Course ID: CMEC27

Molecular Genetics of Schizophrenia: An Update

Course director: Mike Owen

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Educational Objectives: To provide an update on advances in molecular genetics and pharmacogenetics of schizophrenia that will be broadly intelligible to psychiatrists and to outline the likely impact that the sequencing of the human genome will have on this area.

Course description: It is clear from family, twin and adoption studies that there is an important genetic contribution to schizophrenia. The commonest mode of transmission is probably oligogenic or polygenic or a mixture of the two. However the number of susceptibility loci, the disease risk conferred by each locus, and the degree of interaction between loci all remain unknown. In spite of these uncertainties schizophrenia has seemed to many a compelling candidate for molecular genetic studies using both linkage and association approaches.

The majority of systematic linkage studies of schizophrenia have focused upon large, multiply affected pedigrees for analysis. Many studies have been reported but have failed as yet to produce unequivocal, replicated demonstrations of linkage. However, modest evidence for several regions has been reported in more than one data set. The results of a recent meta-analysis of 20 genome scans for linkage will be presented indicating several regions of further follow-up.

Once genes of smaller effect than s = 1.5 are sought the number of affected family members required becomes prohibitively large. For this reason many researchers have sought to take advantage of the potential of candidate gene association studies to identify such loci. Most candidate gene studies have been based upon neuropharmacological studies suggesting that abnormalities in monoamine neurotransmission play a role in the aetiology of schizophrenia. Overall, the results have been disappointing, but it should be noted that the sample sizes in many of the older studies would now generally be regarded as inadequate, particularly in view of the fact that the polymorphic markers in question did not in themselves represent functional variants and few genes have been systematically screened. However, there have been more promising reports of candidate gene associations although the effect sizes are small, in no case has a stringent burden of proof been met, and it is possible that these are false positives or the result of association with a confounding variable such as severity or a co-morbid syndrome.

Finally, prospects for the field following the availability of the draft human genome sequence and the implications for psychiatry for the identification of susceptibility genes will be discussed.

The course will consist of 5 Components as follows
1. Background, Genetic Epidemiology, Linkage Studies. 45 mins, ?MO
2. Tea. 15 mins
3. Association Studies and Pharmacogenetics. 45 mins, NW
4. Future Implications. 45 mins, MO
5. Discussion. 30 mins.

https://doi.org/10.1016/S0924-9338(02)85026-X Published online by Cambridge University Press

The three lectures will be accompanied by PowerPoint presentations, and a refence list for further reading distributed. Discussion and interaction will be encouraged.

Target audience: Psychiatrists, basic scientists, pharmaceutical industry.

Course level: Basic.

https://doi.org/10.1016/S0924-9338(02)85026-X Published online by Cambridge University Press