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Genetics of Schizophrenia: Recent Advances

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ABSTRACT *~ Genetic studies of schizophrenia have been fraught with challenges, yet molecular genetic and genomic methods remain essential to the discovery of the underlying biological mechanisms. Candidate genes and genome scan studies have played a significant role in the search for susceptibility loci. Studies in genetic isolates appear to be providing some of the most consistent results. These populations are characterized by a greater degree of homogeneity, which is hoped to be advantageous in the identification of genes contributing to the disease phenotype. The following review highlights some recent advances in schizophrenia research, with a focus on disease etiology, candidate genes, genome scan studies, and molecular genetic approaches.* Psychopharmacology Bulletin. *2007;40(4):168–177.*

EPIDEMIOLOGY AND FAMILIAL RISK

Schizophrenia, one of the more debilitating neuropsychiatric syndromes, affects as much as 1% of the population worldwide. Despite the fact that schizophrenia is characterized by a strong genetic element, the mode of inheritance remains unclear.[1,2] It is apparent, however, that relatives of schizophrenic patients sustain the most consistent and significant risk for developing schizophrenia. The high degree of heritability (approximately 80%) of schizophrenia has instigated innumerable studies over the last 50 years, resulting in comprehensive twin and adoption studies, as well as family studies. These studies indicate that an individual's risk for schizophrenia is commensurate with their degree of relatedness to a schizophrenic.[3] The monozygotic twin of a schizophrenic is at the greatest risk for developing schizophrenia, approximated at 50%. The risk is only slightly less for an individual born to two schizophrenic parents. The risk for schizophrenia decreases to 10-15% for siblings, dizygotic twins, and individuals parented by only one schizophrenic. This pattern of heredity provides strong support for a significant genetic component, although non-genetic components are likely to contribute to the risk for and expression of schizophrenia.[4]

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Our own studies have focused on the geographically and potentially genetically isolated islands of the Azores and Madeira.[5] Our research indicates that the most densely populated Azorean island has a lifetime prevalence for schizophrenia of less than 0.3%, while the familiality of schizophrenia is approximately 70% . The worldwide prevalence, however, is thought to be 1% with an estimated 10–15% familiality rate.

MOLECULAR GENETIC APPROACHES

Molecular genetic approaches range from variations on classic association studies that examine markers for a particular gene in patients versus those in controls, to linkage studies that focus on the inheritance patterns of a locus or region in the genome and illness in families. Linkage studies, in turn, are either parametric, meaning they test a specific model of inheritance, or non-parametric, defined as being inheritance model independent. In past studies, large multiplex families with schizophrenia were subjected to parametric linkage analysis, focusing on the identification of a single major locus. Given the difficulty encountered in replicating the findings, this analytical model may have been too simple to contend with the genetic complexities of schizophrenia.[4] Consequently, the emergence of non-parametric linkage analyses, which are based on shared alleles, shared by descent, has provided a potentially more replicable methodology. Indirectly, this has been coupled with a move to collect affected sib-pairs. The benefits and limitations of focusing linkage studies on large families, rather than medium-sized families or pairs of relatives, have been extensively documented over the years.[6–9]

Genetic association studies continue to evolve, utilizing both familial association strategies and increasingly sophisticated population-based association strategies to test specific candidate genes and haplotypes. Haplotypes are a series of linked molecular markers that serve to specifically identify a region of chromosome which may include one or more genes. The power of genetic association approaches has been compared with other strategies by Goldin and Weeks,[8] suggesting that an appropriate genetic association strategy may be the most powerful method for testing a reasonable candidate gene.

GENOME SCANNING

Non-parametric methods, such as the statistically powerful and model-independent non-parametric linkage (NPL) analysis detailed by Kruglyak et al.[11] are now being used for studies of etiologically complex disorders, like schizophrenia. Kruglyak et al. employed the GENEHUNTER computer software to perform NPL analysis to the existing data from Straub's Irish schizophrenia family study,[12] revealing

non-parametric and parametric analyses to be equally powerful tools for linkage detection.

Statistical thresholds were mathematically determined to facilitate the process of defining the varying degrees of genetic linkage of a complex trait.[13] Appropriate thresholds have been described for establishing linkage as being suggestive, significant, or confirmed. In general, the occurrence of statistical evidence 0.05 times in a genome scan ($P = 0.00002$ for sib-pair studies) is indicative of significant linkage. Suggestive linkage is considered when a genome scan yields statistical evidence once at random ($P = 0.0007$ for sib-pair studies). The use of specific simulation strategies to set the significance thresholds for each specific population study has become standard. Taking the actual family structures and simulating the chance occurrence of a signal under the condition of no linkage allows for the most accurate assessment of the significance of a finding.

CANDIDATE GENES

Genes implicated in the pathophysiology of a disease are known as candidate genes. Through analysis of allele frequency differences in affected patients versus unaffected controls or using family based association strategies, the candidate gene method can effectively identify genes that play only a small role in the transmission of a complex disorder. The dopaminergic and serotonergic systems, given the effectiveness of some antipsychotic medications that target their system-specific receptors, have been extensively studied utilizing the candidate gene approach.

A case-control study of the Japanese population revealed a potential association between schizophrenia and a functional polymorphism in the DRD2 receptor promoter (−141C Ins/Del; $p < 0.001$).[14] This observation has since been replicated.[15,16] In the Portuguese population, we have replicated these findings.[17] However, other studies failed to confirm these findings.[18–21]

In similar fashion, serotonin receptors are targeted by atypical antipsychotics. Among the serotonin system genes that we have investigated are HTR_{1D}-alpha, HTR_{1D}-beta, HTR_{2A}, and the serotonin transporter gene. The HTR_{1D}-alpha receptor has demonstrated a positive association in a study of Portuguese schizophrenics ($p = 0.002$),[22] and the HTR_{2A} receptor showed an association with schizophrenia in a European population.[23]

Recently, the alpha 7-nicotinic receptor gene (CHRNA7) has been revealed as another candidate gene for schizophrenia studies.[24–26] Our studies in the Portuguese island populations support these findings.[27] The chromosome 22q13 region, along with the 14-3-3η and SYNAPSIN III loci, have been investigated,[28] and the unknown

genomic markers contained within this region have been mapped. Our studies focused on this region have suggested association for both the 14-3-3η locus ($p < 0.01$)[29] and the SYNAPSIN III locus, indicating the possibility that these are susceptibility loci for schizophrenia within the Portuguese population. Furthermore, chromosome 22q exhibited significant linkage in a combined meta-analysis of schizophrenia and bipolar disorder ($p < 0.00000008$).[30]

Neuregulin 1 (NRG1) appears to have a role in oligodendrocyte proliferation and survival. Significant linkage was reported for NRG1 and schizophrenia on chromosome 8p21 (NPL 3.64; $p = 0.0001$).[31] A linkage/association study of the Icelandic population identified a haplotype correlated with schizophrenia, and this study has since been replicated in a set of Scottish patients.[32,33] Further studies of NRG1 are ongoing in our labs and by other groups.

GENETICALLY COMPLEX DISORDERS

Many common disorders, such as diabetes and cancer, exhibit similarly complex patterns of inheritance as schizophrenia. Assuming that schizophrenia is a syndrome made up of a number of different illnesses, no single mode of inheritance may, in fact, be present. Studies based on potentially homogeneous populations are anticipated to maximize the probability that multiple families within each sample will share the same genetic subtype. In our work, we have described this as disease homogeneity. The hypothesis is that many patients suffering with schizophrenia from a homogeneous population may share the same form of the illness, thus allowing a complex set of shared risks to be more easily identified.

There are a number of neuropsychiatric studies that focus on linkage in population isolates. While many of these studies are worthy of mention, we will touch on only a few.

Iceland

A recent study performed linkage analysis using five British and eight Icelandic families.[34] Pedigrees were selected that had a minimum of three generations multiply affected for schizophrenia. LOD-score analyses were performed for both dominant and recessive transmission using the VITESSE and FASTLINK programs, and model-free likelihood-based analyses were conducted using the MFLINK program. Five loci demonstrated significant linkage, based either on the entire set of thirteen pedigrees or on single pedigrees. Chromosomes 1q33.2 (HLOD 3.2; $p = 0.0003$), 5q33.2 (HLOD 3.6; $p = 0.0001$), 8p22.1-22 (HLOD 3.6; $p = 0.0001$), and 11q21 (HLOD 3.1; $p = 0.0004$) demonstrated significant heterogeneity LOD-scores in the whole sample. Similarly,

chromosomes 4q13-31 (LOD 3.2) and 11q23.3-24 (LOD 3.2) showed significant linkage within single families.

Finland

For the past decade, the Finnish population has been considered an ideal genetic isolate for extensive molecular genetic disease studies, including ovarian dysgenesis and aspartylglucosaminuria (AGU). Due to founder effect and genetic drift, sub-isolates in Finland exhibit a high prevalence for at least thirty rare genetic disorders, while some other disease loci are extremely rare in comparison with their prevalence in other populations.[35] In addition, neuronal dysfunction is common to over half of the cloned Finnish disease genes.

A number of linkage studies have reported significant findings for chromosome 1 loci.[34,36] Peltonen's group performed fine-mapping for 221 extended pedigrees (1250 individuals).[37] Two-point and multipoint (SimWalk2) non-parametric analyses based on dominant transmission models were used to analyze the extended families (originating from a Finnish sub-isolate), nuclear families (originating from the rest of Finland), and the combined sample population. Strong evidence of linkage was discovered at the D1S2709 marker (extended family sample LOD 3.21, combined sample LOD 2.71), thus supporting previous studies implicating DISC1 as a schizophrenia susceptibility gene. Linkage was also indicated at markers D1S439 and D1S446 on 1q.

In a similar study, chromosomes 2q and 5q were also identified as containing potential susceptibility genes for schizophrenia, in addition to evidence suggesting linkage for 4q, 9q, and Xp[38] in the Finnish population sample. Based on the results of the genome-wide scan, the 2q (maximum LOD 4.43; $p = 0.013$) and 5q (maximum LOD 3.55; $p = 0.00019$) regions were further investigated using multipoint non-parametric analysis, with allele-sharing suggested at markers D2S427 and D5S1480, respectively. Further investigation of these putative susceptibility loci is underway.

Palau, Micronesia

The geographic and genetic isolation of the Palau islands makes them ideal for the study of complex neuropsychiatric disorders, particularly schizophrenia. Byerley's group conducted a complete ascertainment in Palau in order to characterize the epidemiology of schizophrenia in the population.[39] The lifetime prevalence for schizophrenia in Palau is 1.99%, but males showed a significantly higher prevalence than females (2.77% and 1.24%, respectively). This gender difference also extended to the age of onset for the disorder, averaged at 23.3 years for males and 27.5 years for females. Nearly half of the strictly defined schizophrenia

cases were identified within only eleven families, yet the familial distribution of these affected individuals is sparse. The aggregation of schizophrenia in these families has been attributed to the complex connections formed by marriages between different clans. Given this assessment of schizophrenia etiology in Palau, future studies will focus on the discovery and replication of susceptibility genes; however, the complex multilineal inheritance patterns demonstrated in Palauan pedigrees may complicate further analyses.

More recently, Byerley's group conducted a schizophrenia linkage study of five large multiplex families.[40] Linkage for each pedigree was evaluated using multipoint analysis (SimWalk2) based on dominant and recessive models. The most promising results were found for two regions in two different pedigrees: 5q distal (LOD 3.4, dominant model) and 3q (LOD 2.6, recessive model). Two other pedigrees yielded less promising but still notable scores for 5q and 9p (LOD >2.0).

Costa Rica (Central Valley)

Similarly, researchers have used the Costa Rican Central Valley population to study various complex disorders with evidence of genetic transmission. Previous bipolar studies have strongly implicated linkage with chromosome 18 in the Central Valley population,[41–43] and these findings have prompted similar studies for schizophrenia.

DeLisi's group performed a genome-wide linkage scan on 95 Costa Rican families.[44] No significant linkage appeared to be revealed in this study. When the strict schizophrenia phenotype was applied, however, the highest maximum likelihood score obtained from this genome-wide scan was attributed to chromosome 5q, which has produced evidence for linkage in other studies.[34,38,40,45,46]

Portuguese Islands (the Azores/Madeira)

The Madeiran and Azorean islands were settled by the Portuguese over five hundred years ago. The islands had no native population and underwent a programmed settlement with groups of families being awarded land and the right to settle different areas. The current population of Madeira is 300,000, and of the Azores is 249,000. The Pato group has worked with these populations for the last decade. As part of their studies, over 120 families multiplex for schizophrenia have been studied, as well as an additional 300 patients from small nuclear families.

A number of possible candidate genes are being explored in this population. A transmission disequilibrium test (TDT) was performed on 78 Portuguese trios to determine an association between the −141C Ins allele of the DRD2 receptor promoter and schizophrenia, yielding a $c2 = 8.76$; $p = 0.0031$.[17] We replicated these results using the

family-based association test (FBAT) with 69 multiplex Portuguese pedigrees, which was also consistent with association ($p < 0.038$). FBAT was also used to study the alpha 7-nicotinic receptor gene (CHRNA7). We initially analyzed five families and 25 trios from the Azorean islands using the FBAT and discovered significant linkage disequilibrium between schizophrenia and the L76630 genomic marker ($p = 0.0004$).[27] In a later study, our FBAT analysis of 46 Azorean multiplex pedigrees again revealed significant linkage disequilibrium between L76630 and schizophrenia ($p = 0.00028$).

The Portuguese island population study has also revealed strong linkage evidence on chromosome 5q for schizophrenia for a region that overlaps with all of the studies summarized above.[45] Evidence for possible linkage to 8p appears to be present as well.[45] Further characterization of these findings may allow for the identification of specific risk genes from this region. Multiple converging strategies are being employed to narrow in on the risk alleles.

META-ANALYSES

Meta-analytic methods have further implicated a number of regions in the pathophysiology of schizophrenia. Levinson et al.[46] presented a collaborative effort to study chromosome 1q, combining independently gathered pedigree sets of Canadian, Icelandic/British, Finnish isolate, Finnish national, US and Australian origins to create a large multicenter sample. A total of 779 pedigrees were studied. The NIMH sample set exhibited marginally significant results for the 1q distal region. However, the results were not statistically significant for the other individual sample sets or the large, combined sample. It is important to note that failure to replicate does not fully negate previous findings of promising susceptibility genes.

Badner and Gershon[30] presented evidence that chromosomes 8p, 13q and 22q show the strongest evidence for susceptibility loci for schizophrenia using the Multiple Scan Probability (MSP) meta-analysis technique. A combined meta-analysis of schizophrenia and bipolar disorder showed significance for chromosomal regions 13q and 22q. This modified meta-analysis method proved to be a strong tool for linkage detection in heterogeneous samples.

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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