A likely association between genetic variants at the *GRIN1* gene and schizophrenia with lifetime history of depressive symptoms in a German sample

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Abstract

Genetic variation in glutamatergic signalling pathways is believed to play a substantial role in the etiology of schizophrenia (SCZ). The N-methyl-D-aspartate (NMDA) receptor subunit gene *GRIN1* has been proposed as a candidate gene for SCZ.

We tested for a potential association between SCZ and four SNPs (rs4880213, rs1146020, rs6293, and rs10747050) and one microsatellite marker (position 137303343, build Nov 2002) at *GRIN1* in a German sample of 354 patients and 323 controls.

We found significant associations in single-marker and haplotype-based analyses ($p<0.05$).

Significance was more pronounced ($p<0.01$) in the subset of patients with a life-time history of major depression (MD), a subgroup of SCZ described previously as a promising phenotypic subtype in genetic studies of SCZ.

Although significances did not withstand correction for multiple testing, the results of our exploratory analysis warrant further studies on *GRIN1* and SCZ.

Methods

Study sample

We studied a sample of 354 SCZ cases and 323 population-based control individuals from Germany (Figure 1). Ascertainment, recruitment, and phenotype characterization (based on DSM-IV) procedures are detailed elsewhere (Fangerau et al. 2004). Control individuals were systematically recruited with the help of the local census bureau of the City of Bonn (136 males, 187 females).

Figure 1: Distribution of Age of the Study Sample

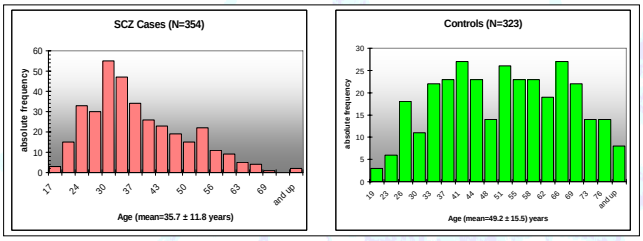
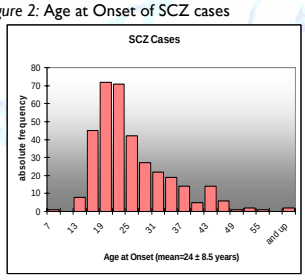


Figure 2: Age at Onset of SCZ cases



The 354 SCZ cases (198 males, 156 females) had a mean age of onset of 24 ± 8.5 years (Figure 2).

Genotyping

- In the *GRIN1* gene, we genotyped one microsatellite (position 137303343, build Nov 2002) and four SNPs (rs4880213, rs11146020, rs6293 and rs10747050) on chromosome 9q34 (called Marker 1 to 5, respectively)
- Genotypes were determined by Masscode™ Technology (QIAGEN Genomics)
- Genotype frequencies for cases and controls were in Hardy-Weinberg equilibrium

Genetic case-control analysis

We performed both single-marker and haplotype analyses with the program COCAPHASE 2.4 (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/).

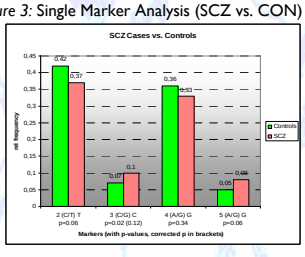
For all analyses, a permutation procedure was used to estimate the significance of the best results, correcting for all loci tested. Ten thousand permutations were performed.

Results

Single-marker analyses (Figure 3) revealed a nominally significant association with marker 3 ($p=0.02$; OR for C-allele=1.59). Markers 2 and 5 fell short of significance ($p=0.06$ and $p=0.06$) and marker 4 did not show significant association.

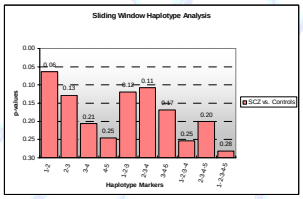
After correction for multiple testing through permutation, the association for marker 3 disappears.

Figure 3: Single Marker Analysis (SCZ vs. CON)



Sliding Windows Haplotype analysis (Figure 4) shows no significant associations for any window size and marker combination (only already permuted p-values shown).

Figure 4: Haplotype Analysis (SCZ vs. CON)



More Results

Previous research on modelling genetic heterogeneity has demonstrated the importance of clinically defined subgroups (Schulze & McMahon 2004; Schulze et al. 2005), such as the group of SCZ patients with a life-time history of major depression (MD) (Schumacher et al., 2005; Hamshere et al., 2006; Williams et al. 2006).

To clarify the relationship between *GRIN1* and SCZ, we identified those SCZ cases with a lifetime history of Major Depression (MD), resulting in a sample of 87 cases (43 males, 44 females, mean age 38.2 ± 12.3 years) (Figure 5).

Figure 5: Distribution of Age and Age at Onset of the SCZ cases with MD

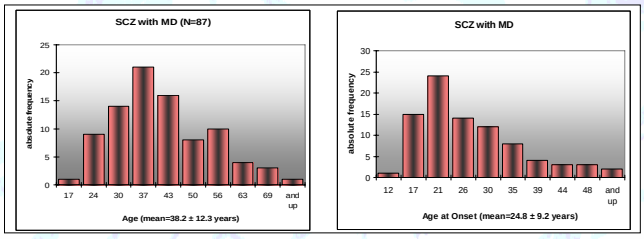
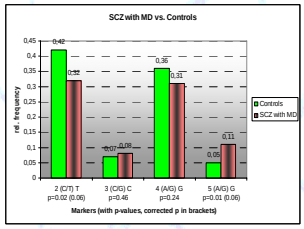


Figure 6: Single-Marker SCZ+MD vs. Controls

Single Marker analysis (SCZ with MD) (Figure 6) shows nominally significant results for marker 2 ($p=0.02$; OR for C-allele=1.55) and marker 5 ($p=0.01$; OR for G-allele=2.26).

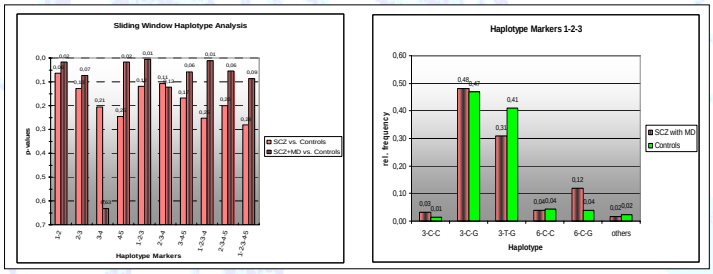
After correction for multiple testing by permutation, these results also disappear.



Sliding Windows Haplotype analysis (SCZ with MD) (Figure 7)) Comparison between the MD subgroup of SCZ patients and controls shows several nominally significant haplotypic associations, with the smallest global $p=0.0023$ (permuted $p=0.005$) for the three-marker-haplotype of markers 1 to 3 (microsatellite (position 137303343, build Nov 2002), rs4880213 and rs11146020).

After further correction for the number of markers/haplotype windows and two phenotypic groups with the Bonferroni procedure, our results cease to be significant (required p-value=0.05/30=0.0017).

Figure 7: Haplotype SCZ+MD vs. Controls Analysis



Summary & Discussion

Functional alterations of N-methy-D-aspartate receptors (NMDARs) are hypothesized to be involved in the etiology of schizophrenia (SCZ). The gene *GRIN1*, which encodes the functionally important NMDAR NR1 subunit, has received increased recent attention as a potential candidate gene for SCZ.

Studies applying a variety of analytical approaches (case-control design, TDT, gene-interaction studies) in other populations reported positive association between *GRIN1* markers and SCZ (Martucci et al. 2003, Canadian sample; Begni et al. 2003, Italian sample; Qin et al. 2005, mainland Chinese sample) and response to treatment with clozapine (Chiu et al. 2003; Taiwanese sample). More recently, Zhao et al. (2006) studied a very large sample of Han Chinese subjects and found significant associations.

Although our exploratory study, the largest in a European population to date, does not reveal an association withstanding the very conservative correction for multiple testing, our results do not exclude the potential involvement of *GRIN1* in the etiology of schizophrenia.

It also suggest that future genetic studies may benefit substantially from stratification for clinically defined SCZ subgroups, such as patients with a lifetime history of Major Depression.

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