Published in final edited form as:

Schizophr Res. 2008 February ; 99(1-3): 365–366.

No association between schizophrenia and polymorphisms of the PlexinA2 gene in Chinese Han Trios

Stephane Budel¹, Sang-ohk Shim¹, Zeny Feng^{2,3}, Hongyu Zhao², Fuki Hisama¹, and Stephen M. Strittmatter¹

¹Department of Neurology, Yale University, New Haven, Connecticut

²Department of Epidemiology, Public Health and Genetics, Yale University, New Haven, Connecticut

³Department of Mathematics and Statistics, University of Guelph, Guelph, Ontario

Letter to the Editors:

Multiple genetic, environmental and developmental factors have been implicated (Hyman, 1999; Riley et al., 2000) in the etiology of schizophrenia. Axon guidance molecules may be considered candidate genes to explain an early developmental abnormality underlying schizophrenia. Plexin A2, a member of the semaphorin receptor family, is an axon guidance receptor widely expressed in the brain (Takahashi et al., 1999). A genome-wide association study of European schizophrenic patients and controls found a significant association between schizophrenia and 3 SNPs at the Plexin A2 locus (*PLXNA2*): rs841865, rs752016 and rs2498028 (Mah et al., 2006). Another study found no association of *PLXNA2* and schizophrenia amongst Japanese (Fujii et al., 2007).

We sought to replicate this association in a DNA sample of 290 Chinese Han Trios (621 schizophrenic patients and 501 controls) obtained from the National Institute of Mental Health (NIMH; www.nimh.nih.gov). Families were excluded if both parents were schizophrenic. We genotyped the same three SNPs at the *PLXNA2* locus: rs841865, rs752016 and rs2498028 using the TaqMan SNP Genotyping Assay (Applied Biosystems, California).

Genotype distribution was performed to test deviation from Hardy-Weinberg equilibrium using the Fisher exact test. LD between pairs of SNPs was measured as D' using Haploview. Structures of haplotypes were analyzed from the parental genotypes based upon LD pattern using the expectation-maximization algorithm (Slatkin and Excoffier, 1996). Conventional TDT statistics were used to analyze transmission disequilibrium between the discrete trait schizophrenia or schizoaffective disorder and the SNPs (Spielman et al., 1993) using the trios from the NIMH with both available parents and one affected offspring. In addition, single marker and haplotype association with schizophrenia were tested using FBAT (Family-Based Association Test) software (Laird et al., 2000; Horvath et al., 2004). FBAT also implements haplotype-based association tests for family-based studies when markers are tightly linked. In our study, all markers were tested as they all had minor allele frequencies greater than 5%.

Correspondence to Stephen M. Strittmatter, Yale University, Program in Cellular Neuroscience, Neurodegeneration and Repair, P.O. Box 9812, New Haven, CT 06536-0812, Email: stephen.strittmatter@yale.edu..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

No Mendelian errors were observed in our analysis. The genotype frequencies of the three SNPs tested were in Hardy-Weinberg equilibrium. The association of single SNP and haplotypes with schizophrenia is shown in Figure 1. Results of single SNP-based association and haplotype-based association tests using FBAT are summarized (Fig. 1C, D). No statistical evidence suggests the association between schizophrenia and 3 SNPs at the *PLXNA2* locus. Thus, using this population of Chinese Han trios, we were unable to replicate an association at the *PLXNA2* locus and schizophrenia (Mah et al., 2006).

In conclusion, we performed a comprehensive analysis of three particular SNPs at the *PLXNA2* locus and failed to replicate a previously reported association of this locus and schizophrenia. Further studies are required to verify the potential role of axon guidance molecules in schizophrenia.

Acknowledgements

The authors thank N.I.H. and the Scottish Rite Association for funding, and Dr. Noam Harel, who assisted with proof-reading of the manuscript. Data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative. Most importantly, we thank the families who have participated in and contributed to these studies.

Data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative. From 1991-97, the Principal Investigators and Co-Investigators were: Harvard University, Boston, MA, U01MH46318, Ming T. Tsuang, M.D., Ph.D., D.Sc., Stephen Faraone, Ph.D., and John Pepple, Ph.D.; Washington University, St. Louis, MO, U01 MH46276, C. Robert Cloninger, M.D., Theodore Reich, M.D., and Dragan Svrakic, M.D.; Columbia University, New York, NY U01 MH46289, Charles Kaufmann, M.D., Dolores Malaspina, M.D., and Jill Harkavy Friedman, Ph.D. The data from the Han Chinese Schizophrenia Linkage Study were collected with funding from grant R01 MH59624 from the US National Institute of Mental Health to Ming T. Tsuang, MD, PhD (Principal Investigator). Other participants in the US were Stephen V. Faraone, PhD (Co-Principal Investigator), Shao Zhu, MD (Project Coordinator) and Xingjia Cui, MD (Project Coordinator). The project leaders in Taiwan were Hai-Gwo Hwu, M.D. (Taiwan Principal Investigator, National Taiwan University Hospital), Wei J. Chen, M.D. Sci.D. (Taiwan Co-Principal Investigator). Other participants in Taiwan were: Chih-Min Liu, M.D., Shih-Kai Liu, M.D., Ming-Hsien Shieh, M.D., Tzung-Jeng Hwang, M.D., MPH, Ming-Ming Tsuang, M.D., Wen Chen Ou Yang, M.D., Ph.D., Chun-Ying Chen, M.D., Chwen-Cheng Chen, M.D., Ph.D. Jin-Jia Lin, M.D., Frank Huang-Chih Chou, M.D., Ph.D., Ching-Mo Chueh, M.D., Wei-Ming Liu, M.D., Chiao-Chicy Chen, M.D. Jia-Jiu Lo, M.D., Jia-Fu Lee, M.D., Ph.D. Seng Shen, M.D., Yung Feng, M.D. Shin-Pin Lin, M.D. Shi-Chin Guo, M.D. Ming-Cheng Kuo, M.D., Liang-Jen Chuo, M.D., Chih-Pin Lu, M.D., Deng-Yi Chen, M.D. Huan-Kwang Ferng, M.D., Nan-Ying Chiu, M.D., Wen-Kun Chen, M.D. Tien-Cheng Lee, M.D. Hsin-Pei Tang, M.D. Yih-Dar Lee, M.D., Wu-Shih Wang, M.D. For-Wey Long, M.D., Ph.D., Tiao-Lai Huang, M.D., Jung-Kwang Wen, M.D., Cheng-Sheng Chen, M.D., Wen-Hsiang Huang, M.D., Shu-Yu Yang, M.D., Mei-Hua Hall, Cheng-Hsing Chen. M.D. The project leaders in the People's Republic of China were Xiaogang Chen M.D., PhD (China Principal Investigator, Institute of Mental Health, Xiang-ya Teaching Hospital, Central South University), and Xingqun Ni, M.D. (Original Principal Investigator, Sun Yatsen University). Other participants in China were: Liwen Tan, M.D., PhD, Liang Zhou, M.D., PhD, Jiajun Shi, M.D., PhD, Xiaoling He, M.D., PhD, Xiogzhao Zhu, M.D., PhD, Lingjian Li, M.D., PhD, Ming Wang, M.D., Tiansheng Guo, M.D., Xiaqi Shen, M.D., PhD, Jinghua Yang, M.D. NH/Northwestern University, Evanston, IL, MH059571, Pablo V. Gejman, M.D. (Collaboration Coordinator; PI), Alan R. Sanders, M.D.; Emory University School of Medicine, Atlanta, GA, MH59587, Farooq Amin, M.D. (PI); University of California, San Francisco, CA, MH60870, William Byerley, M.D. (PI); University of Iowa, Iowa, IA, MH59566, Raymond Crowe, M.D. (PI), Donald Black, M.D.; Washington University, St. Louis, MO, U01, MH060879, C. Robert Cloninger, M.D. (PI); University of Colorado, Denver, CO, MH059565, Robert Freedman, M.D. (PI), Ann Olincy, M.D.; University of Pennsylvania, Philadelphia, PA, MH061675, Douglas Levinson M.D. (PI), Nancy Buccola APRN, BC, MSN, New Orleans, Louisiana; University of Queensland, Queensland, Australia, MH059588, Bryan Mowry, M.D. (PI); Mt. Sinai School of Medicine, New York, NY, MH59586, Jeremy Silverman, Ph.D. (PI). Most importantly, we thank the families who have participated in and contributed to these studies.

References

- Fujii T, Iijima Y, Kondo H, Shizuno T, Hori H, Nakabayashi T, Arima K, Saitoh O, Kunugi H. Failure to confirm an association between the *PLXNA2* gene and schizophrenia in a Japanese population. *Progress in neuro-psychopharmacology & biological psychiatry* 2007;31:873–877. [PubMed: 17346868]
- Hyman SE. Introduction to the complex genetics of mental disorders. *Biol Psychiatry* 1999;45:518–521. [PubMed: 10088041]

- Mah S, Nelson MR, Delisi LE, Reneland RH, Markward N, James MR, Nyholt DR, Hayward N, Handoko H, Mowry B, et al. Identification of the semaphorin receptor PLXNA2 as a candidate for susceptibility to schizophrenia. *Mol Psychiatry* 2006;11:471–478. [PubMed: 16402134]
- Riley BP, Makoff A, Mogudi-Carter M, Jenkins T, Williamson R, Collier D, Murray R. Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. *Am J Med Genet* 2000;96:196–201. [PubMed: 10893497]
- Slatkin M, Excoffier L. Testing for linkage disequilibrium in genotypic data using the Expectation-Maximization algorithm. *Heredity* 1996;76:377–383. [PubMed: 8626222]
- Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet* 1993;52:506–516. [PubMed: 8447318]
- Takahashi T, Fournier A, Nakamura F, Wang LH, Murakami Y, Kalb RG, Fujisawa H, Strittmatter SM. Plexin-neuropilin-1 complexes form functional semaphorin-3A receptors. *Cell* 1999;99:59–69. [PubMed: 10520994]

Figure 1. SNP and linkage analysis at the PlexinA2 locus in Chinese Han Trios

(A) The three markers selected were in Hardy Weinberg equilibrium ($p > 0.05$). oHet: observed heterozygotes; pHet: predicted number of heterozygotes; HWpVal: Hardy-Weinberg p value; %geno: Percent successful genotype; M.E.: Number of Mendelian errors; MAF: Minor Allele Frequency. (B) Linkage Disequilibrium (LD) plot. The relative position of the three SNPs are depicted. (C) Association of specific single markers with the disease. MA: Minor allele. (D) Haplotype association with schizophrenia.