Association of Neuregulin 1 with Schizophrenia Confirmed in a Scottish Population

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Recently, we identified neuregulin 1 (*NRG1*) as a susceptibility gene for schizophrenia in the Icelandic population, by a combined linkage and association approach. Here, we report the first study evaluating the relevance of *NRG1* to schizophrenia in a population outside Iceland. Markers representing a core at-risk haplotype found in Icelanders at the 5′ end of the *NRG1* gene were genotyped in 609 unrelated Scottish patients and 618 unrelated Scottish control individuals. This haplotype consisted of five SNP markers and two microsatellites, which all appear to be in strong linkage disequilibrium. For the Scottish patients and control subjects, haplotype frequencies were estimated by maximum likelihood, using the expectation-maximization algorithm. The frequency of the seven-marker haplotype among the Scottish patients was significantly greater than that among the control subjects (10.2% vs. 5.9%, $P = .00031$). The estimated risk ratio was 1.8, which is in keeping with our report of unrelated Icelandic patients (2.1). Three of the seven markers in the haplotype gave single-point *P* values ranging from .000064 to .0021 for the allele contributing to the at-risk haplotype. This direct replication of haplotype association in a second population further implicates *NRG1* as a factor that contributes to the etiology of schizophrenia.

Introduction

Consistent association has not been found between schizophrenia (MIM 181500) and variants of the many candidate genes tested (O'Donovan and Owen 1999). Here, we present an association study, in which we searched for a haplotype, in the neuregulin 1 gene (*NRG1* [MIM 142445]), that increases the risk of schizophrenia in Iceland (Stefansson et al. 2002). The gene was identified through a genomewide linkage scan, of 33 large extended families with schizophrenia, that pointed to a locus on chromosome 8p. Extensive fine-mapping of the 8p locus and haplotype association analysis of 478 patients with schizophrenia and 394 control individuals narrowed the region of interest to the 5′ end of the large gene. A haplotype made up of several markers within a block of linkage disequilibrium showed significant association with an estimated relative risk of 2.2 (one-sided *P* values of .0000067–.000087). This core haplotype covers 290 kb and contains the first 5′ exon of *NRG1*, encoding the amino terminus of glial growth factor 2 (*GGF2*), and upstream sequences.

Linkage to chromosome 8p (SCZD6 [MIM 603013]) has been reported by a number of research groups (Pulver et al. 1995; Kendler et al. 1996; Levinson et al. 1996; Blouin et al. 1998; Kaufmann et al. 1998; Shaw et al. 1998; Brzustowicz et al. 1999; Gurling et al. 2001; DeLisi et al. 2002; Straub et al. 2002).

Icelanders are thought to be of Norse and Gaelic ancestry (Pálsson and Edwards 1972; Steffensen 1975; Helgason et al. 2001). The linkage results in the Irish population (Kendler et al. 1996; Straub et al. 2002) point to the 8p region are therefore particularly interesting, although the reported intervals in these studies appear to be 10–30 cM telomeric to the interval reported in the Icelandic study. Chromosome 8 has been one of the more problematic chromosomes in terms of sequence assembly and marker orders and has been further complicated by inversion polymorphisms (Giglio et al. 2001) and deletions (Yu et al. 2002). This may, in part, explain the differences in the intervals reported, or there may be a second schizophrenia gene on chromosome 8p.

Here, we present results of haplotype analysis that confirms the presence in a Scottish population of the same

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Table 1

Replication Study Showing Allele Frequencies for Markers and Haplotypes within and Upstream of the *NRG1* Gene

		Frequency (%)							
		Scotland				Iceland			
Marker	Allele[a]	Control Individuals[b]	Patients[b]	*P*	Relative Risk	Control Individuals[b]	Patients[b]	*P*	Relative Risk
Seven-marker haplotype		5.9 (618)	10.2 (609)	.00031	1.8	7.6 (394)	14.4 (402)	.000087	2.1
Five-marker SNP		27.4 (593)	35.4 (596)	.000032	1.5	25.1 (394)	32.1 (402)	.0018	1.4
SNP8NRG221132	G (2)	89.4 (526)	90.9 (574)	.13	1.2	88.0 (252)	90.0 (366)	.14	1.2
SNP8NRG221533	C (1)	30.6 (515)	38.4 (573)	.000064	1.4	29.7 (386)	36.4 (370)	.0028	1.4
SNP8NRG241930	G (2)	60.9 (561)	66.6 (577)	.0021	1.3	65.7 (315)	68.3 (367)	.16	1.1
SNP8NRG243177	T (3)	35.8 (514)	42.4 (568)	.00080	1.3	33.3 (108)	38.9 (321)	.069	1.3
SNP8NRG433E1006	G (2)	88.4 (290)	89.2 (301)	.34	1.1	85.5 (259)	87.3 (366)	.18	1.2
478B14-848	0	31.8 (588)	32.8 (596)	.30	1.1	35.9 (294)	37.5 (340)	.27	1.1
420M9-1395	0	41.2 (541)	42.5 (587)	.27	1.1	45.3 (290)	47.3 (350)	.24	1.1

[a] Numeric values for SNP alleles shown within parenthesis are the same as those given in Stefansson et al. 2002.
[b] Number of genotyped individuals for each marker is given in parenthesis.

seven-marker at-risk haplotype found in Iceland. The at-risk haplotype was found in significant excess in the Scottish patients ($P = .00031$), with a risk ratio of 1.8.

Subjects and Methods

Patients with Schizophrenia

Unrelated patients with schizophrenia ($n = 609$) were all recruited from the Scottish population, were of European ancestry, and met *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM- III-R*) criteria (American Psychiatric Association 1987) for schizophrenia or schizoaffective disorder. Diagnosis was based on psychiatric case note inspection and, when appropriate, through the use of the lifetime version of the Schizophrenia and Affective Disorders Schedule (Spitzer and Endicott 1977). Diagnosis was confirmed by consensus of two senior psychiatrists. Control individuals ($n = 618$) were drawn from the same population and were ethnically matched. Informed consent was obtained from all patients and control individuals. DNA samples were coded to create and preserve anonymity, and genotyping was performed by persons who were blind to diagnostic status of the samples. This study was approved by the Scottish Multiregional Ethics Committee.

Estimation of Haplotype Frequencies and Determination of Statistical Significance

In the present study, we genotyped unrelated patients and control individuals but no relatives. To handle missing genotypes and the lack of familial information to derive the phase, we applied our own implementation of a likelihood approach, using the expectation-maximization (EM) algorithm (Dempster et al. 1977) as a computational tool, to estimate the haplotype frequencies. Under the null hypothesis, the affected and control individuals are assumed to have identical frequencies of all haplotypes. Under the alternative hypothesis, the candidate at-risk haplotype is allowed to have a higher frequency in affected than in control individuals, whereas the ratios of the frequencies of all other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses, and corresponding 1-df likelihood-ratio statistics are used to evaluate statistical significance. Our own computer program was developed to fit our chosen models—and to handle missing genotypes and haplotypes with many markers efficiently; however, our use of the EM algorithm is very similar to methods used by others (Excoffier and Slatkin 1995; Hawley and Kidd 1995; Long et al. 1995). Although applied in a slightly different setting, the 1-df model we use is essentially that used by Clayton and Jones (1999). The method used here is identical to that reported elsewhere, and the data in table 1 for the Icelandic population are exactly the same as those reported in the same article (Stefansson et al. 2002).

SNP Genotyping

Four SNPs (SNP8NRG221132, SNP8NRG221533, SNP8NRG241930, and SNP8NRG243177) were scored using a method based on template-directed primer extension and detection by fluorescence polarization (FP) (Chen et al. 1999). Amplimers can be found on the deCODE Genetics Web site, and detailed sequence information is available through GenBank (accession number AF491780; third-party annotation [TPA] BK000383).

The SNP in the 5′ exon of *GGF2,* SNP8NRG433-E1006, was scored by sequencing 163 bp of the exon.

This exon is very GC rich, and SNP genotyping with the use of the FP assay described above has proved difficult in our hands for this polymorphism. Nested PCR was performed to obtain product for direct sequencing. The first amplification reaction was done using primers CCTACCCCTGCACCCCCAATAAATAAA and CTTCCTGTCGAGTGCCCCCTGCT. The reaction volume was 10 μl, and, for each PCR, 30 ng of genomic DNA was amplified in the presence of 3.5 pmol of each primer, 0.25 U Ampli*Taq* Gold, 0.2 mM dNTPs, 10% dimethyl sulfoxide, and 2.5 mM $MgCl_2$ (buffer was supplied by the manufacturer). Cycling conditions were 95°C for 10 min, followed by 40 cycles at 94°C for 15 s, annealing at 68°C for 30 s, and extension at 72°C for 1 min. The second reaction was performed using the same concentration of inner primers, TGCCACTACTGCTGCTGCT and ACCTTTCCCTCGATCACCAC. Except for the addition of 1 μl of the first amplification reaction, as a template, to 9 μl of the mixture, conditions were the same as in the first amplification reaction described above. Cycling conditions for the second amplification step were 95°C for 10 min, followed by 35 cycles at 94°C for 15 s, annealing at 58°C for 30 s, and extension at 72°C for 1 min. The PCR product was sequenced by direct sequencing after cleaning the PCR product by use of a BigDye Terminator Cycle Sequencing kit (PE Biosystems). The inner primers were used for the cycle-sequencing reaction, and fragments were separated by electrophoresis on ABI 3700 instruments (Applied Biosystems).

Microsatellite Genotyping

Microsatellite markers were genotyped as described by Gretarsdottir et al. (2002). Amplimers for microsatellites 478B14-848 and 420M9-1395 can be found on the deCODE Genetics Web site, and detailed sequence information is available through GenBank (accession number AF491780; TPA BK000383). Allele 0, in table 1, for markers 478B14-848 and 420M9-1395 refers to PCR-product sizes of 219 bp and 274 bp, respectively.

Results

In the present haplotype association analysis, we determined whether a given haplotype among the Scottish patients was in excess of that found in control individuals; therefore, unless otherwise stated, *P* values reported for association tests are one sided and without adjustment for multiple comparison. All case and control subjects in the present study were independent, and likelihoods were therefore computed while treating all affected individuals as independent.

A seven-marker core haplotype consisting of 5 SNPs and two microsatellite markers was previously found in excess in Icelandic patients (Stefansson et al. 2002). In table 1, the data for unrelated Icelandic patients and control individuals are shown in comparison with the data for unrelated Scottish patients and control individuals. We have now genotyped the seven markers that constitute the at-risk haplotype in 609 Scottish patients and 618 Scottish control individuals. The estimated frequency of the at-risk haplotype was higher in the Scottish patients than in the Scottish control individuals, which is in keeping with what was found in the Icelandic population. The estimated haplotype frequency was 10.2% in the Scottish patients and 5.9% in Scottish control individuals, giving a risk ratio of 1.8 (table 1). Carrier frequencies are thus 19.4% and 11.5%, respectively, assuming a multiplicative model. Furthermore, alleles for three of the seven markers—including SNP8NRG221533, which also showed significant single-marker association in the Icelandic population (table 1)—in the haplotype were in significant excess in the Scottish patients with schizophrenia.

The patients with schizophrenia were recruited from a broader geographical area of Scotland than were the control subjects, who were drawn from the city of Aberdeen and five surrounding counties and from the Glasgow region. However, we compared the haplotype frequencies in patients from different areas and found no differences. This suggests that population stratification is not a likely explanation for the observed differences. Also noted is that the issue of multiple comparisons is not a serious concern here, because five of the nine tests produce significant results, and four are significant after Bonferroni adjustment, including the seven-marker at-risk haplotype and allele C for SNP8NRG221533, both of which were in significant excess in the Icelandic population (table 1).

Discussion

The *NRG1* gene was originally identified as a susceptibility gene for schizophrenia by using a combination of a linkage and association approaches based on microsatellite markers and then using SNPs after microsatellite at-risk haplotypes were identified. SNP haplotypes are, in general, more stable and may capture an ancestral haplotype better than microsatellite haplotypes do, but the microsatellite markers are more cost-effective and informative when screening regions for association. Furthermore, the microsatellites may be better suited than SNPs to the capture of more-recent haplotypes and mutations.

The strength of the present study is that we are directly testing seven alleles that constitute one at-risk haplotype. Complications and problems related to multiple testing

are avoided. Transmission/disequlibrium tests can be helpful to avoid population stratification. In the Icelandic study, we reported transmission/disequilibrium data for the at-risk haplotype that were also supportive, although data were available for only a limited number of patients because of the lack of complete triad data. In the present case-control study, we found no evidence for stratification when we compared the frequency of the at-risk haplotype in patients from different areas within Scotland. Although the possibility of bias due to stratification cannot be completely eliminated, we are heartened by the fact that not only are the results with the Scottish sample statistically significant but the frequencies of alleles/haplotypes and estimated relative risks are all very similar to the Icelandic sample.

Although the present study and our previous one show that the seven-marker haplotype is significantly associated with schizophrenia in both Iceland and Scotland, they do not reveal the underlying functional variation. Given that the haplotype overrides the first promoter (among several) of *NRG1* and the first exon of *GGF2,* it is possible that the corresponding functional variation affects the expression or splicing of the *GGF2* isoform. The SNP, SNP8NRG433E1006, is in the first exon of *GGF2*. The SNP allele contributing to the at-risk haplotype was not found in significant excess in patients, relative to control individuals, and it is therefore unlikely to represent the functional variation. The associations of three other SNPs typed within the haplotype were as significant as that of the overriding haplotype in the Scottish samples. However, in both the Icelandic and the Scottish samples, the estimated relative risks of the individual SNPs were less than the relative risk of the seven-marker haplotype, leading us to conclude that none of the individual SNPs can fully account for the underlying functional variation. The discrepancy between statistical significance and estimated relative risk may be explained as follows: The haplotype and the individual SNPs all have incomplete association with the underlying functional variant. As surrogates for the functional at-risk variant, the haplotype, which is rarer and more specific, produces fewer false positives but more false negatives than do the individual SNPs.

In previous work, we and others have shown that mouse mutants for either NRG1 or its receptor, ErbB4, show stereotypic behavioral abnormalities that are similar to those exhibited by normal mice treated with the psychogenic drug phencyclidine (Gerlai et al. 2000; Stefansson et al. 2002). We also showed that brains of *Nrg1* mutant mice had fewer functional N-methyl D-aspartate (NMDA) receptors than did wild-type mice (Stefansson et al. 2002).

One of the roles that *NRG1* plays in the adult CNS is the regulation, in certain neurons, of the expression and phosphorylation of certain neurotransmitter-receptor subunits and their related complexes, in an activity-dependent manner (Ozaki et al. 1997; Rieff et al. 1999; Garcia et al. 2000; Cameron et al. 2001). *NRG1* does not appear to be restricted to a single neurotransmitter system; rather, it appears to play a role in NMDA and acetylcholine, as well as γ-aminobutyric acid–receptor, regulation, at least in certain neuronal systems (Fischbach and Rosen 1997; Ozaki et al. 1997; Rieff et al. 1999; Cameron et al. 2001). Therefore, *NRG1* provides a way of unifying a large body of evidence, coming from many directions, that suggests that multiple neurotransmitter systems and their receptors are involved in schizophrenia by representing a common denominator upstream of neurotransmitter expression and activation. Furthermore, *NRG1* may provide support for the view that schizophrenia is caused by dysregulation of synaptic plasticity in the adult. These new data from a separate outbred white population closely replicate the findings from the Icelandic population and provide strong additional evidence for involvement of *NRG1* as a genetic risk factor for schizophrenia.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

deCODE Genetics, http://www.decode.com/nrg1/markers (for SNPs and microsatellite markers in the *NRG1* locus sequence)

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *NRG1* [accession number AF491780] [TPA BK000383])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *NRG1* [MIM 142445], schizophrenia [MIM 181500], and SCZD6 [MIM 603013])

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