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ABSTRACT

Schizophrenia (SCZ) and bipolar disorder (BPD) are severe heritable psychiatric disorders involving a complex genetic aetiology. *Neuregulin 1* (*NRG1*) is a leading candidate gene for SCZ, and has recently been implicated in BPD. We previously reported association of two *NRG1* haplotypes with SCZ and BPD in a Scottish case–control sample. One haplotype is located at the 5′ end of the gene (region A), and the other is located at the 3′ end (region B). Here, association to haplotypes within regions A and B was assessed in patients with SCZ and BPD in a second Scottish case–control sample and in the two Scottish samples combined. Association to region B was also assessed in patients with SCZ and BPD in a German case–control sample, and in all three samples combined. No evidence was found for association in the new samples when analysed individually; however, in the joint analysis of the two Scottish samples, a region B haplotype comprising two SNPs (rs6988339 and rs3757930) was associated with SCZ and the combined case group (SCZ: $p = 0.0037$, OR = 1.3, 95% CI: 1.1–1.6; BPD + SCZ: $p = 0.0080$, OR = 1.2, 95% CI: 1.1–1.5), with these associations withstanding multiple testing correction at the single-test level (SCZ: $p_{st} = 0.022$; BPD + SCZ: $p_{st} = 0.044$). This study supports the involvement of *NRG1* variants in the less well studied 3′ region in conferring susceptibility to SCZ and BPD in the Scottish population.

Schizophrenia (SCZ) and bipolar disorder (BPD) are severe psychiatric disorders, each affecting approximately 1% of the world's population. Family, twin, and adoption studies [5,24,25,37] support a strong genetic component to both disorders.

Neuregulin 1 (*NRG1*), located on chromosome 8p12, is a key candidate susceptibility gene for SCZ [17], supported by genetic association studies [1,3,7,11,15,19,20,23,30,31,35,36,38,39,41,43] (Fig. 1), meta-analyses [13,22,27,28], and functional plausibility [10,17,26,42]. More recently, *NRG1* has been implicated in BPD, and subgroups of BPD [11,12,14,31,39] (Fig. 1). This suggests that *NRG1* polymorphisms may confer a wider susceptibility to psychiatric illness.

Recently, we reported the association of haplotypes in two regions, A and B, of *NRG1* with SCZ and/or BPD in a Scottish case–control sample [39] (Fig. 1). Region A, which is located at the 5′ end of the gene and includes the promoter region, was found to harbour a rare three-SNP haplotype associated with SCZ ($p = 0.00032$) and the combined SCZ and BPD case group ($p = 0.0017$). Region B, which is located at the 3′ end of the gene and spans the sensory and

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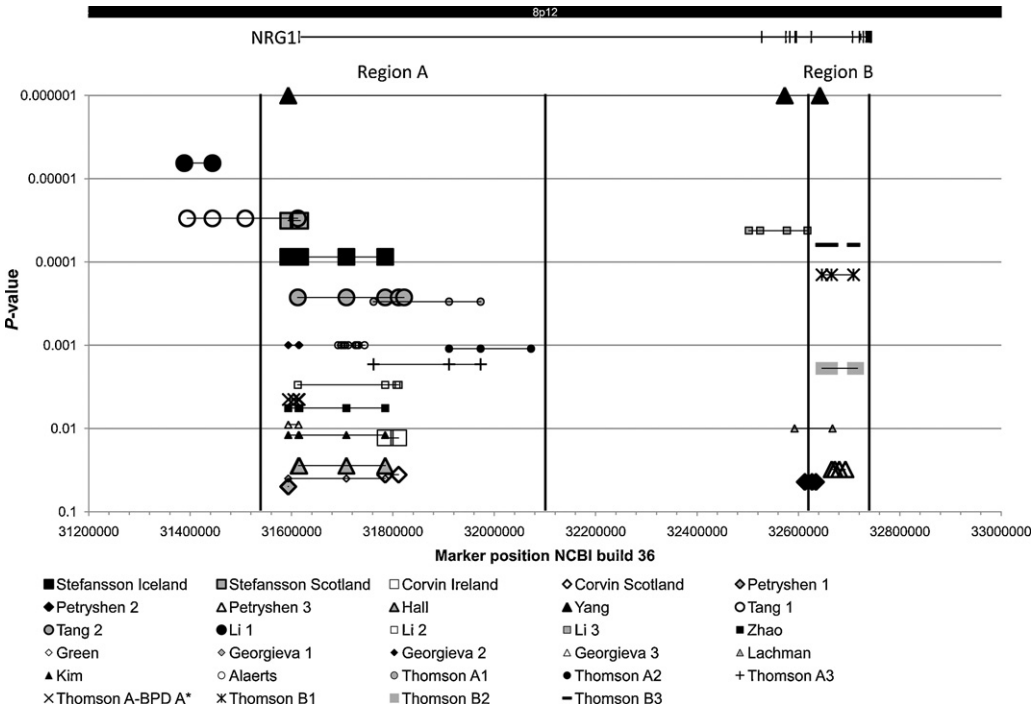

Fig. 1. Most significant individual haplotype *p*-values from previous association studies of *NRG1* and schizophrenia and/or bipolar disorder. The significance of each haplotype is indicated by its location on the *y*-axis and the genomic position of the haplotype, according to NCBI build 36, is indicated by position on the *x*-axis. All SNPs and microsatellites are within chromosome 8p12.

motor neuron derived factor isoform, contained a common three-SNP haplotype associated with both SCZ and BPD ($p = 0.000062$).

Here, we sought to replicate our previous findings by assessing the association of regions A and B to SCZ and/or BPD in a second Scottish case–control sample (Scottish 2). Association to region B, the more significant of the two regions, was also assessed in a German case–control sample. In addition, two joint analyses were carried out, first combining the two Scottish samples (Merged Scottish) and then all three samples (Merged All). Approval to conduct this research was obtained from the Scotland A Research Ethics Committee.

The Scottish 1 case–control sample has been described previously [39]. For the Scottish 2 sample, individuals diagnosed with BPD or SCZ (Supplementary Table 1) were recruited from inpatient and outpatient services at psychiatric hospitals in South-East and South-Central Scotland, and from Ravenscraig Hospital, Greenock, Inverclyde. Diagnoses were reached by consensus between two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM–IV) [2] on the basis of medical and psychiatric histories, case note review, and interview using the Schedule for Affective Disorder and Schizophrenia—Lifetime version (SADS-L) [9].

Control subjects in the Scottish 2 sample were recruited from the same population in South-East and South-Central Scotland and from the Grampian region of Scotland, with the majority (>80%) recruited through the Scottish National Blood Transfusion Service, which only accepts individuals who are not currently taking medication and do not have a chronic illness. The rest were recruited from hospital staff or the general population, and were screened to exclude anyone currently taking medication or with a history of psychiatric illness.

The German case–control sample (Supplementary Table 1) comprised individuals with a lifetime diagnosis of BPD or SCZ, according to DSM-IV criteria, who were recruited from consecutive admissions to the inpatient unit of the Department of Psychiatry and Psychotherapy of the University of Bonn and of the Central Institute of Mental Health in Mannheim. Final diagnoses were reached using a consensus best estimate procedure [21], based on medical records, family history, and information obtained through a structured clinical interview for DSM-III-R (SCID-I) [34].

German control subjects were recruited from the Bonn region of Germany. Both the patient and the control samples were of German ancestry, extending back at least three generations.

Genotyping of the Scottish 1 sample has been described previously [39]. Genotyping of the three region A and three region B SNPs in the Scottish 2 sample was carried out at the Wellcome Trust Clinical Research Facility, Edinburgh, UK, using the Illumina BeadArray platform. The three region B SNPs were genotyped in the German sample using the Illumina BeadArray platform at the University of Bonn, Germany.

For both case–control samples, SNPs with a locus success rate of <90% and samples with a genotyping success rate of <90% were excluded from the analyses. Following these quality control measures, genotype data was available for five SNPs (three region A SNPs and two region B SNPs) in 307 control, 303 SCZ, and 239 BPD subjects in the Scottish 2 sample, and for the three region B SNPs in 397 control, 396 SCZ, and 400 BPD subjects in the German sample (Supplementary Table 1).

All SNPs were assessed for deviation from Hardy–Weinberg equilibrium (HWE) using a χ^2 goodness-of-fit test, with $p \leq 0.05$. None of the SNPs deviated from HWE ($p \geq 0.065$). In order to assess the effect of biases such as population differences prior to combining samples for the merged analyses, the genetic homogeneity of the three control groups was assessed using the χ^2 test-of-independence. None of the SNPs were found to differ significantly between the three control groups (corrected $p_{st} \geq 0.053$; Supplementary Table 2).

Differences in allele and genotype frequencies between cases and controls were assessed using the χ^2 test-of-independence. Haplotype frequency estimation and comparisons between cases and controls were carried out using Cocaphase 2.404 [8]. Haplotypes were assessed in global and individual tests. Haplotypes with

a frequency of less than 1% in cases and controls were grouped for the global test of significance. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the most common haplotype in the control sample as the reference. When the most common haplotype was the haplotype of interest, the second most common haplotype was used as the reference.

Associations directly replicating those identified in the analysis of the Scottish 1 sample [39] were accepted as significant when $p \leq 0.05$, due to the *a priori* evidence for these SNPs. In the separate analyses of the Scottish 2 and German samples, novel associations attaining nominal significance ($p \leq 0.05$) were corrected by permutation analysis. In the merged analyses, all nominally significant associations were corrected by permutation analysis. Permutation analysis (1000 permutations) was performed using Cocaphase 2.404. Corrections were made at two levels: the single-test level (p_{st}) and the experiment-wise level (p_{ew}; Supplementary Table 3). The single-test level corrects for multiple comparisons within a particular subgroup and region, at the single-marker or haplotype level. The experiment-wise level combines *p*-values across diagnostic groups (SCZ, BPD, and combined), and single-marker and haplotype tests to give a regionally corrected *p*-value within each sample. No correction was made for the use of allelic and genotypic tests, as these tests are highly correlated. Permutation analysis was chosen as the method of choice for multiple testing correction as it offers correction suitable for datasets of non-independent variables, such as SNPs in linkage disequilibrium [29].

In the separate sample analyses of the Scottish 2 and German samples, none of the SNPs, or two- or three-marker haplotypes within either region A or region B were significantly associated with SCZ, BPD, or the combined case group in the Scottish 2 sample (best uncorrected *p*-value = 0.14; Table 1). In the German sample, the only significant association was to a three-SNP region B haplotype (C-A-C) in BPD cases at the individual (uncorrected $p_i = 0.020$) but not global (uncorrected $p_g = 0.35$) level (Table 1). However, following correction by permutation analysis the individual *p*-value was not statistically significant (corrected $p_{st} = 0.13$).

In the combined analyses, the only significant single-marker association was between the intronic region B SNP rs6988339 and SCZ in the Merged Scottish sample (uncorrected $p = 0.024$; Table 1). However, this association did not withstand correction for multiple testing (corrected $p_{st} = 0.059$).

The three-SNP region A haplotype (T-T-T; Table 1; Supplementary Table 3), which was nominally associated with SCZ in the initial Scottish sample, was significantly associated with SCZ in the Merged Scottish sample (Scottish 1 and Scottish 2) at the individual level (uncorrected $p_i = 0.028$), however this did not survive multiple testing correction (corrected $p = 0.21$). In contrast to the Scottish 1 sample, this haplotype was not associated with the combined case group.

In keeping with findings in the Scottish 1 sample [39], the two-SNP region B haplotype (Table 1; Supplementary Table 3) comprising SNPs rs6988339 and rs3757930 (G-C) was significantly associated with SCZ and the combined case group in the Merged Scottish analysis, in both the individual (SCZ: uncorrected $p_i = 0.0037$; BPD + SCZ: uncorrected $p_i = 0.0080$) and global (SCZ: uncorrected $p_g = 0.030$; BPD + SCZ: uncorrected $p_g = 0.029$) haplotype tests. These associations remained significant after correction of individual *p*-values by permutation analysis (SCZ: corrected $p_{st} = 0.022$; BPD + SCZ: corrected $p_{st} = 0.044$). This haplotype was more common in cases (SCZ: 32.9%, BPD + SCZ: 32.0%) than controls (27.3%), conferring an increased disease risk (SCZ: OR = 1.3, 95% CI: 1.1–1.6; BPD + SCZ: OR = 1.2, 95% CI: 1.1–1.5). This haplotype was also associated with the combined case group in the Merged All group in the individual (uncorrected $p_i = 0.045$) but not the global (uncorrected $p_g = 0.11$) test of significance. The association in the Merged All group did not remain significant after permutation analysis (corrected $p_{st} = 0.16$).

To compensate for the genotyping failure of one of the region B SNPs in the Scottish 2 sample, the ability of the two-SNP (rs6988339 and rs3757930) region B haplotype to predict the three-SNP region B haplotype was assessed in the Scottish 1 sample. Genotype data was uploaded to Haploview 4.2 and linkage disequilibrium between the two- and three-SNP region B haplotypes calculated. The two-SNP G-C haplotype, which was significant in the Scottish 2 sample, was found to predict the three-SNP A-G-C haplotype, which was significantly associated with SCZ and the combined case group in our original study [39], with an $r^2 > 0.95$ (Supplementary Fig. 1). It therefore seems likely that the same three-SNP haplotype would show significant association in the Scottish 2 sample.

In this study, individual analysis of the two new case–control samples failed to replicate any of our previously reported associations [39]. However, on combining the two Scottish samples, a two-SNP haplotype in region B (rs6988339 and rs3757930) was significantly associated with SCZ and the combined case group, with these associations surviving correction for multiple testing at the single-test, but not experiment-wise, level of permutation analysis.

One interpretation of these results is that *NRG1* risk variants are genetically heterogeneous amongst cases from different populations. Heterogeneity amongst different European populations has been demonstrated for another SCZ- and BPD-risk gene, *DISC1* [18]. To investigate this heterogeneity, Hennah et al. [18] used conditional association analysis to detect *DISC1* variants that confer risk only on certain genetic backgrounds.

Furthermore, SCZ and BPD are likely to be phenotypically heterogeneous. The broad diagnostic categories of SCZ and BPD used to select cases in this study may have obscured a difference in the phenotypic composition of the individual case–control samples. Variants in *NRG1* may be involved in certain sub-phenotypes of SCZ and BPD. Indeed, studies have already demonstrated association of *NRG1* variants with particular aspects of psychiatric illness, including the development of psychotic symptoms, and abnormal P300 electroencephalogram activation [4,12,16,31,33].

An important caveat is the issue of sample size and its corollary, statistical power. In the larger merged Scottish sample we increase power and detect association with a reduced OR, consistent with results from genome wide association studies [6]. Estimates of effect size in the original study are, therefore, probably inflated, following the winner's curse phenomenon [40]. This suggests that the two new samples may have been underpowered to detect a variant of small effect size.

Power to detect the two-SNP (rs6988339 and rs3757930) region B haplotype in the SCZ and combined case groups in the Scottish 2 and German samples, assuming the same effect size as identified in the merged Scottish sample, was assessed using an online genetic power calculator [32]. These calculations indicated approximately 90% power (uncorrected $p \leq 0.05$) to detect this haplotype in all groups (Supplementary Table 4). However, the validity of these calculations is limited by the need to assume complete linkage equilibrium between the genotyped marker(s) and the risk allele(s); this is unlikely to be true. Furthermore, following correction for multiple testing, power to detect differences at adjusted *p*-values will be less than predicted.

In summary, in this study we have found no evidence for association to region A and shown support for the presence of a risk variant for SCZ and/or BPD within, or in LD with, region B in an enlarged case–control sample. These findings contribute to a substantial body of genetic and functional evidence supporting the candidacy of *NRG1* as a SCZ- and BPD-susceptibility gene. Taking into consideration the issues of genetic and phenotypic heterogeneity, and sample size, it seems that our understanding of *NRG1* would be most successfully expanded through association analyses

Table 1
Individual association analysis results for single-, two-, and three-marker haplotypes.

Marker (NCBI build 36 position)	Best individual haplotype *p*-values								
	SCZ			BPD			Combined SCZ and BPD		
	Single	Two	Three	Single	Two	Three	Single	Two	Three
Region A									
rs1503491 (chr8:31761648)									
Scottish 1	*0.61*	***0.024***	***0.00032***	*0.24*	***0.037***	*0.084*	*0.70*	***0.012***	***0.0017***
Scottish 2	0.94	0.87	0.61	0.61	0.79	0.57	0.83	0.81	0.57
Merged Scottish	0.86	0.096	**0.028**	0.51	0.14	0.69	0.79	0.067	0.098
rs553950 (chr8:31910904)									
Scottish 1	***0.028***	***0.0085***		***0.028***	***0.044***		***0.012***	*0.052*	
Scottish 2	0.99	0.68		0.95	0.30		0.96	0.31	
Merged Scottish	0.093	0.074		0.11	0.058		0.058	0.27	
rs327329 (chr8:31973040)									
Scottish 1	*0.44*			*0.85*			*0.74*		
Scottish 2	0.99			0.58			0.78		
Merged Scottish	0.56			0.85			0.65		
Region B									
rs2919390 (chr8:32646497)									
Scottish 1	***0.010***	***0.0012***	***0.00014***	*0.080*	***0.014***	***0.0022***	***0.010***	***0.00084***	***0.000062***
German	0.92	0.31	0.17	0.073	0.12	0.24	0.33	0.74	0.93
rs6988339 (chr8:32665458)									
Scottish 1	***0.010***	***0.0014***		***0.032***	***0.0045***		***0.0059***	***0.00044***	
Scottish 2	0.55	0.48		0.14	0.45		0.69	0.96	
German	0.38	0.26		0.19	0.34		0.80	0.93	
Merged Scottish	**0.024**	**0.0037**		0.55	0.072		0.087	**0.0080**	
Merged all	0.22	0.098		0.19	0.072		0.14	**0.045**	
rs3757930 (chr8:32708660)									
Scottish 1	*0.20*			*0.16*			*0.12*		
Scottish 2	0.69			0.57			0.58		
German	0.16			0.35			0.18		
Merged Scottish	0.17			0.17			0.11		
Merged all	0.85			0.70			0.74		

Global *p*-values are shown for each SNP and individual haplotype *p*-values for two- and three-marker haplotypes for schizophrenia (SCZ), bipolar disorder (BPD), and the combined case group (combined SCZ and BPD). Results from the Scottish 1 sample [39] are shown in italics for comparison. *p*-Values are shown in line with the first SNP of each multi-marker haplotype. Associations attaining nominal significance ($p \leq 0.05$) in the Scottish 1 sample and the threshold level of significance for replication ($p \leq 0.05$) are highlighted in bold.

of larger genetically and/or phenotypically homogenous samples, and interaction analyses to determine the effect of *NRG1* variants on specific genetic backgrounds.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2010.04.056.

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