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Family-Based Association Study of Neuregulin 1 With Psychotic Bipolar Disorder

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Abstract

The Neuregulin 1 gene (*NRG1*) has been associated with schizophrenia, and, to a lesser extent, with bipolar disorder (BP). We investigated the association of *NRG1* with BP in a large family sample, and then performed analyses according to the presence of psychotic features or mood-incongruent psychotic features. We genotyped 116 tagSNPs and four Icelandic “core” SNPs in 1,199 subjects from 314 nuclear families. Of 515 BP offspring, 341 had psychotic features, and 103 had mood-incongruent psychotic features. In single-marker and sliding window haplotype analyses using FBAT, there was little association using the standard BP or mood-incongruent psychotic BP phenotypes, but stronger signals were seen in the psychotic BP phenotype. The most significant associations with psychotic BP were in haplotypes within the 5′ “core” region. The strongest global *P*-value was across three SNPs: NRG241930-NRG243177-rs7819063 (*P*=0.0016), with an undertransmitted haplotype showing an individual *P*=0.0007. The most significant individual haplotype was an undertransmitted two-allele subset of the above (NRG243177-rs7819063, *P*=0.0004). Additional associations with psychotic BP were found across six SNPs in a 270 kb central region of the gene. The most 3′ of these, rs7005606 (*P*=0.0029), is located ~4 kb from the type I *NRG1* isoform promoter. In sum, our study suggests that *NRG1* may be specifically associated with the psychotic subset of BP; however, our results should be interpreted cautiously since they do not meet correction for multiple testing and await independent replication.

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Keywords

Neuregulin 1; bipolar disorder; psychosis; mood-incongruent psychosis; genetic association

Introduction

Phenotypic overlap in a sizeable minority of cases suggests that schizophrenia (SCZ) and bipolar disorder (BP) might share genetic risk factors. Family studies have found shared risk for developing major depression and schizoaffective disorder among relatives of probands with either disorder [Gershon et al., 1982, 1988], the most pronounced overlap being demonstrated in studies that focused on the subset of mood disorder subjects who have psychotic symptoms [Kendler et al., 1993a,b]. Genetic linkage studies have provided evidence for overlapping chromosomal regions in both disorders, and association studies of BP have also provided preliminary evidence of etiologic overlap [Potash, 2006]. Several associations with BP have been published for genes originally identified as positional candidates in SCZ, including the D-Amino Acid Oxidase-Activator (*DAOA*) [Hattori et al., 2003], Disrupted in Schizophrenia 1 (*DISC1*) [Hodgkinson et al., 2004], Dysbindin (*DTNBP1*) [Raybould et al., 2005], and Neuregulin 1 (*NRG1*) genes [Green et al., 2005].

Spanning 1.2 Mb, the human *NRG1* gene consists of over 20 exons and six transcription initiation sites, which give rise to at least 15 mRNA transcripts and a number of protein isoforms that share in common an epidermal growth factor-like (EGF) domain responsible for activating the tyrosine kinase receptors ErbB3 and ErbB4 [Harrison and Law, 2006]. Three main protein isoforms have been functionally characterized: types I and II isoforms contain an immunoglobulin-like domain involved in paracrine signaling; while the type III isoform has two transmembrane domains which anchor the active EGF domain to the cell surface and are involved in cell–cell signaling [Falls, 2003]. *NRG1* plays a vital role in the development of several organ systems, including the peripheral and central nervous systems, where *NRG1* promotes neuronal migration and dendrite development, and regulates oligodendrocyte functioning [Buonanno and Fischbach, 2001]. More recent studies also highlight a role of *NRG1* in the regulation of NMDA, dopamine, and GABA synapse formation [Hahn et al., 2006; Roy et al., 2007; Woo et al., 2007].

The initial association of *NRG1* with SCZ emerged from positional cloning of a linkage peak on chromosome 8p11–21, which implicated a 7-marker haplotype in the 5′ region of the gene, designated as the Icelandic “core” haplotype [Stefansson et al., 2002]. Although extensive sequencing of all exons did not uncover a causal mutation, the original investigators were able to replicate the “core” haplotype association in an independent Scottish case-control sample [Stefansson et al., 2003]. Subsequently, several groups have reported single-marker or haplotype associations in both case-control and family-based SCZ samples. As shown in Figure 1, many of these associations have included parts of the Icelandic “core” haplotype; however, few have replicated the same associated alleles as the original study and, hence, despite a large number of positive reports, the association between *NRG1* and SCZ cannot yet be considered definitive. As several *NRG1* markers (including two of the “core” haplotype SNPs) have recently been shown to manifest significant

population differences, the potential confounding effect of population stratification must also be considered [Gardner et al., 2006].

In the first association study of *NRG1* with BP, Green et al. [2005] genotyped a 3-marker surrogate of the “core” haplotype and found only a nominal association with BP, which became more pronounced in the cases with predominantly mood-incongruent psychotic features, a phenotype that partially overlaps with SCZ and may reflect overlapping genetic vulnerability between the two disorders. Since then, four additional studies have investigated the association of *NRG1* and BP. Fallin et al. [2005] found no association in their family-based Ashkenazi sample, although they had limited coverage of the gene. In a smaller family-based Hispanic sample Walss-Bass et al. [2006] reported nominal associations within the “core” haplotype and cases with “manic psychosis.” Their haplotype, however, consisted of different alleles than the original “core” and was significant at the level of individual, but not global, haplotype *P*-value. Similarly, in another small family-based sample (N=92) genotyped only at the 5′ end of the gene, Cassidy et al. [2006] found a nominal association with a single microsatellite allele, but no association with any of the “core” markers or the haplotype. In a more extensive survey of *NRG1*, Thomson et al. [2007] found several new nominal marker and haplotype associations in the 5′ and 3′ ends of the gene. More recently, Perlis et al. [2008] performed selected genotyping of 11 markers within previously implicated regions of the gene, but found no evidence for transmission distortion in 225 bipolar I disorder (BPI) nuclear families. Finally, Georgieva et al. [2008] recently genotyped the “core” haplotype markers in 251 BPI trios and found significant overtransmission of one of the “core” markers (NRG221533) but not the “core” haplotype itself.

This complex mixture of positive, equivocal and negative results has recently been informed by three BPI genome wide association studies (GWAS) that have provided far greater coverage of the *NRG1* than any of the previous candidate gene studies [Baum et al., 2008; Sklar et al., 2008; Wellcome Trust Case Control Consortium, 2007]. However, none of the GWAS top findings have been found in *NRG1* and, even among their nominally significant associations, there is little consistency across the three studies (Fig. 1).

In this study, we have undertaken the most comprehensive family based linkage disequilibrium (LD)-based survey of the *NRG1* gene to date. Our large sample of nuclear BP families, with extensive phenotypic characterization, has allowed us to test the hypotheses that subjects with psychotic features in general, and with mood-incongruent psychotic features in particular, would show stronger association with *NRG1* compared with the standard BP phenotype.

Materials and Methods

Sample

We selected 1,199 subjects from 314 nuclear families for genotyping from all available independent trios and quads originally ascertained in three BP family studies: the Chicago, Hopkins, NIMH Intramural Program (CHIP) study [McInnis et al., 2003]; the Clinical Neurogenetics (CNG) study [Detera-Wadleigh et al., 1999]; and the NIMH Genetics Initiative BP Collaborative (NIMH) study, waves 1–4 [Genomic survey of bipolar illness in

the NIMH genetics initiative pedigrees: A preliminary report, 1997]. Description of the ascertainment and case assessment can be found in the initial study reports. All subjects signed IRB approved informed consent forms prior to enrolling in the studies.

In the current study, cases were diagnosed with either BPI or schizoaffective disorder, bipolar type (SABP). The 314 pedigrees yielded 515 affected offspring (489 offspring with BPI and 26 with SABP), consisting of 201 quads and 113 trios. Both the CHIP (69 families, 43 trios, and 26 quads) and the CNG (11 families, 4 trios, and 7 quads) samples were ascertained for multiply affected families using primarily the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS) [Endicott and Spitzer, 1978] and Research Diagnostic Criteria (RDC) [Spitzer et al., 1978] for assessment and diagnosis. The NIMH studies (234 families, 168 quads, and 66 trios) used the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994] and Diagnostic and Statistical Manual (DSM) III-R or IV diagnostic criteria. A total of 167 probands in these NIMH families were used in pools for the Baum et al. [2008] NIMH sample. Phenotypic analyses of the NIMH and CHIP samples were facilitated by the recently compiled BP Phenome Database [Potash et al., 2007].

Phenotype Designation

Association was tested using three phenotypic designations: (1) a standard BP group (including a small number of SABP as noted above); (2) a psychotic BP group that was nested within the larger BP group; and (3) a mood-incongruent psychotic BP group that was nested within the psychotic BP group. Cases were designated as psychotic if they had a lifetime occurrence of auditory or visual hallucinations and/or delusions. Mood-incongruent psychosis was defined as the presence of hallucinations or delusions which are inconsistent with depressive or manic themes [further details available in Goes et al., 2007]. Phenotypic information was available for the CHIP and NIMH samples, but for the smaller CNG sample, psychosis information was not available on a subset of subjects, while mood-incongruent psychosis data was not available at all. In total, of the 515 affected offspring, 341 (66.2%) were classified as psychotic (103 quads, 135 trios), and of these, 103 (30.2%) had mood-incongruent psychotic features (19 quads, 65 trios).

SNP Selection

Tag SNPs spanning the RefSeq *NRG1* transcript (1.2 Mb plus 10 kb on either side) were chosen using Carlson's "LD-select" algorithm [Carlson et al., 2004]. Using data from phase I of the HapMap project with tagging parameters of $r^2=0.8$ and a minor allele frequency of 0.1, 124 tagSNPs were chosen to cover *NRG1*. Genotyping was performed at Illumina on a BeadArray platform. Of the 124 initial tagSNPs, three failed Illumina's proprietary design criteria, and six did not genotype in any sample. The remaining 115 SNPs were genotyped with an average missing data rate of 0.8%. Five additional SNPs in the Icelandic "core" haplotype region were genotyped using an ABI 7900HT and TaqMan assays. These SNPs had an average missing data rate of 0.98%, and, of the 220 TaqMan blind duplicates genotyped, five (2.3%) had missing genotypes, while the remaining 215 samples showed 100% concordance.

Analytic Methods

Testing for Hardy–Weinberg equilibrium was performed in Haploview [Barrett et al., 2005]. Using the FBAT software program [Rabinowitz and Laird, 2000], Mendelian errors were found in one family genotyped by Illumina and in an independent family genotyped with the TaqMan method. After cleaning the data, FBAT was used to test for association. Association was tested with the psychotic and mood-incongruent phenotypes by limiting the affection status to only those subjects with the phenotype of interest. We tested single marker association under additive and dominant models. Haplotypes were tested with 2, 3, and 4-marker sliding windows under an additive model, using only individual haplotypes with a frequency of $\geq 5\%$. Reported *P*-values are asymptotic. We used permutations to estimate the significance of our best finding after accounting for all the tests carried out with FBAT. After randomly shuffling the haplotypes across each of the genes that was transmitted to the offspring, we re-calculated the FBAT tests for each SNP and counted the number of replicates out of 10,000 in which there was a more significant finding than what we observed.

Power calculations with the PBAT software package showed that, under an additive model and with an assumed disease prevalence of 1% and an $\alpha=0.05$, our standard BP phenotype sample had $>80\%$ power to detect a risk allele of moderate effect ($OR=1.4$), over a wide range of disease allele frequencies (0.15–0.5). We had $>80\%$ power to detect larger effects of ~ 1.5 in the psychotic subset, and ~ 2.0 in the mood-incongruent psychotic subset under comparable assumptions.

We also tested mood-incongruent psychotic features as a covariate using the Transmission Disequilibrium Test (TDT) as implemented in STATA 9.2 with an adaptation of the *gtrr* function [Cordell et al., 2004]. We formally tested for differences with and without the covariate by fitting a conditional logistic regression model that included a term for the covariate by genotype interaction. Likelihood ratio tests (LRTs) were used to test whether the model including the interaction term provided a better fit to the data than a model without the interaction term.

Results

We successfully genotyped 116 tagSNPs across the *NRG1* gene and four SNPs from the original “core” haplotype. All markers were found to be in Hardy–Weinberg equilibrium. Figure 2a shows the complete single-marker data for the standard, psychotic, and mood-incongruent psychotic BP phenotypes. *P*-values are shown on the y-axis for the most significant single finding at each locus in either the additive or dominant genetic model. Complete data for all models and phenotypes is provided in Supplementary Table I.

Using the standard BP phenotype, we found only minor differences between observed and expected allelic and genotypic transmissions to affected offspring. Among the 17 markers that had a nominal $P<0.05$, the smallest *P*-value (0.016) was observed at rs10954822, under an additive model. With the psychotic BP phenotype, there were 21 SNPs with a nominal $P<0.05$, including six SNPs for which the difference between observed and expected transmissions were statistically significant at the $P<0.01$ level (Table I). These latter SNPs

span about 270 kb in the middle of the gene and are linked by a moderate degree of LD (average inter-marker $D' = 0.54$ and $r^2 = 0.19$). The strongest of these findings was at rs782256, where, under a dominant model, the observed versus expected transmissions to affected cases was 123:103.5 ($P = 0.0019$). However, this finding did not meet study-wide significance criteria in our empirical simulation analyses.

When the mood-incongruent psychotic BP cases were analyzed, five markers showed transmission distortion at the $P < 0.05$ level, but no differences were seen at the $P < 0.01$ level. Among the three strongest SNPs with a nominal $P < 0.05$, one, rs7822917 ($P = 0.012$), was also one of the six strongest for the psychotic phenotype, while two others, NRG221132 ($P = 0.014$) and NRG241930 ($P = 0.017$), were in the “core” haplotype. Because of the small sample size of the mood-incongruence subset, we went on to perform a potentially more powerful analysis incorporating mood-incongruence as a covariate in association (Table II). This confirmed the significance of mood-incongruence for association with NRG221132 and NRG241930, and it was also positive for rs4476964 in the “core” haplotype. Two additional SNPs, rs7013361 and rs4236709, were nominally positive in this analysis, with the latter being 4 kb from the 5' exon of the type I *NRG1* isoform.

Haplotype analyses were performed using 2, 3, and 4-marker sliding windows. Again, the standard BP and mood-incongruent phenotypes did not yield any associations significant at the $P < 0.01$ level. However, the psychotic phenotype revealed five haplotypes significant at $P < 0.01$ (Fig. 2c and Table I): Two haplotypes were in the 270 kb central region of the gene identified in the single SNP analysis, while the remaining three haplotypes were in the “core” haplotype region (see Supplementary Table II).

Discussion

We performed a family-based association study using 120 SNPs across *NRG1*, and, while our findings did not meet an empirically defined significance threshold corrected for multiple testing, we observed several potential findings of interest. Consistent with our a priori hypothesis, we found stronger evidence of associations with the psychotic BP phenotype compared with the standard BP phenotype. Notably, the most significant of these were found in haplotypes within the previously implicated 5' “core” region. Our study, perhaps because of its greater coverage of *NRG1* compared with most previous studies, also found modest associations across six SNPs in a more central 270 kb region of the gene that has received little attention to date. We did not find strong associations with mood-incongruent psychosis, though we did observe two nominal findings in the “core” haplotype region.

Our strongest single-marker findings cluster in a large 270 kb region of the gene that has, as yet, received relatively little attention. Li et al. [2004] found an association between SCZ and a microsatellite marker and a large haplotype in this region, but, until the recent GWAS, only two prior studies had genotyped this area of the gene, finding no significant associations [Addington et al., 2007; Thomson et al., 2007]. Although the three recently performed BP GWAS did not find strong associations within the *NRG1* gene, they have also not examined the psychotic or mood-incongruent subtypes of BP.

In this study, we focused on the psychotic and mood-incongruent psychotic phenotypic subtypes of BP based on the hypothesis that these clinically based distinctions might be phenotypic manifestations of *NRG1* susceptibility alleles shared between BP and SCZ. While most studies of *NRG1* have focused on SCZ, prior work has suggested linkage of psychotic BP to 8p12 [Park et al., 2004], and association of the “core” haplotype with the mood-incongruent subtype of psychotic BP [Green et al., 2005]. Our results show consistency with our prior hypothesis, as the psychotic subtype had stronger overall evidence of association compared with the standard bipolar phenotype. In addition, we also observed nominal associations with two “core” haplotype SNPs (NRG221132 and NRG241930) in the cases with mood-incongruence.

Several limitations of our study should be considered. First, our findings do not withstand correction for the multiple phenotypic and genotypic models employed. Second, our samples were limited in their power to detect risk alleles of small effect. In particular, the mood-incongruent sample consisted of only 84 families. While this sample had adequate power to detect a substantial OR of 2.0, it had only 25–37% power to detect a risk allele with an OR of 1.4. Third, our tagSNPs were selected from Phase I of the HapMap project to sample common variation ($r^2 > 0.8$, $MAF > 0.1$) in *NRG1*; they represent only 56% of the corresponding tagSNPs in Phase II of the HapMap project. Fourth, because our assessment of psychotic and mood-incongruent psychotic features was categorical, it is unclear how comparable it is to the dimensional rating scale of these features employed by Green et al. Finally, we did not have data to examine other potential phenotypic manifestations of genetic overlap between BP and SCZ, such as chronic course of illness, cognitive impairment, or functional decline.

Additional data clarifying the role of *NRG1* in BP and SCZ should emerge from whole genome association studies that are currently being conducted, where the use of clinical phenotypes such as psychosis or mood-incongruent psychosis will shed further light on the potential subtypes of illness most closely associated with genetic variation in *NRG1*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Overview of published *NRG1* association studies in schizophrenia and bipolar disorder. Studies are listed chronologically with an abbreviated year of publication. Genotyped markers are depicted by black vertical lines, and single marker associations with a nominal $P < 0.05$ are highlighted in red. Nominal haplotype associations are indicated as a red line across the relevant markers. For illustrative purposes, in close regions with more than one contiguous haplotype, only the most significant haplotype is highlighted. CC and FAM refer to case-control and family-based study designs, respectively. ‡ Association results reflects the updated analysis by the same research group using the same cases with an enlarged control group as described in Green et al. [2005]. *These are results from pooled DNA samples [Stefansson et al., 2002, 2003; Williams et al., 2003; Yang et al., 2003; Bakker et al., 2004; Corvin et al., 2004; Hall et al., 2004; Hong et al., 2004; Iwata et al., 2004; Kampman et al., 2004; Li et al., 2004; Tang et al., 2004; Thiselton et al., 2004; Zhao et al., 2004; Duan et al., 2005; Fallin et al., 2005; Green et al., 2005; Petryshen et al., 2005; Cassidy et al., 2006; Fukui et al., 2006; Ingason et al., 2006; Kim et al., 2006; Lachman et al., 2006; Walss-Bass et al., 2006; Addington et al., 2007; Benzel et al., 2007; Rosa et al., 2007; Thomson et al., 2007; Turunen et al., 2007; WTCCC, 2007; Baum et al., 2008; Georgieva et al., 2008; Ikeda et al., 2008; Jungerius et al., 2008; Perlis et al., 2008; Sanders et al., 2008; Sklar et al., 2008; Vilella et al., 2008].

Fig. 2.

a: Single marker association P values in the cases with standard BP (red), psychotic BP (blue), and mood-incongruent psychotic BP (green). For each marker, P values represent the best nominal value from either the additive or dominant genetic models. b: Graphical representation of *NRG1* genes with exons highlighted in blue. c: Two, three, and four SNP global haplotype P values in cases with psychotic BP. The best findings referenced in Table I are identified by the symbols † (NRG241930-NRG2243177-rs7819063), § (NRG2243177-rs7819063), ¶ (rs4476964-NRG241930-NRG2243177-rs7819063), ‡ (rs2129533-rs716144-rs43117533-rs10503906), and * (rs6651144-rs7005606).

Table 1
Single marker and Haplotype Association findings with P Values <0.01 in Analyses of Cases With Standard BP, Psychotic BP, and Mood-Incongruent Psychotic BP

Markers	Model	Allele(s)	Freq	Standard BP			Psychotic BP			Mood-incongruent psychotic BP		
				S/E (S) ^a	P _{individual}	P _{global}	S/E (S) ^a	P _{individual}	P _{global}	S/E (S) ^a	P _{individual}	P _{global}
rs7822564	Add	G	0.31	271:254	0.1003		179:160.5	0.0236		56:53	0.5076	
	Dom			183:167.5	0.0524		123:103.5	0.0019		33:29	0.2059	
rs901561	Add	G	0.33	281:260.5	0.0451		183:165	0.0279		55:51.5	0.4250	
	Dom			175:159.8	0.0523		120:102.8	0.0061		30:27.3	0.3860	
rs2129533	Add	C	0.36	323:299	0.0259		209:189.5	0.0246		61:56	0.2809	
	Dom			191:172.3	0.0214		131:113	0.0061		35:31.8	0.3543	
rs7822917	Add	G	0.73	405:404.5	0.9600		260:262	0.8003		61:66	0.2253	
	Dom			68:74.5	0.1484		34:44.5	0.0039		9:14.0	0.0124	
rs1579033	Add	C	0.31	289:268.5	0.0567		188:166	0.0086		64:56.5	0.1159	
	Dom			206:187.8	0.0350		130:112.8	0.0107		38:34.5	0.3334	
rs7005606	Add	G	0.44	365:341	0.0308		248:221.5	0.0029		81:73.5	0.1394	
	Dom			182:168.5	0.0868		123:107.5	0.0150		36:32.8	0.3450	
rs6651144 rs7005606		T-G	0.39	354.8:333	0.0480	0.1283	239:214.7	0.0052	0.0066	79.3:71.4	0.1149	0.0898
NRG2243177-rs7819063		T-T	0.06	42.8:54.7	0.0126	0.0462	22.9:36.1	0.0004	0.0039	7.2:9.9	0.1508	0.5529
NRG241930-NRG2243177-rs7819063		G-T-T	0.06	39.2:50.5	0.0174	0.0182	19.7:32.3	0.0007	0.0016	6.6:9.3	0.1630	0.0983
rs4476964-NRG241930-NRG2243177-rs7819063		G-G-T-T	0.06	39.1:49.7	0.0256	0.0583	19.7:31.5	0.0013	0.0071	6.6:9.3	0.1605	0.1316
rs2129533-rs716144-rs4317533-rs10503906		G-G-G-G	0.20	209:188.3	0.0100	0.0225	133.8:114.7	0.0067	0.0068	42.2:41.2	0.5923	0.2486

^aS = FBAT test statistic reflecting the association between a phenotype and a genetic marker; E(S) = expected FBAT test statistic under the null hypothesis of no transmission distortion.

Table II
SNPs With Significant Covariate Effects for Mood-Incongruent Psychotic Features

Marker	Location (NCBI35)	Risk allele (freq.)	Genetic model	Non-MICP BP OR (95% CI) ^a	MICP BP OR (95% CI) ^a	P-value ^b
NRG221132	31593282	A (0.115)	Dom	0.94 (0.65, 1.36)	3.23 (1.20, 8.69)	0.0133
rs4476964	31612210	C (0.775)	Add	1.33 (1.05, 1.68)	0.67 (0.42, 1.08)	0.0105
NRG241930	31613877	T (0.355)	Dom	1.08 (0.81, 1.44)	2.20 (1.13, 4.27)	0.0452
rs7013361	32482830	A (0.280)	Rec	0.61 (0.37, 1.01)	2.13 (1.29, 5.05)	0.0147
rs4236709	32529652	G (0.221)	Add	0.78 (0.62, 0.98)	1.44 (0.86, 2.40)	0.0303

^a Odds ratio (OR) for the association of each SNP with bipolar disorder in the presence or absence of the mood-incongruence covariate.

^b P values reflect the significance of the covariate-genotype interaction in the association model.