LETTERS TO THE EDITOR

Effects of a neuregulin 1 variant on conversion to schizophrenia and schizophreniform disorder in people at high risk for psychosis

Molecular Psychiatry (2009) 14, 118–119; doi:10.1038/mp.2008.1

One of the most important challenges in the prediction and early diagnosis of psychosis is to decrease the rate of false-positive cases. Here, we report a variant of the neuregulin 1 (NRG1) gene (SNP8NRG243177/rs6994992, TT genotype), which is associated with 100% psychosis conversion rate during a 12-month follow-up period in people at high clinical risk for psychosis.

Recently, Hall et al. found that the SNP8NRG243177 risk allele of the NRG1 gene, but not other SNPs (http://www.decode.com/nrg1/markers), is specifically related to the development of psychosis. They investigated 79 high-risk subjects from families with at least two individuals with schizophrenia (Edinburgh High Risk Study). These high-risk subjects were followed up for up to 10 years. Results revealed that all 12 high-risk subjects with the T/T SNP8NRG243177 genotype (100%) developed psychosis. As an alternative of the traditional high-risk approach, which focuses on the long-term follow-up of individuals with affected family members and with higher genetic vulnerability, others attempted to define clinical high-risk syndromes (‘at-risk’ mental state) that precede frank psychosis in clinical settings. However, it is unknown whether clinically ‘at-risk’ individuals, who develop psychosis, carry vulnerability genotypes.

Sixty-seven Hungarian individuals with Central European ancestry were recruited from the South Hungarian Crisis Management and Psychosis Prevention Outpatient Unit (1999–2005). All participants fulfilled the criteria of Attenuated Psychotic Symptoms (APS) and Brief Limited Intermittent Psychotic Symptoms (BLIPS) according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria. Toxicological screening, head MRI and EEG were performed. Participants were followed up for 12 months (regular weekly visits) and received supportive psychotherapy, anxiolytics and antidepressants. The CAARMS criteria were used to define full threshold psychosis, and each psychotic patient was diagnosed according to the diagnosis and statistical manual of mental disorders (DSM-IV) criteria using structured clinical interview for DSM-IV disorders (SCID-I) and SCID-II (Table 1). All participants were fully informed and gave their written informed consent.

Genomic DNA was extracted from venous blood samples. Genotyping was performed using a Sequenom MassARRAY (Sequenom, San Diego, CA, USA) system (triplicate run, error rate < 0.2%). The clinical assessors (SK and IK) were blind to genetic data. From the whole sample, 31 individuals developed psychosis (46.3%). From these individuals, 24 (77.4%) were diagnosed with schizophrenia and 7 (22.6%) were diagnosed with schizophreniform disorder. Table 1 shows that all individuals who carried the SNP8NRG243177 T/T genotype developed psychosis. The distribution of genotypes varied from the Hardy–Weinberg equilibrium ($\chi^2 = 27.43$, $P = 1.63 \times 10^{-7}$), with a deficit of heterozygotes (Table 1). The $\chi^2$ test comparing all genotypes revealed a significant difference ($\chi = 48.77$, df = 2, $P = 2.58E-11$; Fisher’s exact test: $P = 1.81E-14$). $\chi^2$ tests also indicated significant differences in psychosis conversion rate between individuals with T/T and T/C genotype ($\chi = 21.26$, df = 1, $P = 4.0E-6$; Fisher’s exact test: $P = 1.28E-05$), as well as between individuals with T/T and C/C genotype ($\chi = 47.53$, df = 1, $P = 5.41E-12$; Fisher’s exact test: $P = 1.14E-13$).

One-way analysis of variance (ANOVA) indicated a significant main effect of genotype on IQ ($F = 6.15$, df = 1.64, $P < 0.005$) and on global assessment of functioning (GAF) scores ($F = 9.17$, df = 1.64; $P < 0.001$). Tukey’s honestly significant difference (HSD) tests indicated that individuals with T/T genotype had lower IQ and GAF scores relative to individuals with C/C genotype ($P < 0.005$ and $P < 0.001$, respectively) (Table 1).

For the analysis of population stratification, 20 single nucleotide polymorphism (SNPs) were genotyped in 230 control participants with Central European ancestry (recruited from the general population) and in our high-risk participants for the region chr8 (31520000–32854000 (NCBI Build 34)): rs10954811, rs1503491, rs553950, rs327329, rs7007662, rs14871672, rs726906, rs1481747, rs7015249, rs1487141, rs901561, rs1545961, rs1946098, rs10091429, rs6468099, rs6986716, rs10954842, rs2347501, rs10096770 and rs10993464 (see Thompson et al.). We used the method of Pritchard and Rosenberg and the Genomic Control (GC) method. This analysis revealed no evidence for population stratification ($P > 0.5$).

To examine the possibility that high-risk subjects were hemizygous rather than homozygous, we measured gene dosage effect using real-time PCR (SNPs investigated: rs31576593, rs4513929, SNP8NRG221132, SNP8NRG243177, rs6994992 and SNP8NRG221132, respectively).
SNP8NRG243177

| SNP8NRG221533, rs10096573, rs4268090, rs4452759, rs4733263, rs4476964, SNP8NRG241930, SNP8NRG243177, rs7819063, rs4733267, rs11783236 and rs7000831; see Addington et al.7 and http://www.hapmap.org/.

The primary measure was threshold cycle (Ct value). We adapted the comparative method with double-dye oligonucleotides (TaqMan probes, Applied Biosystems, Foster City, CA, USA) of Bubner and Baldwin.8 We found no evidence for hemizygosity in our sample. The distribution of the genotypes deviated from the Hardy–Weinberg equilibrium. Since genotyping errors were controlled, this may be due to the fact that the participants were recruited on the basis of ‘at-risk’ mental states, which may have resulted in a biased enrichment for people with the T/T risk genotype. In this respect, the small sample size is a critical factor, which is a general problem in the research of ‘at-risk’ mental states. Two other possible confounding factors related to excessive homozygosity (population stratification and hemizygosity) also were excluded.

NRG1 is one of the most important candidate genes, playing a crucial role in many aspects of the pathophysiology of schizophrenia (neuronal development, synaptic plasticity, glutamatergic neurotransmission and glial functioning). The SNP8NRG243177 variant is of special relevance. Using a bioinformatic approach, Law et al.9 showed that this variant affects the binding of transcription factors to the 5’ promoter region of the gene and is associated with the expression of a newly described isoform of the protein. Further studies are necessary to elucidate how this variant leads to pathological processes that increase the risk of psychosis, and how this genetic trait may interact with environmental factors. Given that this study confirms and extends an earlier report,1 it is tempting to speculate on use in psychosis risk prediction, especially in clinically high-risk populations.


doi:10.1038/mp.2008.77

Molecular Psychiatry (2009) 14, 119–120;

Studies reporting correlations between genetic variants and human phenotypes, including disease risk as well as individual differences in quantitative phenotypes such as height, weight or personality, are notorious for the difficulties they face in providing robust evidence.3 Notably, in many cases an initial finding is followed by a large number of attempts at replication, some positive, some negative.3–5 Although there has been debate over the statistical arguments concerning the strength of evidence in association studies,3 there has been less interest in understanding why it is that some genetic associations...