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Letter to the Editor

Decreased peripheral expression of neuregulin 1 in high-risk individuals who later converted to psychosis

Dear Editors,

Efforts to identify individuals with high psychosis risk have focused on biological markers that show a marked association with later conversion to full-blown psychosis. Hall et al. (2006) found that a variant in the human neuregulin 1 *(NRG1)* promoter region is associated with increased development of psychotic symptoms in high-risk individuals. These results were replicated in a Hungarian sample (Kéri et al., 2009). NRG1 plays an important role in neurodevelopment and synaptic plasticity by the regulation of glutamatergic and gamma-amynobutiric acidergic (GABAergic) neurons, and its risk variants are related to altered gene expression in postmortem brain tissue (Law et al., 2006). Previous studies demonstrated decreased peripheral NRG1expression in schizophrenia (Chagnon et al., 2008; Zhang et al., 2008), but it is not clear whether these changes can reliably predict psychosis conversion in high-risk individuals.

In order to elucidate this issue, we enrolled 97 help-seeking individuals who visited the outpatient units of the University of Szeged, Bács-Kiskun Country Hospital, and Semmelweis University, Hungary. The control group included 50 healthy volunteers with a negative family history for psychotic disorders. Ultra-high-risk status was evaluated using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (McGorry et al., 2003; for a study description, see Kéri et al., 2009).

For the measurement of NRG1 isoforms, we adopted the protocol of Zhang et al. (2008). Blood was drawn from the cubital vein into a sterile plastic tube. Total RNA was extracted and reverse transcribed into first-strand cDNA. Two isoforms of NRG1 were measured using semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) (glial growth factor-2 [GGF2, type II] and heregulin beta 3 [HRG-beta3, type I]; upstream primer: 5′-CTTTCTTGTTGCTGCATCTCC-3′; downstream primer: 5′-CACCCTTTT-CAGGATGTGGT-3′). Glyceraldehyde-3-Phosphate Dehydrogenase (G3PDH) was the internal control because its level is unchanged in schizophrenia (upstream primer: 5′-ACCACAGTCCATGCCATCAC-3′; downstream primer: 5′-TCCACCACCCTGTTGCTGTA-3′). We used cDNA for amplification with upstream and downstream primers of NRG1 and G3PDH, Taq DNA polymerase, dNTP, and PCR buffer. The protocol of the DNA thermal cycler included the following steps: initial denaturation at 95 °C for 5 min, cycles at 94 °C for 45 s, annealing at 65 °C (G3PDH at 62 °C) for 30 s, and extension at 72 °C for 90 s (35 cycles for NRG1 and 30 for G3PDH). Following the electrophoresis of the PCR products (2.0% agarose gel containing ethidium bromide), the optical density of NRG1 (type I and III combined) and G3PDH mRNA was determined. The ratio of the NRG1 and G3PDH mRNA optical density was the dependent measure (Zhang et al., 2008).

Of the 97 high-risk individuals enrolled in the study, 31 participants (32%) developed psychotic disorders (schizophrenia, schizophreniform disorder, psychotic mood disorder) by the end of the 12-month follow-up period (for demographic details, we refer to Kéri et al., 2009). None of the participants received psychotropic medications before the first psychotic episode. The ANOVA conducted on the NRG1/G3PDH ratios revealed a significant main effect of group ($F(1,144) = 16.58$, $p < 0.001$). Scheffé's tests indicated that converters who developed psychosis had lower NRG1/G3PDH ratios compared with healthy controls ($p < 0.001$) and with non-converter high-risk individuals who did not develop psychosis ($p < 0.001$). Non-converters did not differ from controls ($p = 0.19$) (Fig. 1). Age, education, IQ, Global Assessment of Functioning (GAF) scores, and CAARMS values did not correlate with NRG1 mRNA expression ($r < 0.1$, $p > 0.5$). There was no significant difference between male and female participants in either group ($p > 0.1$). When age and gender were included in the ANOVA as co-variants, the results remained the same.

These preliminary results suggest that peripheral NRG1 mRNA expression may be a biological marker of psychosis conversion in high-risk individuals. Limitations of this study include a small sample size, overlap among groups circumventing a reliable discriminant analysis, semi-quantitative nature of RT-PCR, and the combined measurement of two NRG1 isoforms. It is also possible that peripheral leukocyte mRNA levels do not accurately reflect those in the brain, although consistent alterations in neuronal and peripheral NRG1 expression have been documented in schizophrenia (Hashimoto et al., 2004; Petryshen et al., 2005). Therefore, the results of the present study must be replicated in an independent and larger sample.

Contributors

S.K. and O.K. designed the study and wrote the first draft of the paper. I.K. performed the experimental measurements and analyzed the data. All authors contributed to the final version of the manuscript.

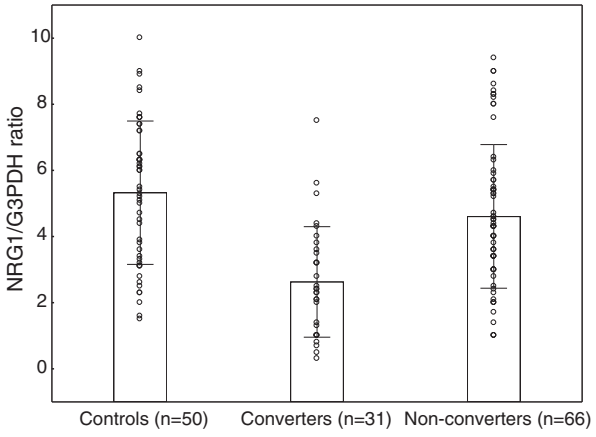

Fig. 1. Mean NRG1/G3PDH mRNA ratios in healthy controls, high-risk individuals who later developed psychosis (converters), and in those who did not develop psychosis (non-converters). Error bars indicate standard deviations.

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Conflict of Interest

The authors declare no conflict of interest.

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