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Basic Helix-loop-Helix Transcription Factor *NEUROG1* and Schizophrenia: Effects on Illness Susceptibility, MRI Brain Morphometry and Cognitive Abilities

Beng-Choon Ho, MRCPsych[1], **Eric Epping, M.D.Ph.D**[1], **Kai Wang, Ph.D**[2], **Nancy C. Andreasen, M.D.Ph.D**[1], **Amy Librant, B.S**[1], and **Thomas H. Wassink, M.D**[1]

[1] Department of Psychiatry, University of Iowa Carver College of Medicine

[2] Department of Biostatistics, University of Iowa College of Public Health Iowa City, Iowa, USA

Abstract

Transcription factors, including the basic helix-loop-helix (bHLH) family, regulate numerous genes and play vital roles in controlling gene expression. Consequently, transcription factor mutations can lead to phenotypic pleiotropy, and may be a candidate mechanism underlying the complex genetics and heterogeneous phenotype of schizophrenia. Neurogenin1 (*NEUROG1; a.k.a. Ngn1 or Neurod3*), a bHLH transcription factor encoded on a known schizophrenia linkage region in 5q31.1, induces glutamatergic and suppresses GABAergic neuronal differentiation during embryonic neurodevelopment. The goal of this study is to investigate *NEUROG1* effects on schizophrenia risk and on phenotypic features of schizophrenia. We tested 392 patients with schizophrenia or schizoaffective disorder and 226 healthy normal volunteers for association with *NEUROG1*. Major alleles on two *NEUROG1*-associated SNPs (rs2344484-C-allele and rs8192558-G-allele) were significantly more prevalent among patients ($p \leq .0018$). Approximately 80% of the sample also underwent high-resolution, multi-spectral magnetic resonance brain imaging and standardized neuropsychological assessment. There were significant rs2344484 genotype main effects on total cerebral gray matter (GM) and temporal GM volumes ($p \leq .05$). C-allele-carrier patients and healthy volunteers had smaller total cerebral GM and temporal GM volumes than their respective T-homozygous counterparts. rs2344484-C-allele was further associated with generalized cognitive deficits among schizophrenia patients but not in healthy volunteers. Our findings replicate previous association between *NEUROG1* and schizophrenia. More importantly, this is the first study to examine brain morphological and neurocognitive correlates of *NEUROG1*. rs2344484-C-allele may affect *NEUROG1*'s role in transcription regulation such that brain morphology and cognitive abilities are altered resulting in increased susceptibility to develop schizophrenia.

Keywords

candidate gene; endophenotype; MRI; cognition; schizophrenia; neurogenin

Introduction

Schizophrenia is a neuropsychiatric syndrome defined clinically by a varied constellation of signs and symptoms, including hallucinations, delusions, diminished affect, decreased motivation, emotional impoverishment, and disorganized thought processes and behaviors.

Address for correspondence: Dr. Beng-Choon Ho, Department of Psychiatry, W278 GH, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, Phone: 319/384-9299, Fax: 319/353-8656, Email: beng-ho@uiowa.edu.

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Underlying the heterogeneous clinical manifestations are disease-related traits of diffuse brain volumetric deficits (Honea et al. 2005; Shenton et al. 2001; Steen et al. 2006; Vita et al. 2006; Wright et al. 2000) and generalized cognitive deficits involving multiple cognitive domains (Blanchard and Neale 1994; Heinrichs and Zakzanis 1998; Mohamed et al. 1999; Taylor and Abrams 1984).

Genetic epidemiological research indicates that schizophrenia is largely heritable (Sullivan et al. 2003). Genome-wide linkage studies have identified chromosomal regions harboring potential disease genes (Owen et al. 2004) from which follow-up fine mapping has implicated putative susceptibility genes (e.g.(Brzustowicz et al. 2004; Chumakov et al. 2002; Fanous et al. 2007; Schwab et al. 2003; Stefansson et al. 2002)). Most agree that schizophrenia is genetically complex. Common alleles each with minor effects are thought to interact together to manifest the disorder (i.e. 'common disease-common variants' hypothesis). As with other complex genetic disorders (Botstein and Risch 2003; Goldstein et al. 2003), schizophrenia likely involves allelic heterogeneity (different disease-causing mutations within the same gene) and/or locus heterogeneity (different disease-causing mutations in different genes). Other molecular genetic mechanisms (such as dynamic mutations/expanding trinucleotide repeats, genomic imprinting, mitochondrial inheritance, deletion/insertions of variable repetitions of DNA stretches) may also explain the complex, non-Mendelian pattern of inheritance and phenotypic heterogeneity of schizophrenia. However, whether alternate genetic hypotheses (e.g. (McClellan et al. 2007; Walsh et al. 2008; Xu et al. 2008)) to the 'common disease-common variant' assumption are plausible remains a topic of much debate (Craddock et al. 2007).

In this study, we examined whether a ubiquitous transcription factor (Neurogenin 1 (*NEUROG1 a.k.a. Ngn1 or Neurod3*)) may confer increased risk for schizophrenia, and how *NEUROG1* genetic variations may be related to brain volume deficits and cognitive impairment in schizophrenia. Although gene expression can be controlled at multiple stages (histone acetylation, gene methylation, initiation of transcription, processing of transcript, transport to the cytoplasm, translation of mRNA, mRNA stability, or protein stability), the majority of regulatory events occur at the initiation of gene transcription (Mitchell and Tjian 1989). Transcription factors regulate the initiation and level of gene transcription by binding to a wide variety of cis-acting DNA elements. Because transcription factors control the expression of many genes required in transcriptional regulation, mutations in transcription factors have led to disorders and consequent phenotypic pleiotropy (Latchman 1996). Thus, genetic variations associated with transcription factors may be another mechanism underlying the complex genetics and heterogeneous phenotypic manifestations of schizophrenia.

NEUROG1 is located on Chr 5q31, a region previously implicated in multiple schizophrenia linkage studies (Kendler et al. 2000; Schwab et al. 1997; Skol et al. 2003; Zaharieva et al. 2008). A recent linkage study found strong evidence that quantitative trait loci within the 5q region influence abstraction/mental flexibility, as well as nominal evidence for linkage to a variety of cognitive domains and to schizophrenia liability (Almasy et al. 2008). *NEUROG1* gene itself was recently tested for association (Fanous et al. 2007). The major alleles of rs8192558 and rs2344484 were found to be over-transmitted to schizophrenia patients. We, therefore, sought to replicate this association. In this study, we further investigated the relationships between *NEUROG1* with MRI brain morphometry and with neurocognition in a large cohort of schizophrenia patients and healthy normal volunteers.

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Experimental/Materials and Methods

Subjects

Three hundred and ninety-two patients with schizophrenia-spectrum disorders and 226 healthy normal volunteers (HNV) were obtained through the University of Iowa Mental Health Clinical Research Center (MHCRC). These subjects participated in various MHCRC research studies approved by the University of Iowa institution review board. All subjects gave written informed consent to undergo research assessments, and provided blood for DNA analyses. Out of these 618 subjects, approximately 80% of them also had magnetic resonance (MR) brain morphometric imaging and standardized neuropsychological test data.

Patients were evaluated using a semi structured interview instrument, Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992), from which schizophrenia (N=363) or schizoaffective disorder (N=29) diagnoses meeting DSM-III-R or DSM-IV criteria were based. HNV were recruited from the community through newspaper advertisements. They were initially screened by telephone, and further evaluated using an abbreviated version of the CASH to exclude subjects with current or past medical, neurological or psychiatric illnesses, or with family history of schizophrenia in first-degree relatives.

Patients and HNV were of comparable age (Mean=28.6 (SD=10.3) and 27.7 years (SD=8.1) respectively; T=1.05, df=616, p=0.29) and ethnicity (90.3% and 92.9% Caucasians respectively; χ^2=1.23, p=0.26). A significantly greater proportion of patients were male (73.7% versus 56.1% in HNV; χ^2=20.1, p<0.0001).

Genetic Analyses

DNA was prepared by high-salt extraction from whole blood (Lahiri and Nurnberger 1991). 1ng/ul DNA was amplified using ABI (Applied Biosystems, Foster City, CA) 2720 thermocyclers, ABI Taqman®SNP Genotyping 5′ nuclease assays and ABI Taqman® universal PCR Master Mix. The Taqman®assays consisted of fluorescently labeled VIC and FAM 5′ to 3′ MGB probes and unlabelled forward and reverse primers. Alleles on *NEUROG1* SNPs rs2344484 and rs8192558 were called using ABI Prism 7900 end point read allelic discrimination software. Replicate samples were included on all genotyping plates to ensure accurate allele calling.

MRI Acquisition and Image Processing

Approximately 80% (173 HNV and 319 patients) of subjects who provided blood samples for DNA analyses also underwent magnetic resonance (MR) brain scans. High-resolution brain anatomical MR data in this study were collected from one of two imaging protocols.

Scans performed prior to calendar year 2000 (termed ‘MR5’) were obtained on a 1.5-Tesla GE (General Electric Medical Systems, Milwaukee, Wisconsin) Signa MR scanner. For MR5 imaging protocol, three-dimensional T1-weighted images were acquired in the coronal plane using a spoiled GRASS sequence (SPGR). The parameters were: echo time (TE)=5ms, repetition time (TR)=24ms, numbers of excitations (NEX)=2, rotation angle=45 degrees, field of view (FOV)=26×24×18.8 cm, and a matrix of 256×192×124. Two-dimensional PD and T2 sequences were acquired as follows: 3.0 or 4.0 mm thick coronal slices, TR=3000ms, TE=36ms (for PD) and 96ms (for T2), NEX=1, FOV=26×26 cm, matrix=256×192.

Scans obtained in 2000 or later (termed ‘MR6’) were obtained on a 1.5 T GE CVMRi scanner using T1- and T2-weighted sequences. For MR6 imaging protocol, the T1 sequence was obtained as a 3D volume in the coronal plane using a SPGR with the following parameters: TE=6 ms, TR=20 ms, flip angle=30°, FOV=160×160×192 mm, matrix = 256×256×124,

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NEX=2. The MR6 T2 images were acquired using a 2D fast spin-echo sequence in the coronal plane. The parameters were: TE=85 ms, TR=4800 ms, slice thickness/gap=1.8/0.0 mm, FOV=160×160 mm, matrix=256×256, NEX=3, number of echoes=8, number of slices=124.

Of the 492 subjects with brain morphometric MRI data, there were 232 MR5 scans and 260 MR6 scans. The frequency distributions of patients and HNV across scanning protocols did not differ significantly (Table 1). Genotype frequency distributions (whole sample, within patients or within HNV) did not differ significantly across scanning protocols either (χ^2=2.65, p≥0.27). There were no significant differences in sociodemographic characteristics between HNV with MR5 scans and HNV with MR6 scans. Patients in each imaging protocol were also comparable on sociodemographics and illness characteristics (Table 1).

MR images were processed using the locally developed BRAINS (Brain Research: Analysis of Images, Networks, and Systems) software package. Detailed descriptions of image analysis methods for measuring lobar gray matter (GM) volumes have been provided elsewhere (Andreasen et al. 1993; Andreasen et al. 1994; Andreasen et al. 1996; Harris et al. 1999). In brief, the T1-weighted images were spatially normalized and re-sampled so that the anterior-posterior axis of the brain was realigned parallel to the anterior-posterior commissure line, and the interhemispheric fissure was aligned on the other two axes. The T2-weighted images were aligned to the spatially normalized T1-weighted image using an automated image registration program (Woods et al. 1992). These images were then subjected to a linear transformation into standardized stereotaxic Talairach atlas space (Talairach and Tournoux 1988) to generate automated measurements of frontal, temporal, parietal, and occipital lobes, cerebellum, and subcortical regions (Andreasen et al. 1996). To further classify tissue volumes into GM, white matter (WM) and cerebrospinal fluid (CSF), we employed a discriminant analysis method of tissue segmentation based on automated training class selection that utilized data from the T1, T2 and PD sequences (Harris et al. 1999). In this study, we examined total cerebral GM volumes, GM volumes sub-divided by Talairach atlas-based cerebral lobes (frontal, temporal, and parietal), and lateral ventricles.

Neurocognitive Assessment

Approximately 80% (162 HNV and 329 patients) of study participants who provided blood samples for DNA analysis also underwent neurocognitive assessment. They were administered a comprehensive cognitive battery by psychometrists who have been trained in standardized assessment and scoring procedures. Testing generally took approximately 4 hours to complete and, when necessary, occurred over several sessions.

Full scale IQ, verbal IQ and performance IQ scores were derived from the Wechsler Adult Intelligence Scale – Revised Edition. Based on a priori theoretical considerations (Green et al. 2004; Hill et al. 2004; Kareken et al. 1995; Milev et al. 2005; Saykin et al. 1994), 33 test variables from the standardized neuropsychological battery were further grouped into 5 cognitive domains: verbal memory, processing speed/attention, problem solving, language skills, and visuospatial skills. These groupings of cognitive domains had good internal consistency (Median Cronbach's alpha=0.80; Range=0.75 to 0.85) (Ho et al. 2003; Milev et al. 2005). The component neuropsychological test variables used to compute each cognitive domain score have been previously described (Milev et al. 2005). Prior to deriving cognitive domain scores, the raw test score from each of the neuropsychological test variable was converted to a z score (Mean=0, SD=1) based on norms established using a separate database of 419 healthy volunteers. Scores were reversed where necessary so that a larger negative score indicates poorer performance below the mean. Using these z scores, each domain score is the summed average of its component neuropsychological test variables.

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Statistical analyses

Genotype and allele frequencies of *NEUROG1* SNPs (rs2344484 and rs8192558) in patients and HNV were compared using Chi-square tests. The strength of association for major allele on each SNP was further estimated using odds ratio. Because major allele for these two SNPs have been associated with schizophrenia (Fanous et al. 2007), analyses of genetic effects on MRI brain morphometry and on neurocognition compared major allele carriers versus homozygotes of the minor allele. In this paper, only rs2344484 genotype effects on brain morphometry and on neurocognition will be presented. rs8192558 analyses will not be shown since both SNPs are in high linkage disequilibrium (D'=0.90; r^2=0.46). Furthermore, the relatively small number of rs8192558 T-homozygotes (N=13 HNV and 17 patients) yielded low statistical power ($\beta \leq 0.12$) even though rs8192558 genotype effects on brain morphometry and on neurocognition were similar to those of rs2344484 genotype effects. The former set of analyses is available upon request.

The effects of *NEUROG1* rs2344484 genotype on total cerebral GM, lobar GM and lateral ventricular volumes were analyzed using ANCOVAs. In each general linear model, the respective MRI volume was the dependent measure and genotype the independent variable. Intracranial volume, age, gender, imaging protocol (dummy binary variable) and diagnostic grouping were entered as covariates. A genotype-by-diagnostic group interaction term was also included in each general linear model to assess whether genotype effects on brain volumes differed across patients and HNV.

Analyses of the relationships between *NEUROG1* rs2344484 grouping and neurocognition were also performed using ANCOVAs. The dependent measure in each ANCOVA was WAIS-R measures of IQ and cognitive domain scores. Genotype grouping was the independent measure. Age, gender and diagnostic grouping were entered as covariates; together with a genotype-by-diagnostic group interaction term so as to detect the differential effects alleles might have on neurocognition across diagnostic groups.

Addition of antipsychotic treatment variables (i.e. lifetime CPZ-equivalent exposure to all antipsychotics, lifetime CPZ-equivalent atypical antipsychotics exposure or CPZ-equivalent typical antipsychotics exposure) into statistical models did not change ANCOVA results for MRI brain volumes or cognition. Since there were no significant main effects of antipsychotic treatment or genotype-antipsychotic treatment interaction effects on brain volumes or on neurocognition, antipsychotic treatment variables were excluded as covariates in the general linear models.

Lastly, two-marker *NEUROG1* haplotype association analyses with schizophrenia, MRI brain volumes and neurocognition were also performed using expectation-maximization algorithms (results not shown but available upon request). Haplotype associations were generally weaker but consistent with the SNP genotype findings reported below.

Results

rs2344484 and rs8192558 genotype and allele frequency distributions for the sample are summarized in Table 2. Genotype frequency distributions on both SNPs differed significantly between patients and HNV ($X^2 \geq 11.5$, $p \leq 0.003$). The major alleles of rs2344484 and rs8192558 (C and G respectively) were significantly more prevalent among schizophrenia patients than in HNV (Table 2; $X^2 \geq 9.8$, $p \leq 0.0018$; Odds ratios≥1.51).

To assess potential spurious association that may arise secondary to ethnic stratification, comparison of *NEUROG1* genotype and allele frequency distributions was repeated using only subjects of Caucasian ancestry. Restricting to only Caucasian subjects (354 patients and 210

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HNV), rs2344484-C-allele and rs8192558-G-allele remained significantly associated with schizophrenia (data not shown but available upon request). Similarly, when patients with schizoaffective disorder (N=29) were excluded from the patient sample, the associations between *NEUROG1* SNPs and patients were again unchanged. Furthermore, there were no significant associations between gender and *NEUROG1* genotype for the entire sample or within each comparison groups ($\chi^2 \leq 2.85$, $p \geq 0.24$).

NEUROG1 Effects on MRI Brain Volumes

There were significant rs2344484 genotype main effects on total cerebral GM and temporal GM volumes (Table 3; $F \geq 3.92$, df=1,491, $p \leq .05$). C-allele carrier patients and HNV had smaller total cerebral GM and temporal GM volumes than their respective T-homozygous counterparts. Genotype main effects on lateral ventricles approached but did not achieve statistical significance (F=2.98, df=1,491, p=.08). There were no significant genotype main effects on frontal or parietal GM volumes. There were no significant genotype-by-group interactions on any of the MRI brain volume measures ($F \leq 1.91$, df=1,491, $p \geq .17$).

NEUROG1 Effects on Cognitive Abilities

Although there were no significant rs2344484 genotype main effects on any of the WAIS-R IQ measures (Table 3; $F \leq 0.90$, df=1,490, $p \geq .34$), genotype-by-group interaction effects were significant for Verbal IQ and Full Scale IQ ($F \geq 3.69$, df=1,490, $p \leq .05$). This suggests that the relationships between rs2344484 genotype and general cognitive abilities may be different in patients compared to those in HNV. Among patients, there were statistically significant main effects of genotype on Verbal IQ and Full Scale IQ ($F \geq 4.57$, df=1,328, $p \leq .05$) but not on Performance IQ (F=2.39, df=1,328, p=.12). C-allele carrier patients had poorer Verbal IQ and poorer Full Scale IQ than T-homozygous patients. No significant genotype main effects on Verbal, Performance or Full Scale IQ were observed in HNV ($F \leq 0.33$, df=1,161, $p \geq .57$).

To further assess whether the effects of *NEUROG1* in schizophrenia were on specific aspects of cognition versus affecting generalized cognitive abilities, we explored the relationships between rs2344484 genotype and cognitive domain scores using ANCOVA (Table 4). When age and gender but not Full Scale IQ were entered as covariates, there were significant main effects of rs2344484 genotype on Verbal Memory, Language and Visuospatial Abilities cognitive domain scores (Table 4; $F \geq 3.83$, df=1,328, $p \leq .05$). C-allele carrier patients had poorer Verbal Memory, Language and Visuospatial Abilities performance than T-homozygotes. C-allele carrier patients also had lower Problem Solving cognitive domain scores than T-homozygotes; this approached but did not achieve statistical significance (F=2.79, df=1,328, p=.09). When Full Scale IQ was entered as an additional covariate in the general linear models, main effects of genotype on cognitive domain scores were no longer statistically significant ($F \leq 1.29$, df=1,328, $p \geq .26$).

Discussion

In this study, we replicated previous association between *NEUROG1* and schizophrenia (Fanous et al. 2007) providing further support for *NEUROG1* as a schizophrenia susceptibility gene. Our study extends current knowledge regarding *NEUROG1*'s role in influencing human brain volumes and in mediating phenotypic features of schizophrenia. We found rs2344484-C-allele conferred total cerebral and temporal lobe GM volume deficits in HNV as well as in schizophrenia patients. Additionally, rs2344484-C-allele was associated with poorer general cognitive abilities among schizophrenia patients by affecting several cognitive domains, including verbal memory, language and visuospatial abilities. These genotype effects on neurocognition appear to be specific to schizophrenia patients as these were not observed among HNV. Thus, rs2344484-C-allele may affect *NEUROG1*'s role in transcription

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regulation such that brain morphology and cognitive abilities are altered resulting in increased susceptibility to develop schizophrenia.

Although major alleles on both SNPs were significantly associated with schizophrenia, genotype effects on brain volumes and on neurocognition were found only with rs2344484 but not with rs8192558. This lack of significant associations between rs8192558 and phenotypic features of schizophrenia may, in part, be related to low statistical power as there were few T-homozygous subjects in our study sample. But, with both SNPs being in linkage disequilibrium, the rs2344484 genotype effects on temporal GM volume deficits and on generalized cognitive dysfunction could still theoretically be attributable to rs8192558. Similarly, we cannot rule out the possibility that these rs2344484-phenotype associations may be due to linkage dysequilibrium between rs2344484 and other nearby SNPs, or with other nearby genes besides *NEUROG1*. Nevertheless, even though additional studies will be needed to map out the effects of rs8192558 and rs2344484 on *NEUROG1* functions, these two SNPs may lie within cis-regulatory elements acting as promoters and/or enhancers of *NEUROG1*. rs8192558 is located within the 5′-UTR of *NEUROG1* while rs2344484 is ~5kb 5′ from the end of the 5′-UTR. Variations within the 5′-UTR have been known to direct promoter activity and alter gene expression. In *NEUROG1*, its highly conserved 5′-UTR region has been shown to regulate gene expression during neurodevelopment in the mouse (Murray et al. 2000). Besides regulatory element(s) within the 5′-UTR, several other cis-regulatory sequences located many kilobases 5′ of the *NEUROG1* coding region are also known to enhance *NEUROG1* expression (Blader et al. 2003; Gowan et al. 2001; Nakada et al. 2004). Like *NEUROG1*, other bHLH transcription factor genes (e.g. *NEUROG2 (*a.k.a. *Ngn2), ATOH1 (*a.k.a. *Math1), ASCL1 (*a.k.a. *Mash1*) too possess multiple regulatory enhancer elements that reside in relatively distant regions 5′ of the respective genes (Helms et al. 2000; Simmons et al. 2001; Verma-Kurvari et al. 1998). Although speculative, it is therefore not inconceivable that rs2344484 may modulate enhancer(s) located 5′ of the *NEUROG1* coding region, and in turn, affect transcription regulatory functions of *NEUROG1*.

NEUROG1 encodes a basic helix-loop-helix (bHLH) transcription factor, which is expressed primarily in the dorsal ventricular zone and dorsal thalamus during neurodevelopment (Fode et al. 2000; Gradwohl et al. 1996; Ma et al. 1997; McCormick et al. 1996; Sommer et al. 1996). It has been implicated in neuronal differentiation of cortical progenitor cells, a crucial initial step during embryonic neurodevelopment. It induces neurogenesis by functioning as a transcriptional activator. *NEUROG1* forms dimers with other ubiquitous bHLH proteins (e.g. E12 or E47). Via their positively charged basic domains, these heterodimers then bind to DNA sequences containing the E box consensus motif, CANNTG (Gradwohl et al. 1996). E box binding is vital for bHLH proteins to activate tissue-specific gene expression that promotes neuronal differentiation (Cau et al. 1997). Potentially relevant to the etiopathogenesis of schizophrenia, *NEUROG1* transcription factor is essential for the specification of glutamatergic neurons in deeper layers of the neocortex as well as in repressing differentiation of subcortical GABAergic neurons (Bertrand et al. 2002; Schuurmans et al. 2004; Sun et al. 2001). *NEUROG1* functions in a partially redundant manner with *NEUROG2*, another closely related bHLH transcription factor. Its pivotal role in cell fate determination of glutamatergic and GABAergic neurons requires complex interactions with a host of other transcription factors and with cortical patterning genes, such as *PAX6, NEUROD6 (*a.k.a. *Math2), NEUROD1 (*a.k.a. *Neurod), NEUROD2 (*a.k.a. *Ndrf), SLC17A7 (*a.k.a. *Vglut1), SLC17A6 (*a.k.a. *Vglut2), ASCL1 (*a.k.a. *Mash1), GAD67 (*a.k.a. *Gad1)* (Fode et al. 2000; Schuurmans et al. 2004). Thus, given these functions of *NEUROG1* transcription factor, our findings of significant *NEUROG1* effects on smaller temporal GM volumes and generalized cognitive deficits are in keeping with prevailing neurodevelopmental (Murray and Lewis 1987; Weinberger 1987), glutamatergic (Goff and Coyle 2001; Olney and Farber 1995) and GABAergic (Lewis and Gonzalez-Burgos 2008) etiologic theories of schizophrenia.

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Mutations in transcription factors have been associated with a growing number of human diseases (Latchman 1996). The phenotypes in such diseases are often pleiotropic, which is consistent with the vital role transcription factors have in controlling the expression of many genes. Since ubiquitous transcription factors like bHLH act as master regulators of numerous genes, genetic variations in *NEUROG1* and other bHLH genes may lead to misexpression of other downstream transcription factors during critical developmental periods, and in turn mediate the heterogeneous phenotypic manifestations of schizophrenia. Thus, future studies need to investigate the effects other bHLH transcription factors may have on brain morphometry and neurocognition, especially those bHLH genes which have already been associated with schizophrenia, including *NPAS3, OLIG2 (*a.k.a. *Oligo2)* and *CLOCK* (Georgieva et al. 2006; Hermann et al. 2006; Kamnasaran et al. 2003; Pickard et al. 2005; Pieper et al. 2005; Takao et al. 2007).

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Table 1

Comparison of sociodemographics and illness characteristics among study participants across MR imaging protocols [a]

	MR5 (N=232)	MR6 (N=260)	X^2 (p)
Healthy volunteers	73	100	2.63 (.10)
Patients	159	160	

Healthy volunteers	MR5 (N=73)	MR6 (N=100)	T (df=171)/X^2 (p)
Age	28.8 (8.0)	28.2 (8.7)	0.42 (.68)
Gender (% males)	50.7	58.0	0.91 (.34)
Ethnicity (% Caucasians)	97.3	91.0	2.78 (.10)
Parental SES	2.7 (0.7)	2.8 (0.4)	1.84 (.07)

Patients	MR5 (N=159)	MR6 (N=160)	T (df=317)/X^2 (p)
Age	29.8 (10.3)	29.6 (9.6)	0.15 (.88)
Gender (% males)	71.7	72.5	0.03 (.87)
Ethnicity (% Caucasians)	91.8	90.0	0.32 (.57)
Parental SES	3.0 (0.8)	3.0 (0.8)	0.14 (.89)
Age of illness onset (years)	22.2 (6.7)	21.2 (6.9)	1.29 (.20)
Duration of illness (years)	7.6 (8.6)	8.5 (7.5)	1.02 (.31)
Daily antipsychotic dose [b]	293.7 (430.8)	278.0 (294.1)	0.38 (.70)
Ever needed clozapine (%)	8.2	12.5	1.61 (.20)

[a] MR5: scans obtained prior to calendar year 2000; MR6: scans obtained in 2000 or later

[b] Chlorpromazine milligram-equivalent

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Table 2

Comparison of *NEUROG1* genotype (N (%)) and allele frequencies (%) between healthy normal volunteers and schizophrenia probands

	Healthy Volunteers	Patients	X^2 (p)/Odds Ratio (95% CI)
N	226	392	
rs2344484			
CC	72 (31.8)	181 (46.2)	
CT	117 (51.8)	166 (42.3)	12.5 (.002)
TT	37 (16.4)	45 (11.5)	
C-allele			
Frequency	57.7	67.4	11.5 (.0007)
Relative Risk	0.77	1.17	1.51
(95% CI)	(0.67 – 0.90)	(1.06 – 1.28)	(1.19 – 1.92)
rs8192558			
GG	110 (48.7)	246 (62.8)	
GT	100 (44.2)	125 (31.9)	11.7 (.003)
TT	16 (7.1)	21 (5.3)	
G-allele			
Frequency	70.8	78.7	9.8 (.0018)
Relative Risk	0.77	1.18	1.52
(95% CI)	(0.66 – 0.90)	(1.06 – 1.32)	(1.17 – 1.99)

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Table 3

Comparison of MRI brain volumes (least square mean (SD) (cubic centimeters)) and WAIS-R IQ scores in healthy volunteers and schizophrenia patients across rs2344484 genotype groupings

	Healthy Volunteers		Patients		Genotype F (p)	Genotype by Group F (p)
MRI brain volumes [a]	CC/CT (N=145)	TT (N=28)	CC/CT (N=280)	TT (N=39)		
Cerebral GM	662.46 (41.59)	682.37 (26.10)	663.24 (37.80)	668.57 (35.79)	5.79 (.02)	1.91 (.17)
Frontal GM	250.40 (18.93)	251.72 (14.55)	246.58 (20.69)	248.63 (20.50)	0.38 (.54)	0.02 (.89)
Temporal GM	157.04 (10.28)	160.64 (6.45)	155.19 (8.61)	156.40 (7.92)	3.92 (.05)	0.95 (.33)
Parietal GM	137.98 (11.32)	132.38 (8.47)	127.56 (50.15)	125.63 (33.51)	0.43 (.51)	0.10 (.75)
Lateral ventricles	15.03 (5.94)	12.43 (5.22)	16.61 (9.10)	15.44 (7.96)	2.98 (.08)	0.43 (.51)
Cognitive abilities [b]	CC/CT (N=136)	TT (N=26)	CC/CT (N=290)	TT (N=39)		
Verbal IQ	109.5 (11.1)	107.9 (8.6)	89.3 (11.7)	94.1 (13.8)	0.90 (.34)	3.84 (.05)
Performance IQ	110.7 (11.5)	109.4 (10.0)	88.7 (13.9)	92.6 (13.3)	0.51 (.48)	2.10 (.15)
Full Scale IQ	111.2 (11.2)	109.5 (8.4)	88.0 (12.4)	92.7 (13.7)	0.82 (.37)	3.69 (.05)

[a] Covariates: intracranial volume, age, gender and diagnostic grouping (df=1,491)

[b] Covariates: age, gender and diagnostic grouping (df=1,490)

GM: gray matter; CC/CT: C-allele carriers; TT: T-homozygotes

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Table 4

Comparison of cognitive domain scores between rs2344484 genotype groupings among schizophrenia patients

Cognitive Domains	CC/CT (N=290)	TT (N=39)	Genotype [a] F (p)	
			Without FS IQ	With FS IQ
Verbal memory	−1.43 (0.93)	−1.04 (0.81)	5.61 (.02)	1.29 (.26)
Processing speed/Attention	−1.27 (0.98)	−1.07 (1.02)	1.36 (.22)	0.05 (.83)
Problem solving	−1.57 (1.03)	−1.27 (1.06)	2.79 (.09)	0.02 (.89)
Language	−1.40 (1.14)	−0.99 (1.16)	4.24 (.04)	0.48 (.49)
Visuospatial abilities	−1.17 (1.23)	−0.76 (0.98)	3.83 (.05)	0.41 (.52)

[a]Covariates: age, gender and with or without WAIS-R Full Scale IQ (df=1,328)

CC/CT: C-allele carriers; TT: T-homozygotes