

THE FUTURE

Schizophrenia is a syndrome that is likely not only to be genetically complex, but also characterized by phenotypic complexity. Many researchers have begun to explore endophenotypes that are typically easier to define and quantify and may be more closely associated with a specific genetic factor. Our group has decided to explore the alternate phenotype of psychosis. Psychosis, defined as a lifetime episode of hallucinations and/or delusions, is an integral part of the definition of schizophrenia. However, psychosis is also an important symptom cluster in some patients with bipolar disorder, as well as in patients with other mood disorders. We plan to test the hypothesis that psychosis may be associated with genetic factors that sometimes appear associated with schizophrenia and alternately may appear in patients suffering from bipolar disorder.

Ongoing collaborative efforts employing both large data sets and meta-analytic methods are beginning to help narrow in on a number of replicated regions of interest. There is also a growing potential to merge molecular genetics and functional genomics in the investigation of multiple risk genes. The convergence of genetics and genomics can be seen when association findings for candidate genes begin to correlate with consistent genome scan linkage results and significant alterations in gene expression. This work will be further expanded by the new field of proteomics. Proteomics promises to elucidate biological mechanisms and expression patterns at the level of the protein, and in fact, some researchers have already applied this technology to the study of psychiatric disorders.⁴⁷⁻⁴⁹ 

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REFERENCES

1. Tsuang MT, Faraone SV. *The Genetics of Mood Disorders*. Baltimore, Md: Johns Hopkins Press; 1990.
2. Faraone SV, Kremen WS, Tsuang MT. Genetic transmission of major affective disorders: Quantitative models and linkage analyses. *Psychol Bull.* 1990;108:109-27.
3. Gottesman II, Shields J. *Schizophrenia: The Epigenetic Puzzle*. Cambridge, Ma: Cambridge University Press; 1982.
4. Pato CN, Lander ES, Schultz SC. Prospects for the Genetic Analysis of Schizophrenia. *Schizo Bulletin.* 1989;15(3):365-72.
5. Pato CN, Azevedo MH, Pato MT, et al. Selection of Homogeneous Populations for Genetic Study: The Portuguese Genetics of Psychosis Project. *Am J Med Genet (Neuropsychiat Genet).* 1997;74:286-8.
6. Greenberg DA. There is more than one way to collect data for linkage analysis. What a study of epilepsy can tell us about linkage strategy for psychiatric disease. *Arch Gen Psychiatry.* 1992;49:745-50.
7. Goldin LR. The increase in type 1 error rates in linkage studies when multiple analyses are carried out on the same data: A simulation study (Abstract). *Am J Hum Genet.* 1990;47:A180.
8. Goldin LR, Weeks DE. Two-locus models of disease: Comparison of likelihood and nonparametric methods. *Am J Hum Genet.* 1993;53(Suppl): 1006.
9. Weeks DE, Lehner T, Squires-Wheeler E, Kaufmann C, Ott J. Measuring the inflation of the lod score due to its maximization over model parameter values in human linkage analysis. *Genet Epidemiol.* 1990;7:237-43.
10. Risch N. Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *Am J Hum Genet.* 1990;46(2):229-241.
11. Kruglyak L, Daly M, Daly MPR, Lander E. Parametric and Nonparametric Linkage Analysis: A Unified Multipoint Approach. *Am J Hum Genet.* 1996;58:1347-1363.
12. Straub RE, MacLean CJ, O'Neill FA, et al. A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Nat Genet.* 1995 Nov;11(3):287-93.
13. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet.* 1995;11:241-7.
14. Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Hum Molec Genet.* 1997;6(4):577-82.
15. Jonsson EG, Mothen MM, Neidt H, et al. Association between a promoter polymorphism in the dopamine D2 receptor gene and schizophrenia. *Schizophr Res.* 1999;40:31-6.
16. Ohara K, Hagai M, Tami K, et al. Functional polymorphism of -141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. *Psychiatry Res.* 1998;81:117-23.
17. Schindler KM, Pato MT, Dourado A, et al. Association and linkage disequilibrium between a functional polymorphism of the dopamine-2 receptor gene and schizophrenia in a genetically homogeneous Portuguese population. *Mol Psychiatry.* 2002;7(9):1002-5.
18. Li T, Arranz M, Aitchison KJ, et al. Case-control, haplotype relative risk and transmission disequilibrium analysis of a dopamine D2 receptor functional promoter polymorphism in schizophrenia. *Schizophr Res.* 1998;32:87-92.
19. Talerico T, Ulpian C, Liu IS. Dopamine D2 receptor promoter polymorphism: no association with schizophrenia. *Psychiatry Res.* 1999;85:215-9.
20. Stober G, Jatzke AH, Jungkunz G, et al. Insertion/deletion variant (-141 C Ins/Del) in the 5' regulatory region of the dopamine D2 receptor gene: lack of association with schizophrenia and bipolar disorder. *J Neural Transm.* 1998;105:101-9.
21. Arranz MJ, Munro J, Li T, et al. A polymorphism in the promoter region of the dopamine D2 receptor gene (DRD2) and drug response: association studies. *Schizophr Res.* 1998;29:127.

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