System (Applied Biosystems). The primers used were: 5'-CAAAGTGTTGGGTAATTAGAAG-3', 5'-AAAGTGTTGGGTAATTAGAAGG-3', and 5'-TACCAGTTGGAACACTTAATCGG-3'. Protocols were as described by Liu et al. (2005).

A Monte Carlo approach (Sham and Curtis, 1995) was used in the case-control analysis with 100,000 simulations, in order to estimate exact test probability values. Transmission (TDT) and pedigree (PDT) disequilibrium tests, and haplotype-based haplotype relative risk (HHRR) analyses were used in the family-based samples. We did not find any difference between cases and controls when genotype or allele frequencies were compared ($\chi^2 = 1.188$; 2 d.f.; $p = 0.515$ and $\chi^2 = 1.130$; 1 d.f.; $p = 0.288$, respectively). The results summarized in Tables 1 and 2 showed no evidence of significant association for rs2292238 using any of the above strategies. Furthermore, no evidence of association was found when the probands of the family trios were added to the affected sample of the case-control study (data not shown). The sample sizes we could get in this study would have a sufficient statistical power to detect the presence of a significant association, if present.

### Acknowledgments

We thank all the subjects participating in this study, as well as to the psychiatrists and mental health workers who helped us. This work was supported by grants (07DZ22917, 2006CB910601, 2006BA105A05, 2006AA02A407, 2007CB947300, 30700457, 2010CB529600) and the Shanghai Leading Academic Discipline Project (B205).

### References


**Associate Editor:** Paulo A. Otto

License information: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.