first exon, which is the promoter region for type II and is far upstream from the exons of all other isoforms.[11,12] The functional allele contributing to the increased risk for schizophrenia has not been identified in NRG-1, nor is there evidence that any of the associated variations would impact gene expression or function. As two single SNPs associated with schizophrenia were located around the promoter region of NRG-1 and the first exon of GGF, these SNPs might regulate the expression levels of NRG-1 isoforms and/or isoform–isoform ratios. However, no obvious allele effects of these SNPs on NRG-1 expression patterns were observed in this small sample. The estimated relative risks of each of these markers alone were less than that of the seven-marker core haplotype.[11,12] Taken together, these two SNPs do not appear to be functional alleles, at least in terms of the regulation of NRG-1 expression in human DLPFC. However, the possible relative decrease in type II expression may be regulated by an as yet unidentified allele in linkage disequilibrium with the associated haplotype.

Our findings offer preliminary evidence that abnormal expression of NRG-1 isoforms in DLPFC may be related to the pathophysiology of schizophrenia, but the evidence is weak. The biologic implications of our results are unknown, but they are at least conceptually consistent with evidence that schizophrenia involves genetic abnormalities in developmental/plasticity-related processes.[51,52] Additional studies are needed to characterize NRG-1 expression in schizophrenia, including slide-based mRNA analyses, protein analyses, neuroleptics effects, diagnostic specificity, and further exploration of genotype based variation.

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References

1 Pulver AE, Lasseter VK, Kasch L, Wolyniec P, Nestadt G, Blouin JL et al. Schizophrenia: a genome scan targets chromosomes 3p and 8p as potential sites of susceptibility genes. Am J Med Genet 1995; 60: 252–260.
2 Kendler KS, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F et al. Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of high-density schizophrenia families. Am J Psychiatry 1996; 153: 1534–1540.
3 Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G et al. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet 1998; 20: 70–73.
4 Kaufmann CA, Suarez B, Malaspina D, Pepple J, Svrakic D, Markel PD et al. NIMH Genetics Initiative Millenium Schizophrenia Consortium: linkage analysis of African-American pedigrees. Am J Med Genet 1998; 81: 282–289.
5 Shaw SH, Kelly M, Smith AB, Shields G, Hopkins PJ, Loftus J et al. A genome-wide search for schizophrenia susceptibility genes. Am J Med Genet 1998; 81: 364–376.
6 Brzustowicz LM, Honer WG, Chow EW, Little D, Hogan J, Hodgkinson K et al. Linkage of familial schizophrenia to chromosome 13q32. Am J Hum Genet 1999; 65: 1096–1103.
7 Gurling HM, Kalsi G, Brynjolfson J, Sigmundsson T, Sherrington R, Mankoo BS et al. Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q322, 5q33.2, and 8p21–22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3–24 and 20q12.1–11.23. Am J Hum Genet 2001; 68: 661–673.
8 Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 2002; 7: 405–411.
9 DeLisi LE, Mesen A, Rodriguez C, Bertheau A, LaPrade B, Llach M et al. Genome-wide scan for linkage to schizophrenia in a Spanish-origin cohort from Costa Rica. Am J Med Genet 2002; 114: 497–508.
10 Straub RE, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C et al. Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. Mol Psychiatry 2002; 7: 542–559.
11 Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S et al. Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet 2002; 71: 877–892.
12 Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E et al. Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am J Hum Genet 2003; 72: 83–87.
13 Fischbach GD, Rosen KM. ARIA: a neuromuscular junction neuregulin. Annu Rev Neurosci 1997; 20: 429–458.
14 Murphy S, Krainock R, Tham M. Neuregulin signaling via erbB receptor assemblies in the nervous system. Mol Neurobiol 2002; 25: 67–77.
15 Gerlai R, Pisacane P, Erickson S. Heregulin, but not ErbB2 or ErbB3, heterozygous mutant mice exhibit hyperactivity in multiple behavioral tasks. Behav Brain Res 2000; 109: 219–227.
16 Buonanno A, Fischbach GD. Neuregulin and ErbB receptor signaling pathways in the nervous system. Curr Opin Neurobiol 2001; 11: 287–296.
17 Ozaki M, Sasner M, Yano R, Lu HS, Buonanno A. Neuregulin-beta induces expression of an NMDA-receptor subunit. Nature 1997; 390: 691–694.
18 Yang X, Kuo Y, Devay P, Yu C, Role L. A cysteine-rich isoform of neuregulin controls the level of expression of neuronal nicotinic receptor channels during synaptogenesis. Neuron 1998; 20: 255–270.
19 Rieff HI, Raetzman LT, Sapp DW, Yeh HH, Siegel RE, Corfas G. Neuregulin induces GABA(A) receptor subunit expression and neurite outgrowth in cerebellar granule cells. J Neurosci 1999; 19: 10757–10766.
20 Liu Y, Ford B, Mann MA, Fischbach GD. Neuregulins increase alpha7 nicotinic acetylcholine receptors and enhance excitatory synaptic transmission in GABAergic interneurons of the hippocampus. J Neurosci 2001; 21: 5660–5669.
21 Freedman R, Leonard S, Gault JM, Hopkins J, Cloninger CR, Kaufmann CA et al. Linkage disequilibrium for schizophrenia at the chromosome 15q13–14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). Am J Med Genet 2001; 105: 20–22.
22 Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M et al. Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry 2002; 59: 1085–1096.
23 Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK et al. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001; 50: 825–844.
24 Kleinman JE, Hyde TM, Herman MM. Methodological issues in the neuropathology of mental illness. In: Bloom FE, Kupfer DJ (eds). Psychopharmacology: The Fourth Generation of Progress. Raven Press, Ltd: New York, 1999, pp 859–864.

25 Torrey EF. *Surviving schizophrenia*. Harper & Row: New York, 1983.
26 Weickert CS, Hyde TM, Lipska BK, Hearman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Mol Psychiatry* 2003; **8**: 592–610.
27 Garratt AN, Britsch S, Birchmeier C. Neuregulin, a factor with many functions in the life of a schwann cell. *BioEssays* 2000; **22**: 987–996.
28 Cannella B, Pitt D, Marchionni M, Raine CS. Neuregulin and erbB receptor expression in normal and diseased human white matter. *J Neuroimmunol* 1999; **100**: 233–242.
29 Chaudhury AR, Gerecke KM, Wyss JM, Morgan DG, Gordon MN, Carroll SL. Neuregulin-1 and erbB4 immunoreactivity is associated with neuritic plaques in Alzheimer disease brain and in a transgenic model of Alzheimer disease. *J Neuropathol Exp Neurol* 2003; **62**: 42–54.
30 Tokita Y, Keino H, Matsui F, Aono S, Ishiguro H, Higashiyama S *et al*. Regulation of neuregulin expression in the injured rat brain and cultured astrocytes. *J Neurosci* 2001; **21**: 1257–1264.
31 Loeb JA, Hmadcha A, Fischbach GD, Land SJ, Zakarian VL. Neuregulin expression at neuromuscular synapses is modulated by synaptic activity and neurotrophic factors. *J Neurosci* 2002; **22**: 2206–2214.
32 Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 2001; **25**: 1–27.
33 Tsai G, Coyle JT. Glutamatergic mechanisms in schizophrenia. *Annu Rev Pharmacol Toxicol* 2002; **42**: 165–179.
34 Anton ES, Marchionni MA, Lee KF, Rakic P. Role of GGF/neuregulin signaling in interactions between migrating neurons and radial glia in the developing cerebral cortex. *Development* 1997; **124**: 3501–3510.
35 Schmid RS, McGrath B, Berechid BE, Boyles B, Marchionni M, Sestan N *et al*. Neuregulin 1-erbB2 signaling is required for the establishment of radial glia and their transformation into astrocytes in cerebral cortex. *Proc Natl Acad Sci USA* 2003; **100**: 4251–4256.
36 Weickert CS, Kleinman JE. The neuroanatomy and neurochemistry of schizophrenia. *Psychiatr Clin North Am* 1998; **21**: 57–75.
37 Lewis DA, Cruz DA, Melchitzky DS, Pierri JN. Lamina-specific deficits in parvalbumin-immunoreactive varicosities in the prefrontal cortex of subjects with schizophrenia: evidence for fewer projections from the thalamus. *Am J Psychiatry* 2001; **158**: 1411–1422.
38 Pierri JN, Volk CL, Auh S, Sampson A, Lewis DA. Decreased somal size of deep layer 3 pyramidal neurons in the prefrontal cortex of subjects with schizophrenia. *Arch Gen Psychiatry* 2001; **58**: 466–473.
39 Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry* 2001; **49**: 741–752.
40 Selemon LD, Mrzljak J, Kleinman JE, Herman MM, Goldman-Rakic PS. Regional specificity in the neuropathologic substrates of schizophrenia: a morphometric analysis of Broca's area 44 and area 9. *Arch Gen Psychiatry* 2003; **60**: 69–77.
41 Meyer D, Birchmeier C. Multiple essential functions of neuregulin in development. *Nature* 1995; **378**: 386–390.
42 Riethmacher D, Sonnenberg-Riethmacher E, Brinkmann V, Yamaai T, Lewin GR, Birchmeier C. Severe neuropathies in mice with targeted mutations in the ErbB3 receptor. *Nature* 1997; **389**: 725–730.
43 Canoll PD, Musacchio JM, Hardy R, Reynolds R, Marchionni MA, Salzer JL. GGF/neuregulin is a neuronal signal that promotes the proliferation and survival and inhibits the differentiation of oligodendrocyte progenitors. *Neuron* 1996; **17**: 229–243.
44 Vartanian T, Corfas G, Li Y, Fischbach GD, Stefansson K. A role for the acetylcholine receptor-inducing protein ARIA in oligodendrocyte development. *Proc Natl Acad Sci USA* 1994; **91**: 11626–11630.
45 Raabe TD, Clive DR, Wen D, DeVries GH. Neonatal oligodendrocytes contain and secrete neuregulins *in vitro*. *J Neurochem* 1997; **69**: 1859–1863.
46 Raabe TD, Francis A, DeVries GH. Neuregulins in glial cells. *Neurochem Res* 1998; **23**: 311–318.
47 Calaora V, Rogister B, Bismuth K, Murray K, Brandt H, Leprince P *et al*. Neuregulin signaling regulates neural precursor growth and the generation of oligodendrocytes *in vitro*. *J Neurosci* 2001; **21**: 4740–4751.
48 Hof PR, Haroutunian V, Copland C, Davis KL, Buxbaum JD. Molecular and cellular evidence for an oligodendrocyte abnormality in schizophrenia. *Neurochem Res* 2002; **27**: 1193–1200.
49 Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD *et al*. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA* 2001; **98**: 4746–4751.
50 Wolpowitz D, Mason TB, Dietrich P, Mendelsohn M, Talmage DA, Role LW. Cysteine-rich domain isoforms of the neuregulin-1 gene are required for maintenance of peripheral synapses. *Neuron* 2000; **25**: 79–91.
51 Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry* 1999; **45**: 395–402.
52 Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003; **361**: 417–419.