Association of Variants in DISC1 With Psychosis-Related Traits in a Large Population Cohort

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Context: There is an abundance of data from human genetic studies and animal models that implies a role for the disrupted in schizophrenia 1 gene (DISC1) in the etiology of schizophrenia and other major mental illnesses.

Objective: To study the effect of previously identified risk alleles of DISC1 on quantitative intermediate phenotypes for psychosis in an unselected population.

Design: We examined 41 single-nucleotide polymorphisms within DISC1 and performed tests of association with 4 quantitative phenotypes.

Setting: Academic research.

Participants: Individuals from an unselected birth cohort in Finland. Originally, everyone born in the catchment area in 1966 (N=12,058) was included in the study. Of these, 4,651 (38.6%) attended the 31-year follow-up and could be included in the study.

Main Outcome Measures: Scores on 4 psychometric instruments selected to function as proxies for positive and negative aspects of psychotic disorders, including the Perceptual Aberration Scale, Revised Social Anhedonia Scale, Revised Physical Anhedonia Scale, and Schizoidia Scale by Golden and Meehl.

Results: Carriers of the minor allele of marker rs821577 had significantly higher scores on social anhedonia (P < .001). The minor allele of marker rs821633 was strongly associated with lower scores on social anhedonia when analyzed dependent on the absence of the minor alleles of markers rs1538979 and rs821577 (P < .001).

Conclusions: Variants in DISC1 affect the level of social anhedonia, a cardinal symptom of schizophrenia in the general population. DISC1 might be more central to human psychological functioning than previously thought, as it seems to affect the degree to which people enjoy social interactions.

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DISRUPTED IN SCHIZOPHRENIA 1 (DISC1) (OMIM 605210) is arguably one of the most relevant susceptibility genes for psychiatric disorders to date. It was identified as a susceptibility gene by linkage in a large Scottish family1 and by later demonstration that the linked translocation disrupts 2 novel genes, large protein-coding DISC1 and smaller DISC2.2 On the more general clinical population level, the gene has been shown to be linked3 and associated4 with schizophrenia in the Finnish population. DISC1 has also been studied in several other populations and has been shown to be associated with psychiatric,5,18 cognitive,6,19,20 memory,9,11 and neuroimaging8,12 phenotypes. In the ascertained studies performed so far, the estimate of the effect size of the risk variants has been low (eg, the odds ratio for schizophrenia in a European collaborative study22 was < 2). This is not surprising because it has, for example, been shown that the risk of schizophrenia for siblings of persons with the disorder (compared with the general population) that is attributable to a single gene variant cannot be greater than 3, probably much less.23 The reported associations and subsequent studies of the DISC1 gene and its protein could provide invaluable insight into the etiology of schizophrenia and other psychiatric disorders by shedding light on which molecular pathways may be involved in the molecular pathologic features behind the disorder. However, to assess the clinical importance of the previous findings, general population cohorts need to be studied rather than the unique families or heavily ascertained samples studied so far. Given the low odds ratio (< 2) for carriers of risk alleles of the gene and the low prevalence...
of the disorder (1%), any unascertained general population collection aimed at identifying differences in prevalence of end-state diagnosis between carriers and non-carriers of risk variants would have to be unreasonably large. Therefore, in the present population cohort study, we chose to study intermediate phenotypes of the disorder that can be assessed in the entire cohort and that at the same time are associated with the risk of end-state diagnosis.

For the explicit purpose of verification of psychosis susceptibility gene findings made in ascertained populations, we collected proxy measures of psychosis proneness and DNA samples in an unselected birth cohort in northern Finland. For large population cohorts, diagnostic interviews or extensive neuropsychological and physiological testing is not feasible. Therefore, in this study we used the best available questionnaire-based proxies of psychosis proneness. Common concepts of psychosis proneness follow a stress-diathesis model in which the neurobiologic vulnerability is expected to be present in the general population as a latent trait or taxon24,25 that can be assessed in the form of schizotypy (ie, psychoticlike) enduring personality features by self-rated psychometric tests. Several measures have been proposed that, for example, tap schizophrenialike peculiarities of perception (perceptual aberration) and reduction in the individual capability to appreciate physical pleasure (physical anhedonia) or social contact (social anhedonia). Individuals scoring high in these dimensions are assumed to bear a behavioral endophenotype26 that increases their risk to develop overt psychotic syndromes, and indeed follow-up investigations of the original cohorts have provided evidence of varying degree for the presence of these behavioral traits.26 However, most of the molecular genetic research on schizophrenia to date is selective in that it focuses on samples of unrelated individuals with schizophrenia (population association studies) or on family samples with several affected relatives (linkage studies). The molecular characterization of a broader schizotypia,25 estimated to be present in 10% of the population, remains elusive, although this could add considerably to the validity of any genetic finding in samples selected for the presence of manifest schizophrenia.

A previous study22 of case-control samples from 4 centers in Europe specified 3 single-nucleotide polymorphisms (SNPs) that affect the risk of schizophrenia and bipolar disorder. That study included a subsample from Finland and was considered more comprehensive and generalizable than previous association investigations in the genetically isolated Finnish population.26 The 3 SNPs affected the risk of schizophrenia because the minor allele of one of the markers (rs821633) increased the risk of schizophrenia when analyzed as a single variant and when dependent on the presence of the minor alleles of 2 other markers (rs1538979 and rs821577). However, the same minor allele was protective when rs821633 was analyzed dependent on the absence of the minor alleles of the 2 other markers. The risk of bipolar disorder was increased by the minor allele of rs821577. For this phenotype, the same minor allele of rs821633 was protective in that study. Our primary hypothesis was that the same combinations of alleles of the 3 SNPs that were associated with the risk of schizophrenia and bipolar disorder in the previous study22 would correspondingly be associated with scores on the psychosis proneness scales in the general population. Such a finding would provide strong support for the previous association findings. For the first time to our knowledge, it would extend the finding of a reported psychosis susceptibility gene to psychosis-related quantitative intermediate phenotypes in the general population.

METHODS

SUBJECTS AND ASSESSMENT

The Northern Finland Birth Cohort 1966 study was started in 1965 in the 2 northernmost provinces in Finland (Oulu and Lapland). Data on the individuals born into this cohort and on their mothers and fathers were collected from the 24th gestational week. The cohort included 12,055 mothers, and they had 12,068 deliveries (13 women delivered twice). Cases belonging to our survey period were determined by the calculated term. The study population comprised 96.3% of all births during 1966 in that area. Altogether, 12,231 children were born into the cohort, and 12,098 of them were live born.29 The original cohort data have been supplemented by data collected by postal questionnaires at the ages of 1, 14, and 31 years and by various hospital records and national register data, as well as by a physical examination at age 31 years. The data analyzed in this study were included in a questionnaire offered to individuals at the 31-year follow-up. A total of 4651 individuals completed the questionnaire and provided a DNA sample and written informed consent; this represented 40.3% of 11,541 individuals who could be contacted at age 31 years and 77.1% of 6033 individuals who took part in the follow-up study at age 31 years. Of 4651 individuals, 55.7% were female and 44.3% were male. To avoid the confounding effect of state-related effects of diagnosis or treatment on the scores of the traits used, all individuals with a psychiatric diagnosis according to the Finnish Hospital Discharge Register between 1982 and 1997 were excluded from the analysis (n = 124). Because few individuals were affected with schizophrenia (n=28), no association tests were performed between the selected markers and af?cction status.

The scales that were used included the Perceptual Aberration Scale (PER),30 Revised Social Anhedonia Scale (RSAS) (L. Chapman, PhD, unpublished test, 1982),31 Revised Physical Anhedonia Scale (RPAS) (L. Chapman, PhD, unpublished test, 1978),31 and Schizoidia Scale (SCHD) by Golden and Meehl.32 These scales were selected to assess normal properties that correspond to positive and negative aspects of psychotic disorders. As described previously,33 the scales were translated into Finnish by a native speaker and were then professionally back-translated into English and corrected. The scale items were mixed into a single pen-and-paper questionnaire with items from other scales and were tested in a sample of employees from the National Public Health Institute. The psychometric properties of these scales in this specific setting have been previously reported.34,35 Recent psychometric studies have shown that the dimensions of schizotypy measured by the RSAS and RPAS are not interchangeable indicators of a single taxon, as originally proposed by Meehl, but rather represent different underlying latent traits, namely, perceptual aberration as opposed to social anhedonia.36 Both of these traits, but not physical anhedonia, were valid predictors of later psychoses and psychotic-like experiences.37 Further work on the same longitudinal sample as that reviewed by Blanchard et al38 showed that social anhedonia, after controlling for the effects of the other psychos
proneness measures, independently and most clearly predicted later schizophrenia-spectrum personality disorders, social dysfunction, and poor quality of relationships. Therefore, among the diverse measures of schizotypy proposed to date, social anhedonia is probably most suitable as a behavioral intermediate phenotype of schizophrenia in population samples and was selected for our molecular genetic study of psychosis proneness in the population.

**GENOTYPING**

Forty-one SNPs in **DISC1** and **TSNAX** were selected to cover all regions of interest based on previous findings and all major haplotype blocks from control individuals in a previous study of **DISC1** in the Finnish population. The haplotype block structure in that study was determined using a computer program (Haploviev [http://www.broad.mit.edu/mpg/haploviev/]), and all SNPs were genotyped for the TSNAX-DISC1 region in the HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) population (International HapMap Project Web site [http://www.hapmap.org]). The blocks were defined using the solid spine of linkage disequilibrium (LD) (correlation coefficient between pairs of loci, D’ > 0.8). Adjacent blocks were combined with Hedricks multilalllelic D’ > 0.9. Thirty-four markers were genotyped by matrix-associated laser desorption ionization time-of-flight mass spectrometry (Sequenom Inc, San Diego, California), and 1 marker was genotyped by the S'-nuclease method (Applied Biosystems, Foster City, California), both according to the manufacturers’ protocols. The 40 markers genotyped by mass spectrometry were amplified in 2 multiplex reactions. Samples with success rates of less than 90% were excluded (134 of 4561 [2.9%]). The markers had success rates ranging from 97.07% to 99.55% (mean SD, 99.10% [0.47%]). No markers deviated from Hardy-Weinberg equilibrium at the P < .01 level. To assess the level of possible population stratification within the sample, we compared the allele frequencies in our sample with the allele frequencies identified in a Finnish control population by a previous study. These were performed using the χ² test. The absolute number of markers in our study was 41, but taking into account the intermarker LD using the procedure by Nyholt, the number of effective marker loci was 39.61. This means that a type I error rate of α = .05 corresponds to P = .001.

**STATISTICAL ANALYSIS**

The analyses were performed using commercially available software (SPSS, version 15.0 for Windows; SPSS Inc, Chicago, Illinois). Because all test variables were slightly right skewed, logarithmic transformation was performed for each variable. After transformation, the RSAS, RPAS and SCHD reached normality. However, the PER could not be normalized because its mode score was 0 (range, 0-35) (Table 1). This variable was considered nonnormally distributed in all analyses.

The association analyses were performed using an independent-samples t test for the normally distributed traits and using the Mann-Whitney test for the PER. Dominant and recessive genetic models were applied in the analyses. Because of sex specificity in many previous findings on **DISC1** and female preference in the previously reported interplay of 3 SNPs, all tests were performed for the combined sample and for men and women separately. The 41 SNPs were tested individually for association. To estimate the statistical significance of our findings, the most stringent of multiple comparison correction methods was used, namely, Bonferroni correction, which minimizes the risk of type I errors. Given the 2 inheritance models tested (recessive and dominant), the 3 sex classifications used (combined, women separately, and men separately), the 4 outcome measures (RPAS, RSAS, PER, and SCHD), and the number of independent marker loci, the total number of tests in our study was 2 × 3 × 4 × 39.61 = 9506.4. This means that a type I error rate of α = .05 corresponds to P < .001. This is the threshold we used to assess statistical significance in the tests of individual markers. This correction is obviously overly conservative because the 4 phenotypes are not independent of each other, association in the separate sexes is not independent, and dominant and recessive analyses are not independent. However, all of these issues make our threshold overly conservative, as we preferred to err on the side of caution in our interpretation.

To test our primary hypothesis (ie, the previously reported interplay between SNPs rs1538979, rs821577, and rs821633), these SNPs were further analyzed dependent on the absence of rick alleles at the other 2 loci. The multiple minor alleles at these marker loci were analyzed against all others (marker combinations, rs1538979 and rs821577, rs821577 and rs821633, rs1538979 and rs821633, and rs1538979, rs821577, and rs821633). Also, the minor alleles at only 1 of 3 marker loci were analyzed against all others. No P value correction was performed for these tests because they were strictly hypothesis based. Effect sizes for the significant variants were estimated using Cohen d.30

### ASSOCIATION ANALYSES OF INDEPENDENT SNPs

All 41 SNPs were tested for association with the 4 outcome measures, namely, the RSAS, RPAS, PER, and SCHD, applying dominant and recessive genetic models. SNP rs821577 displayed significant association after correcting for multiple testing in the combined sample under the dominant genetic model. Carriers of the minor allele of this SNP had significantly higher scores on the RSAS in the combined sample (P < .001), with a minor allele frequency (f) of 0.44 and Cohen d of 0.09 (Tables 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>PER</th>
<th>RSAS</th>
<th>RPAS</th>
<th>SCHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.33/2.54/2.06</td>
<td>9.39/8.08/11.03</td>
<td>15.02/12.70/17.94</td>
<td>2.54/2.77/2.25</td>
</tr>
<tr>
<td>SD</td>
<td>3.17/3.27/3.03</td>
<td>5.44/4.70/5.64</td>
<td>6.98/5.85/7.70</td>
<td>1.41/1.36/1.40</td>
</tr>
<tr>
<td>Range</td>
<td>0-35 For all</td>
<td>0-40 For all</td>
<td>0-61 For all</td>
<td>0-7 For all</td>
</tr>
</tbody>
</table>

Abbreviations: PER, Perceptual Aberration Scale; RPAS, Revised Physical Anhedonia Scale; RSAS, Revised Social Anhedonia Scale; SCHD, Schizoidia Scale by Golden and Meehl.
Women contributed most to the statistical significance when sex-specific analysis was performed ($P = .001$, $d = 0.13$ in women; and $P = .04$, $d = 0.05$ in men).

Modest uncorrected association with higher scores on the RPAS were detected in the combined ($P = .02$, $d = 0.08$) and female ($P = .006$, $d = 0.13$) samples. SNPs rs11122381 and rs821592 were associated with significant recessive effect on the RSAS when only women were included in the analyses. Female carriers of the minor alleles of these SNPs had significantly lower scores on the RSAS, with $d = 0.32$ for rs11122381 and $d = 0.24$ for rs821592 ($P = .001$ for both) (Table 2).

Because the threshold to maintain a type I error rate of $\alpha = .05$ after multiple testing correction was $P < .001$ uncorrected, the following 3 SNPs remained significant even after correction: marker rs821577 when analyzed in the combined sample and markers rs11122381 and rs821592 when women analyzed separately.

Although no other SNPs survived multiple testing correction, SNP rs821616, which has previously been shown to be associated with schizophrenia and cognitive aging,8,20,40 displayed modest uncorrected association with lower scores on the SCHD in our sample, $P = .02$ (minor allele $f$, 0.32) in the combined sample and in the male sample.

The genotype frequencies in our sample correspond well to the frequencies in the Finnish control population used in the previous study.22 None of the SNPs reached $P < .001$, which was the Bonferroni corrected threshold for $\alpha = .05$. No markers deviated from Hardy-Weinberg equilibrium at the $P < .01$ level. Taken together, these results suggest that no significant population stratification exists in the sample.

### Table 2. Results for the 3 Single-Nucleotide Polymorphisms Demonstrating Significant Association With Social Anhedonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>$P$ Valuea</th>
<th>Minor Allele Positive</th>
<th>Minor Allele Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs821577</td>
<td>Dominant</td>
<td>&lt;.001</td>
<td>9.55 (9.36-9.74)</td>
<td>9.04 (8.76-9.33)</td>
</tr>
<tr>
<td>rs11122381</td>
<td>Recessive</td>
<td>.007</td>
<td>8.55 (7.88-9.23)</td>
<td>9.44 (9.28-9.61)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs821577</td>
<td>Dominant</td>
<td>&lt;.001</td>
<td>8.27 (7.64-8.50)</td>
<td>7.67 (7.36-7.98)</td>
</tr>
<tr>
<td>rs11122381</td>
<td>Recessive</td>
<td>&lt;.001</td>
<td>6.32 (5.67-6.97)</td>
<td>8.17 (7.98-8.37)</td>
</tr>
<tr>
<td>rs821592</td>
<td>Recessive</td>
<td>&lt;.001</td>
<td>6.77 (6.20-7.34)</td>
<td>8.19 (7.99-8.38)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs821577</td>
<td>Dominant</td>
<td>.04</td>
<td>11.14 (10.83-11.44)</td>
<td>10.84 (10.36-11.33)</td>
</tr>
<tr>
<td>rs11122381</td>
<td>Recessive</td>
<td>.02</td>
<td>11.24 (10.18-12.30)</td>
<td>11.04 (10.77-11.30)</td>
</tr>
<tr>
<td>rs821592</td>
<td>Recessive</td>
<td>.02</td>
<td>11.71 (10.89-12.53)</td>
<td>10.98 (10.71-11.26)</td>
</tr>
</tbody>
</table>

**a** $P$ values significant at the Bonferroni-corrected $\alpha = 0.00005$ level are boldfaced.

**b** Carriers of the minor allele in the dominant model analyses and carriers of the homozygous minor allele in the recessive model analyses.

**c** Noncarriers of the minor allele in the dominant model analyses and noncarriers of the homozygous minor allele in the recessive model analyses.

### Table 3. Summary of $P$ Values for the Interplay of 3 Single-Nucleotide Polymorphisms in the Combined Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>PER</th>
<th>RSAS</th>
<th>RPAS</th>
<th>SCHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent of genetic background</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1538979</td>
<td>.76</td>
<td>.61</td>
<td>.33</td>
<td>.17</td>
</tr>
<tr>
<td>rs821577</td>
<td>.87</td>
<td>&lt;.001</td>
<td>.02</td>
<td>.53</td>
</tr>
<tr>
<td>rs821633</td>
<td>.29</td>
<td>.44</td>
<td>.97</td>
<td>.34</td>
</tr>
<tr>
<td>Dependent on the absence of other minor alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1538979</td>
<td>.44</td>
<td>.65</td>
<td>.72</td>
<td>.52</td>
</tr>
<tr>
<td>rs821577</td>
<td>.25</td>
<td>.20</td>
<td>.90</td>
<td>.39</td>
</tr>
<tr>
<td>rs821633</td>
<td>.55</td>
<td>&lt;.001</td>
<td>.008</td>
<td>.26</td>
</tr>
<tr>
<td>Dependent on carrying multiple minor alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1538979, rs821577</td>
<td>.81</td>
<td>.70</td>
<td>.66</td>
<td>.71</td>
</tr>
<tr>
<td>rs1538979, rs821633</td>
<td>.38</td>
<td>.74</td>
<td>.59</td>
<td>.42</td>
</tr>
<tr>
<td>rs821577, rs821633</td>
<td>.34</td>
<td>&lt;.001</td>
<td>.07</td>
<td>.26</td>
</tr>
<tr>
<td>rs1538979, rs821577, rs821633</td>
<td>.26</td>
<td>.78</td>
<td>.89</td>
<td>.56</td>
</tr>
</tbody>
</table>

**Abbreviations:** See Table 1.

3, and 4). Women contributed most to the statistical significance when sex-specific analysis was performed ($P < .001$, $d = 0.13$ in women; and $P = .04$, $d = 0.05$ in men). Modest uncorrected association with higher scores on the RPAS were detected in the combined ($P = .02$, $d = 0.08$) and female ($P = .006$, $d = 0.13$) samples. SNPs rs11122381 and rs821592 were associated with significant recessive effect on the RSAS when only women were included in the analyses. Female carriers of the minor alleles of these SNPs had significantly lower scores on the RSAS, with $d = 0.32$ for rs11122381 and $d = 0.24$ for rs821592 ($P < .001$ for both) (Table 2). Because the threshold to maintain a type I error rate of $\alpha = .05$ after multiple testing correction was $P < .001$ uncorrected, the following 3 SNPs remained significant even after correction: marker rs821577 when analyzed in the combined sample and markers rs11122381 and rs821592 when women analyzed separately.

Although no other SNPs survived multiple testing correction, SNP rs821616, which has previously been shown to be associated with schizophrenia and cognitive aging,8,20,40 displayed modest uncorrected association with lower scores on the SCHD in our sample, $P = .02$ (minor allele $f$, 0.32) in the combined sample and in the male sample.

The genotype frequencies in our sample correspond well to the frequencies in the Finnish control population used in the previous study.22 None of the SNPs reached $P < .001$, which was the Bonferroni corrected threshold for $\alpha = .05$. No markers deviated from Hardy-Weinberg equilibrium at the $P < .01$ level. Taken together, these results suggest that no significant population stratification exists in the sample.

### INTERPLAY OF 3 SNPs

A previous study22 described the modulation of effect when SNPs rs1538979, rs821577, and rs821633 were reanalyzed dependent on the genotypes at the other SNPs. Because these 3 were the only SNPs displaying significant interplay in the previous study, we restricted our interplay testing to these SNPs. Again, significant association was detected with the RSAS and RPAS but not with...
Table 4. Interplay of 3 Single-Nucleotide Polymorphisms on the Revised Social Anhedonia Scale (RSAS) and Revised Physical Anhedonia Scale (RPAS) in the Combined Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSAS</th>
<th>RPAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent of genetic background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs821577</td>
<td>9.55 (9.36-9.74)</td>
<td>9.04 (8.76-9.33)</td>
</tr>
<tr>
<td>rs821633</td>
<td>9.33 (9.14-9.52)</td>
<td>9.51 (9.20-9.82)</td>
</tr>
<tr>
<td>Dependent on the absence of other minor alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1538979</td>
<td>9.78 (8.18-11.38)</td>
<td>9.37 (9.21-9.54)</td>
</tr>
<tr>
<td>rs821577</td>
<td>9.55 (9.18-9.93)</td>
<td>9.34 (9.16-9.52)</td>
</tr>
<tr>
<td>rs821633</td>
<td>8.82 (8.47-9.17)</td>
<td>9.53 (9.34-9.71)</td>
</tr>
<tr>
<td>Dependent on carrying multiple minor alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1538979, rs821577</td>
<td>9.37 (8.90-9.85)</td>
<td>9.39 (9.22-9.56)</td>
</tr>
<tr>
<td>rs821577, rs821633</td>
<td>9.58 (9.34-9.81)</td>
<td>9.20 (8.98-9.43)</td>
</tr>
<tr>
<td>rs1538979, rs821633</td>
<td>9.32 (8.89-9.76)</td>
<td>9.39 (9.22-9.57)</td>
</tr>
<tr>
<td>rs1538979, rs821577, rs821633</td>
<td>9.45 (8.91-10.00)</td>
<td>9.37 (9.20-9.54)</td>
</tr>
</tbody>
</table>

* Significant differences are boldfaced.

a Carriers of the minor allele in the dominant model analyses and carriers of the homozygous minor allele in the recessive model analyses.

b Noncarriers of the minor allele in the dominant model analyses and noncarriers of the homozygous minor allele in the recessive model analyses.

In this study, we observed significant associations between markers in DISC1 and the trait of social anhedonia. This quantitative phenotype is assessed by a self-rated questionnaire and is designed as a proxy of psychosis proneness. A previous investigation of schizophrenia and bipolar disorder in a European collaborative study reported associations between 3 of the SNPs genotyped in this study and schizophrenia and bipolar disorder. In the previous study, the minor allele of rs821633 increased the risk of schizophrenia when the person also carried the minor alleles of SNPs rs1538979 and rs821577. However, dependent on the absence of the minor alleles of rs1538979 and rs821577, the minor allele of rs821633 decreased the risk for schizophrenia in the study. For bi-
polar disorder, the minor allele of rs821577 was an independent risk factor, while the minor allele of rs821633 was protective in the absence of other risk alleles. In the present study, we specifically set out to verify these findings in an entire birth cohort. Therefore, these 3 SNPs and their interplay were of primary interest. In addition, the allelic diversity of DISC1 was extensively monitored by genotyping 41 markers.

Of the 3 markers reported in the previous study, 
rs821577 was significantly associated with social anhedonia after correction for multiple testing. In fact, we observed exactly the same pattern of risk as that described for bipolar disorder. The minor allele of rs821577 was significantly associated with higher scores on social and physical anhedonia, while the minor allele of rs821633 was significantly associated with lower scores on both of these traits when analyzed while covarying for the effect of rs821577. This effect of rs821633 was not observed in an unconditioned association analysis but was observed only when the effect of rs821577 was eliminated. Therefore, it seems that the risk-increasing effect of rs821577 is dominant over the protective effect of rs821633. Such interactions are unlikely to be detected except by direct hypothesis testing and should be replicated in other samples.

Marker rs821633 was not associated in itself with any outcome measures when analyzed regardless of genetic background. This is in contrast to the previous study of schizophrenia. However, it should not be too surprising that a study of a self-rated questionnaire in the general population could give slightly different results than a study of schizophrenia in a highly selected sample, although they are generally in line with each other. It has been shown in mice that 2 separate mutations in Disc1 can cause greatly different psychiatric phenotypes (depressive vs schizophrenialike) in the same mouse strain. It is possible that slightly different variants could be associated with schizophrenia vs social anhedonia in humans.

Markers rs11122381 and rs821592 displayed significant associations with social anhedonia when only women were included in the analyses. The carriers of minor alleles of these 2 SNPs had significantly lower scores on the variable. These markers are located in proximity (in the same LD block) to the nonsynonymous SNP rs821616. Although this marker did not survive correction for multiple testing in the present study, it has been previously reported to associate with schizophrenia and related traits. It has been hypothesized that previous association findings might reflect an association of not only rs821616 but also other SNPs in high LD with rs821616. Our finding further supports this concept of a larger region possibly contributing in the psychosis proneness. Considering that markers rs11122381 and rs821592 associate significantly with social anhedonia in the general population, this locus is relevant in terms of psychosis proneness.

After the data collection for this study was designed and initiated in 1997, several important studies of the included scales were published. They have shown that social anhedonia, after controlling for the effects of the other psychosis proneness measures, independently and most clearly predicts later schizophrenia-spectrum personality disorders, social dysfunction, and poor quality of relationships. In our study, the RSAS was associated with the DISC1 genotypes. Taken together with the strong level of statistical significance (P < 10^-3), these findings support a role of DISC1 in regulating the level of psychosis proneness in the general population.

DISC1 has been previously linked with positive and negative aspects of schizophrenia. It has been shown that DISC1 is strongly associated with negative symptoms of schizophrenia and with learning and memory-related traits. Other studies have implicated the role of DISC1 in memory and cognition. Along with the previous findings, the present study supports the involvement of DISC1 in the negative symptoms of schizophrenia. Although not conceptually identical phenomena, other psychiatric disorders that have been associated with DISC1 display some form of social isolation as a core clinical feature. Autism and affective disorders, which have been shown to associate with DISC1 variants, are particularly characterized by deficits in social interaction. This could serve as a link that ties these diverse findings together. Although this possibility remains speculative, it is supported by 3 published Disc1 mouse models that report altered social interaction in carriers of Disc1 variants. Mutations in exon 2 of mouse Disc1 cause depressivelike or schizophreniclike behavior depending on where in the exon the mutation is introduced. Early postnatal, but not adult, induction of a C-terminal portion of Disc1 in mice results in depressivelike traits and reduced sociability. There are conflicting reports from other populations that DISC1 variants are associated with positive symptoms, specifically delusions. Therefore, we cannot say that we completely understand the genotype-phenotype relationship of DISC1 and psychiatric traits.

In the present study, all recognized variants displayed more significant association with social anhedonia in the female sample compared with the male sample. This is in line with the previous multicenter study in which SNPs rs1538979, rs821577, and rs821633 displayed female preference. Previous studies have reported variants in DISC1 demonstrating female preference in association with schizophrenia and bipolar disorder. It is unclear what the significance of this sex preference is and whether DISC1 expresses sex-specific effects. The possible sex-dependent effects in gene expression might be due to hormones, genetic imprinting, or interaction with sex-linked genes.

In this study, we have shown for the first time (to our knowledge) an effect of a susceptibility gene for schizophrenia on psychosis-related traits in an unselected birth cohort. This finding adds significantly to the relevance of DISC1 as a risk factor for mental illness in the general population and not just in unique or heavily ascertained samples studied so far. The approach of using human genetics as a means to study the etiology of psychiatric disorders is based on the assumption that a better understanding of the molecular genetic mechanisms underlying the disorders could lead to development of better preventive or treatment methods. To assess whether new genetic findings identified in highly ascertained samples such as translocation families and high-density
families have relevance for the more general psychiatric traits in the general population, studies performed in unselected birth cohorts are essential. Because extensive diagnostic or neuropsychological assessment is not feasible in large population cohorts, we used pen-and-paper questionnaire–based proxies of psychosis proneness. This use of proxy measures instead of direct face-to-face examination–based quantitative traits urges caution in the interpretation of our finding. In particular, any conclusion on the role of DISC1 in clinical psychotic disorders based on this study is necessarily indirect. However, it would be expected that any limitation in the validity of the measures used in our study as proxies for psychosis proneness would tend to decrease the statistical power of our replication effort. Therefore, given our replication of the pattern of risk modification previously published for the 3 SNPs studied, we suggest that the outcome measures used at least partially reflect similar traits as those of broadly defined psychosis. Although the statistical significance of our finding is strong, the effect sizes are small ($d \approx 0.32$). This is to be expected when studying traits with multifactorial backgrounds. In the previous study, the odds ratio for schizophrenia among markers in DISC1 was less than 2, meaning that, although statistically significant, the identified markers explain only a small part of the population variance of these traits. One needs to be cautious when drawing clinical conclusions from such large cohort studies with strong statistical significance but with small effect sizes.

In addition to the previous vast literature on DISC1 demonstrating its role in psychiatric, cognitive, memory, and neuroimaging phenotypes, there is now evidence that variants in the gene affect the level of social anhedonia, a cardinal symptom of schizophrenia, in the general population. The scales used in this study have a wide distribution of outcomes among the healthy population, and the overlap between cases and controls of any psychotic disorder is significant. Still, the scales were designed to measure psychosis proneness and have been shown to have some positive predictive value for overt psychotic symptoms. This finding demonstrates that DISC1 might be more central to human psychological functioning than previously thought. In fact, it seems to affect the degree to which people enjoy social interactions. Social anhedonia could be a primary deficit causally linked to overt clinical symptoms. Alternatively, it reflects some underlying process also involved in the origin of schizophrenia. Either way, DISC1 needs to be regarded as a central gene for psychiatric genetics. DISC1 cannot be marginalized as important in a few clinical cases but rather affects the psychosis proneness of the general population.

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