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