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