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Association study of Neuregulin-1 gene polymorphisms in a north Indian schizophrenia sample

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Abstract

Background—Neuregulin-1 (*NRG1*) gene polymorphisms have been proposed as risk factors for several common disorders. Associations with cognitive variation have also been tested. With regard to Schizophrenia (SZ) risk, studies of Caucasian ancestry samples indicate associations more consistently than East Asian samples, suggesting heterogeneity. To exploit the differences in linkage disequilibrium (LD) structure across ethnic groups, we conducted a SZ case-control study (that included cognitive evaluations) in a sample from the north Indian population.

Methods—*NRG1* variants (n= 35 SNPs, three microsatellite markers) were initially analyzed among cases (DSM IV criteria, n = 1007) and controls (n=1019, drawn from two groups) who were drawn from the same geographical region in North India. Nominally significant associations

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Contributors: Prof. B.K. Thelma and Prof. V. L. Nimgaonkar designed the study and wrote the protocol. Prof. Deshpande and her team provided the research samples; Prof. R.E. Gur and Prof. R.C. Gur provided the neurocognitive battery and Dr. Triptish Bhatia did the cognitive analysis. Dr. A. M. Bhagwat is the Ph D supervisor for Prachi Kukshal. Prachi Kukshal managed the literature searches did the genetic analysis and wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

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with SZ were next analyzed in relation to neurocognitive measures estimated with a computerized neurocognitive battery in a subset of the sample (n=116 cases, n=170 controls).

Results—Three variants and one microsatellite showed allelic association with SZ (rs35753505, rs4733263, rs6994992, and microsatellite 420 M9-1395, $p = 0.05$ uncorrected for multiple comparisons). A six marker haplotype 221121 (rs35753505-rs6994992-rs1354336-rs10093107-rs3924999-rs11780123) showed ($p=0.0004$) association after Bonferroni corrections. Regression analyses with the neurocognitive measures showed nominal (uncorrected) associations with emotion processing and attention at rs35753505 and rs6994992, respectively.

Conclusions—Suggestive associations with SZ and SZ-related neurocognitive measures were detected with two SNPs from the *NRG1* promoter region in a north Indian cohort. The functional role of the alleles merits further investigation.

Keywords

Schizophrenia; *NRG1*; association; SNP and microsatellite markers; Haplotypes; cognition

1. INTRODUCTION

Schizophrenia (MIM 181500, SZ) is a common, lifelong disorder with a life time prevalence of 0.8% among Indian adults (Saha et al., 2005; Faraone et al., 2002). The relatively high heritability of SZ has motivated intensive gene mapping efforts (Shirts and Nimgaonkar, 2004; Talkowski et al., 2007, 2010; Chen et al., 2009; Greenwood et al., 2012). Meta-analysis of 32 genome-wide linkage studies of SZ suggested linkage on chromosome 8p (16-33 Mb) (Ng et al., 2009) for 22 European-ancestry samples. Recently, genome-wide association studies (GWAS) have identified several relatively common single nucleotide polymorphisms (SNPs) that are associated with SZ (Shi et al., 2009; Potkin et al., 2009; McClay et al., 2010; Shi et al., 2011; Ripke et al., 2011).

Several studies have focused on the signaling protein *NRG1* and its receptor *ERBB4*. A variety of *NRG1* isoforms (estimated $n = 30$) are produced by alternative splicing (Tan et al., 2007; Liu et al., 2011). They are expressed in varying proportions at relatively high levels in a variety of peripheral tissues as well as the brain. In the brain, *NRG1* is considered to be a pleiotropic growth factor with an integral role in its development, organization, and function (Li et al., 2006). *NRG1* plays key roles in several neurotransmitter systems, including (*N*-methyl-D-aspartate), acetylcholine, as well as *gamma*-Aminobutyric acid (Fischbach and Rosen, 1997; Ozaki et al., 1997; Rieff et al., 1999; Cameron et al., 2001).

Several *NRG1* SNPs have been reported to be associated with SZ, albeit at nominal levels of significance (Bertram et al., 2005; Falls, 2003a, b; Farrer et al., 2001; Harrison and Weinberger, 2005; Hashimoto et al., 2004; Gardner et al., 2006). Stefansson et al. (2002) first reported linkage to a locus on Chromosome 8 in an Icelandic sample and subsequently a replicated association with a 7-marker risk haplotype in a Scottish sample (Stefansson et al., 2003). Meta-analysis of 26 published case-control and family-based association studies showed association of SNP8NRG221132, 420M9-1395, 478B14-848 and suggested population stratification for SNP8NRG221533 (Gong et al., 2009). Another meta-analysis of

13 studies reported association with six markers between two adjacent, but distinct haplotypes blocks in Caucasian and Asian ancestry samples (Li et al., 2006). Another group found non-significant association of SNP8NRG221533 after taking study design and ancestry into account (Munafo et al., 2008; Munafo et al., 2006). Only one study has been reported from South Asia. This study from Pakistan investigated two SNPs in 100 cases and 70 adult controls. It suggested nominal association with the exonic SNP rs3924999 (Naz et al., 2011).

Impairment in several cognitive domains has been reported in SZ (Heinrichs et al., 1997; Goldberg and Green, 2002; Buchanan et al., 2005; Snitz et al., 2006; Gur et al., 2007; Reichenberg and Harvey, 2007; Barch and Smith, 2008; Ranganath et al., 2008; Tandon et al., 2009; Yokley et al., 2012). *NRG1* SNPs may also be associated with cognitive dysfunction, particularly attention (Yokley et al., 2012); spatial memory and social behavior (O'Tuathaigh et al., 2007). The *NRG1* SNP8NRG221533 (rs35753505) has most widely been evaluated in relation to cognition (Kurnianingsih et al., 2011). A role for *NRG1* in SZ has also been supported by animal studies using *NRG1* and *ErbB4* mutant mice (Bao et al., 2003; Gerlai et al., 2000; Rimer et al., 2005; Stefansson et al., 2002; Corfas et al., 2004; Steinthorsdottir et al., 2004; Gu et al., 2005), which exhibit behaviors similar to those of established rodent models of SZ (Lipska, 2004).

NRG1 polymorphisms have been proposed as risk factors for several other common disorders, including Alzheimer's disease (Chaudhury et al., 2003; Go et al., 2005); epilepsy (early myoclonic encephalopathy; Backx et al., 2009), stroke (Shyu et al., 2004; Xu et al., 2004) breast cancer (Raj et al., 2001), multiple sclerosis (Cannella et al., 1999; Viehaver et al., 2001), bipolar disorder (Goes et al., 2008; Moon et al., 2011; Prata et al., 2009; Thomson et al., 2007; Walker et al., 2010) and Hirschsprung Disease (Garcia-Barcelo et al., 2009; Tang et al., 2011).

In sum, *NRG1* likely plays a key role in brain development and neurotransmitter function. With regard to SZ risk, the results from Caucasian ancestry samples appear to be more consistent whereas the results from the Asian samples are variable, suggesting locus heterogeneity. In order to exploit the differences in LD structure across ethnic groups, we investigated a north Indian population using a case-control design. *NRG1* SNP associations with cognitive variation were further tested in a sub-group of this sample.

2. METHODS

2.1 Recruitment and diagnostic assessment

The recruitment and assessment of the sample has been described in prior studies (Bhatia et al., 2008). Briefly, patients with a clinical diagnosis of SZ or schizoaffective disorder were referred from the outpatient department of Dr. Ram Manohar Lohia Hospital, as well as other private and public psychiatric facilities in Delhi, India. All patients (n=1007) were assessed using the Hindi versions of the Diagnostic Interview for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS) (Nurnberger et al., 1994; Deshpande et al., 1998; <http://www.grb.nimh.nih.gov/gi.html>). This information was synthesized with

available medical records and presented to board certified psychiatrists who assigned consensus diagnoses.

The control samples (n=1019) included non-psychotic adults (n=521) who were recruited from the same communities in which the patients resided. Care was taken not to include multiple related individuals as controls. At the time of recruitment, detailed family information was obtained with the use of a semi-structured questionnaire and care was taken to avoid recruitment of 1st and 2nd degree relatedness in our case-control cohort. We also included a control group comprising neonatal blood samples from live births at Lok Nayak Hospital, New Delhi; this group could not therefore be screened for psychotic illness (n=498). DIGS and FIGS were administered on mothers of all neonatal controls to evaluate for psychotic illness in the parents and other first or second degree relatives. Neonatal blood was not taken if any family member was reported to have psychotic illness. No information apart from gender was provided about these anonymous samples.

All participants (except the neonatal control samples) provided written informed consent. Written informed consent was obtained from mothers for the neonatal sample. The study was approved by Institutional Ethical Committee at Dr. Ram Manohar Lohia (RML) Hospital, New Delhi, and the Institutional review board at the University of Pittsburgh, USA.

2.2 Cognitive evaluation

The Hindi version of the Penn Cognitive Neuropsychiatric Battery (CNB) (Bhatia et al., 2011; Gur et al., 2001) was administered to a subset (n=256) of participants comprising cases (n=116) and adult controls (n=140). The following cognitive domains were assessed: abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotional processing. The CNB evaluates accuracy, speed and efficiency for each domain. As these indices are correlated for any one domain, we analyzed the accuracy measures for parsimony.

2.5 Selection of polymorphisms

A total of 35 SNPs and three microsatellite markers were tested. We selected markers based on prior reported associations and based on local LD ($r^2 > 0.8$; Indian, GIH data in Hapmap, www.hapmap.org). We also focused on SNPs in exonic regions and in the 5' sequences, the latter because it has been proposed that regulatory variants in *NRG1* may be particularly involved in pathogenesis (Law et al., 2006).

2.4 Genotype assays

DNA was extracted and used for genotyping the SNPs based on primer extension reaction chemistry in the MALDI-TOF mass spectrometry platform (www.sequenom.com/plex/) using iPLEX® Gold reagents. An ABI 3730 machine was used for fragment analysis of the fluorescent labeled microsatellite markers. Quality checks were performed by using duplicates and CEPH samples in each plate.

2.5 Statistical analysis

Hardy Weinberg equilibrium (HWE) was examined for each SNP. All SNPs conforming to HWE estimates ($p > 0.01$) were included in the association analyses. LD values (r^2) were estimated for the genotyped data using the Tagger algorithm in Haploview version 4.1 (Barrett et al., 2005; <http://www.broad.mit.edu/mpg/haploview/>). Heterogeneity between neonatal and adult control groups with regard to allele frequencies was also tested using Haploview software. Case-control associations for individual SNPs were evaluated using the Trends test in PLINK (<http://pngu.mgh.harvard.edu/~purcell/plink/>). Associations with microsatellite markers were assessed using CLUMP software (Sham and Curtis, 1995; <http://www.smd.qmul.ac.uk/statgen/dcurtis/software.html>). SNPs which showed association either for allelic or model-wise tests were included for haplotype analysis, using PLINK and UNPHASED (Dudbridge, 2003, 2008). Power was estimated using Quanto software (Gauderman and Morrison, 2006; <http://hydra.usc.edu/gxe/>).

Multivariate analyses were used to test associations between individual SNPs and accuracy for cognitive domains using the Statistical Package for Social Sciences (SPSS Version 16, <http://hydra.usc.edu/gxe/>). Linear regression analyses were conducted separately for each cognitive domain to test associations between cognitive variables and two SZ associated SNPs. The normalized cognitive domain scores adjusted for age were the outcome variables and genotypes for individual SNPs, gender and diagnosis were used as covariates for these analyses.

3. RESULTS

3.1 Demographic data

Men constituted 56.8% of the cases and 55.74% of the controls. There were no significant case-control differences with regard to gender in the two groups. There was a significant difference in the ages of the cases and the controls (mean $\pm$ standard deviation, SD; adult controls: 43.03 ± 14.0 ; cases: 29.9 ± 8.95).

3.2 Quality control for genotype assays

All the SNPs were in HWE ($p > 0.01$). Of the 2044 participants in the study, genotypes from individuals with less than 90% genotype calls were excluded from all analysis ($n = 18$). Therefore, a total of 2026 participants were analyzed ($n=1007$ cases, $n=1019$ controls). Overall, the call rate was over 97% for the SNPs and over 95% for the microsatellite markers.

3.3 LD patterns

LD between pairs of SNPs was estimated for the control individuals using r^2 values (Supplementary Figure 1). Overall, the patterns of LD resembled those observed in Caucasian ancestry individuals (www.hapmap.org). The SNPs genotyped were generally not in tight LD with the following notable exceptions: rs6988339 and rs10691392 ($r^2 = 0.9$) and rs6994992 and rs4733263 ($r^2 = 0.97$).

3.4 Case-control comparisons

The adult and the neonatal control samples did not differ significantly with regard to genotype or allele frequencies for any of the polymorphisms (Supplementary Table I). Test of heterogeneity performed for each SNPs did not show significant differences between the two groups of controls (Supplementary Table I). Since the distribution of the polymorphisms was comparable in the two groups, the control groups were pooled for all further analysis.

Three polymorphisms were nominally associated with SZ risk ($p < 0.05$ uncorrected for multiple comparisons, Table 1; Supplementary table II) of which rs6994992 and rs4733263 are in LD: rs35753505 ($p=0.04$; OR=1.15(95% confidence intervals, CI, 1.01-1.31), rs4733263 ($p=0.04$; OR=1.14(95% CI, 1.01-1.31)), rs6994992 ($p=0.026$; OR=1.15(95% CI, 1.02-1.3)), but none withstood Bonferroni corrections.

One microsatellite marker 420_M9-1395 ($p=0.016$) located in 5' region also showed nominal association (Table 1; Supplementary table II). Four more SNPs showed genotypic association. TT genotype of rs3924999 a Val>Leu missense polymorphism in exon 11 and GG genotype in rs11780123 in 3' region showed association (0.02 and 0.01 respectively) under a Dominant model. TT genotype of rs1354336 and rs10093107 showed association (0.009 and 0.008 respectively) under Recessive model (Table 1).

3.5 Haplotypic association

Using the 6 associated SNPs in linkage equilibrium namely rs35753505, rs6994992, rs1354336, rs10093107, rs3924999 and rs11780123 (Table 1), two to six SNP sliding window haplotypes (frequency >5%) were constructed and global p values were tabulated (Table 2a). Out of 74 haplotypes constructed using Plink, 18 haplotypes were significantly different. A five-marker haplotype comprised of rs6994992-rs1354336-rs10093107-rs3924999-rs11780123 ($p=0.0004$) and a six-marker haplotype with rs35753505-rs6994992-rs1354336-rs10093107-rs3924999-rs11780123 ($p=0.0004$) remained significant after Bonferroni corrections (alpha value $0.05/74=0.0006$; Table 2b). Notably, most of the associations were driven by the two promoter SNPs rs35753505 and rs6994992 (Table 2a and b; Supplementary Table II).

3.6 Cognitive variables

Computerized neurocognitive data were available for cases and adult controls ($n=256$). In this group, there were no significant gender difference (61.2% and 60% males, respectively for controls and cases). The mean age of the controls (47.97, SD 15.0) was significantly higher ($F=126.532$; $p=4.3 \times 10^{-24}$) than those of cases (31.0, SD 9.32). Therefore, the cognitive measures were adjusted for age. We analyzed eight neurocognitive domains, namely abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotion processing (Gur et al., 2007). Of the three allelic associated SNPs only rs35753505 and rs6994992 were used for further cognitive analysis as rs4733263 was in LD with rs6994992. Following linear regression analysis, an association between rs35753505 and emotion processing was noted ($p=0.031$). At rs6994992, an association with attention was noted ($p=0.047$; Table 3). There was no

significant interaction between SNP genotype and case-control status at either locus (data not shown).

3.7 Power analysis

The sample has > 85% power to detect associations with SZ risk having an OR of 1.5 or greater, for SNPs having minor allele frequencies (MAF) greater than 5%, assuming alpha = 0.05, uncorrected for multiple comparisons.

4. DISCUSSION

Three SNPs namely rs35753505, rs4733263 and rs6994992 showed modest allelic association and four additional SNPs rs1354336, rs10093107, rs3924999 and rs11780123 namely showed genotypic (dominant or recessive) association and one microsatellite marker (420M9-1395) showed modest allelic association with SZ in our north Indian sample (Table 1), though it should be noted that the associations did not remain significant following Bonferroni corrections for multiple comparisons. rs6994992 was also reported to be associated with SZ in Caucasian samples (Hall et al., 2006; Law et al., 2006). Notably, the risk allele at this SNP (T) is associated with increased type IV *NRG1* messenger RNA levels (Law et al., 2006), lower prefrontal (and temporal) activation and development of psychotic symptoms in individuals at high risk for SZ (Hall et al., 2006). This SNP maps upstream of the *NRG1* type IV 5'-exon (Steinthorsdottir et al., 2004; Law et al., 2006; Tan et al., 2007; Shamir and Buonanno, 2010). It is associated with diminished activation in medial prefrontal cortex and at the right temporo-occipital junction (Hall et al., 2006). The other associated polymorphisms may also have functional effects, as associations with cortical volumes have been reported at 420_M9-1395 (Addington et al., 2007) and rs6994992 (Mata et al., 2009, 2010). 420M9-1395 and rs35753505 may influence brain development (Addington et al., 2007). In addition, reduction of white matter fractional anisotropy was associated with rs35753505 in the anterior cingulum (Wang et al., 2009; Kurnianingsih et al., 2011). As the associated polymorphisms are localized to the 5' region, it is possible that variation in the promoter region of *NRG1* elevates risk for SZ. Indeed, post-mortem studies reveal altered *NRG1* mRNA levels in the prefrontal cortex of SZ patients (Harrison and Law, 2006), as well as the hippocampal region (Law et al., 2006) and neuroimaging studies reveal changes in subcortical white matter myelination in the frontal lobe (Konrad and Winterer, 2008). *NRG1* variants likely modulate brain activation during episodic memory processing in key areas for memory encoding and retrieval, with SZ risk alleles showing hyper activation in areas associated with elaborate encoding strategies (Krug et al., 2010). Exonic SNP rs3924999, a missense variant present in *NRG1* (Val > Leu in exon 11) increased the risk of schizophrenia (Walss-Bass et al., 2006a). Genotypic association of this SNP has been observed for antisaccades and smooth pursuit eye movements (Schmechtig et al., 2010) and lower prepulse inhibition, an endophenotype of schizophrenia (Hong et al., 2008). This suggests an impact of *NRG1* polymorphism on the neural mechanisms underlying visuospatial sensorimotor transformations, a mechanism that has been found to be impaired in patients with schizophrenia and their relatives.

We also found significant 5- and 6-marker haplotypic association withstanding Bonferroni correction (Table 2b) and the associations seems to be primarily attributable to the promoter SNPs rs6994992 (Table 2a and b). However, a significantly associated truncated haplotype (Table 2b) suggests contributions of the 3' marker (rs11780123) also. Of note, functional imaging studies have report intragenic epistasis between 5' and 3' markers in *NRG1* (Nicodemus et al., 2010; Moon et al., 2011).

The associations between rs35753505 and rs6994992 and cognitive functions noted here are consistent with prior reports in Caucasian samples; e.g., (Yokley et al., 2012) and (O'Tuathaigh et al., 2007), though there are some reports of non-significant associations (Crowley et al., 2008). In healthy participants, rs35753505 was not associated with working memory or task performance (Krug et al., 2008; Kircher et al., 2009a), but was associated with semantic verbal fluency (Kircher et al., 2009b) and sustained attention (Stefanis et al., 2007). rs6994992, originally identified as part of the so-called deCODE haplotype, could be specifically related to disruption of normal frontal and temporal lobe function, premorbid intelligence levels and the emergence of psychotic symptoms (Harrison and Law, 2006; Li et al., 2006). Individuals with the TT genotype at this SNP also had reduced white matter density and structural connectivity (McIntosh et al., 2008), impaired frontal and temporal lobe activation (Hall et al., 2006), and cognition (Hall et al., 2006; Stefanis et al., 2007; Sprooten et al., 2009), including reduced spatial working memory capacity (Stefanis et al., 2007) and emotion processing (Keri and Kelemen, 2008).

There are some limitations in the present study. First, several associations did not withstand Bonferroni corrections for multiple comparisons. Thus, the effects of *NRG1* polymorphisms in this, the largest Indian sample analyzed to date are likely to be modest. Second, the sample included adult, as well as neonatal controls, though there was no significant difference in allele frequencies between these two groups. There is a modest (~1%) probability that some of the neonatal controls will be diagnosed with SZ in later life (estimated n= approximately 5). Such misdiagnosis would tend to diminish observed associations. Finally, population substructure as a potential source for the association could not be evaluated in the sample using Principle Components Analysis (PCA) or Multi Dimensional Scaling (MDS), as ancestry informative or genome wide markers were not evaluated.

In conclusion, nominal associations with SZ were noted with three *NRG1* polymorphisms. Two of the associated SNPs were also associated with cognitive variation in the combined case-control sample. These associations are consistent with prior reports, predominantly in Caucasian samples. As the associated polymorphisms and haplotypes are localized to the 5'*NRG1* sequences, they may reflect subtle alterations in gene expression. Further investigations of *NRG1* function in the brain, as well as functional studies of the associated polymorphisms are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association of *NRG1* with SZ

SNP	BP	MA	MAF		Trends Test		Models			
			Fca	Fco	CHISQ	p(df=1)	Dominant		Recessive	
							CHISQ	p(df=1)	CHISQ	p(df=1)
rs35753505*	31593683	T	0.37	0.34	4.43	0.04	6.14	0.01		6.176
rs4733263	31610016	G	0.50	0.47	4.17	0.04	3.04	0.08		4.185
rs6994992**	31615123	T	0.50	0.47	4.99	0.03	3.22	0.07	3.419	4.992
420M9-1395#	31,665,413., 31,665,691 (-)	(CA)14	0.003	0.0005	18.70	0.02 (df=8)				
rs1354336	31713684	T	0.13	0.13	0.002	0.96			6.745	8.667
rs10093107	32145991	T	0.43	0.46	3.58	0.06			7.076	7.201
rs3924999	32572900	T	0.43	0.40	1.71	0.19	5.81	0.02		8.026
rs11780123	32750870	G	0.14	0.16	3.57	0.06	6.49	0.01		10.19

BP: genomic location (base pairs). MA: Minor allele; MAF: Minor allele frequency; Fca: Minor allele frequency in cases; Fco: Minor allele frequency in unaffected controls Aliases:

* SNP8NRG221533;

** SNP8NRG243177;

Microsatellite Marker rs4733263 and rs6994992 are in LD ($r^2=0.9$).

Table 2a
Sliding Window haplotype analysis of nominally associated SNPs

Name	Map Information	2- mhap	3- mhap	4- mhap	5- mhap	6- mhap
rs35753505	31593683	0.09	0.28	0.39	0.01	0.01
rs6994992	31615123	0.05	0.04	0.02	0.02	
rs1354336	31713684	0.17	0.24	0.09		
rs10093107	32145991	0.13	0.11			
rs3924999	32572900	0.05				
rs11780123	32750870					

2-mhap: Global p-values of successive two marker haplotypes generated using UNPHASED. Data are presented in the same format for each adjacent pair of markers down this column.
3-mhap: Global p-values of three marker haplotypes generated using UNPHASED. Data are presented in the same format for each set of three adjacent markers down this column. Similarly, 4-, 5- and 6-mhap denote haplotypes incorporating the respective number of SNPs
Haplotypes with a frequency lower than 5% were not included in the analysis;

Table 2b

Significant haplotypes of associated SNPs

SNPs	Haplotype	Freq.	OR	chi Sq.	P
2 SNP window					
rs35753505-rs6994992	22	0.35	1.15	4.45	0.0348
rs35753505-rs6994992	11	0.51	0.87	5.15	0.0233
rs694992-rs1354336	21	0.45	1.17	5.51	0.0189
rs694992-rs1354336	11	0.43	0.86	5.43	0.0198
rs10093107-rs3924999	12	0.26	1.17	4.12	0.0424
rs3924999-rs11780123	21	0.36	1.15	4.41	0.0358
3 SNP window					
rs35753505-rs6994992-rs1354336	221	0.33	1.17	4.81	0.0284
rs35753505-rs6994992-rs1354336	111	0.42	0.86	5.41	0.0201
rs694992-rs1354336-rs10093107	112	0.18	0.83	4.12	0.0424
rs694992-rs1354336-rs10093107	211	0.26	1.25	8.00	0.00468
rs10093107-rs3924999-rs11780123	121	0.22	1.24	6.36	0.0116
4 SNP window					
rs35753505-rs6994992-rs1354336-rs10093107	1112	0.18	0.83	4.19	0.0408
rs35753505-rs6994992-rs1354336-rs10093107	2211	0.18	1.26	6.27	0.0123
rs694992-rs1354336-rs10093107-rs3924999	2112	0.13	1.45	10.50	0.00122
rs1354336-rs10093107-rs3924999-rs11780123	1121	0.20	1.21	4.44	0.035
5 SNP window					
rs35753505-rs6994992-rs1354336-rs10093107-rs3924999	22112	0.09	1.57	10.10	0.00148
rs694992-rs1354336-rs10093107-rs3924999-rs11780123	21121	0.11	1.57	12.80	0.000352*
6 SNP window					
rs35753505-rs6994992-rs1354336-rs10093107-rs3924999-rs11780123	221121	0.08	1.75	12.60	0.000396*

Freq: Frequency of Haplotypes (>5%);

Allele 2 in haplotypes represent minor allele;

* Haplotypes significant after Bonferroni corrections (alpha value 0.05/74= 0.0006)

Table 3
Significant associations between cognitive variables and *NRG1* SNPs

Outcome variable	Covariates	Unstandardized coefficient		Std. Error	Standardized Coefficients	t	p value	95% Confidence Interval for B	
		B						Lower	Upper
Emotion processing	(Constant)	0.948		0.264		3.588	0.0004	0.428	1.468
	Gender	0.075		0.121	0.037	0.622	0.535	-0.163	0.313
	Diagnostic status	-0.558		0.119	-0.279	-4.671	4.90×10^{-06}	-0.793	-0.322
	rs35753505	-0.26		0.119	-0.161	-2.17	0.031	-0.49	-0.02
Attention	(Constant)	0.901		0.298		3.029	0.003	0.314	1.488
	Gender	0.192		0.142	0.09	1.348	0.179	-0.089	0.473
	Diagnostic status	-0.645		0.133	-0.324	-4.834	2.73×10^{-06}	-0.908	-0.382
	rs6994992	-0.237		0.118	-0.164	-1.997	0.047	-0.47	-0.003