Identification of Schizophrenia Susceptibility Genes in an Ethnically Homogeneous, Family-Based, Arab Israeli Sample

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On the topic:

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Abstract:

There is strong evidence supporting a heritable basis for schizophrenia, a severe neuropsychiatric disorder that has its onset in adolescence and early adulthood and has a lifetime prevalence of ~1%. Concerted efforts are being mounted to identify the specific genes that confer susceptibility to schizophrenia. These efforts have had limited success. We have taken the approach that the likelihood of finding schizophrenia susceptibility genes should be increased in ethnically homogeneous samples. In a genome-wide linkage study of schizophrenia in Arab Israeli families with multiple affected individuals, we previously reported significant evidence for a susceptibility locus at chromosome 6q23.2-q24.1 and suggestive evidence at chromosomes 10q22.3-26.3, 2q36.1-37.3 and 7p21.1-22.3 (1). To focus on the linkage peak and to identify susceptibility genes within the 6q23 region, fine-mapping was performed in the linkage sample (2) and extensive SNP genotyping was done in an expanded sample of Arab-Israeli nuclear families from the same geographical region of Israel (3, 4). The most significant genetic association with schizophrenia was detected within a genomic region that contains the \textit{AHI1} gene and the nearby \textit{C6orf217} gene (3, 4). The top SNP associations were further replicated in an independent case-control sample of Icelandic ancestry (5) and recently in large European and Spanish/German case-control samples (6, 7) and also in patients with autism. Translational studies from our laboratory provided convergent support for association of \textit{AHI1} with schizophrenia by demonstrating increased \textit{AHI1} expression in lymphoblast cell lines from schizophrenia patients in the Arab Israeli family sample and association of increased \textit{AHI1} expression with homozygosity for the over-expressed A allele of SNP \textit{rs932150}, in brain samples from the Stanley Collection (8). Notwithstanding our replicated identification of schizophrenia susceptibility genes in the 6q region, additional associated variants could have been missed in our genome wide linkage study. With finer microsatellite mapping of the 10q23-q26 region we demonstrated stronger evidence for linkage with schizophrenia and identified a possible genetic interaction with the 6q23 region (9). To identify additional schizophrenia susceptibility genes, we applied a family-based GWAS strategy in an enlarged Arab Israeli family sample and found genome-wide significant association (best p-value=1.22x10^{-11}) for 8 SNPs within or near highly reasonable functional candidate genes for schizophrenia. Of particular interest are a group of SNPs within and flanking the transcriptional repressor \textit{LRRFIP1} gene. To determine replicability of the significant associations beyond the Arab-Israeli population, we genotyped the SNPs in Jewish Israeli and German case-control samples and found replication of associations near the \textit{ACSL3, UGT1} subfamily and \textit{EFHD1} genes. Overall, this GWAS, which emphasizes the important contribution of family based studies, identifies promising candidate genes for schizophrenia.

References


