nature neuroscience

PERSPECTIVE

Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia

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Schizophrenia is a devastating psychiatric disease that affects 0.5–1% of the world's adult population. The hypothesis that this disease is a developmental disorder of the nervous system with late onset of its characteristic symptoms has been gaining acceptance in past years. However, the anatomical, cellular and molecular bases of schizophrenia remain unclear. Numerous studies point to alterations in different aspects of brain development as possible causes of schizophrenia, including defects in neuronal migration, neurotransmitter receptor expression and myelination. Recently, the gene that encodes neuregulin-1 (*NRG1*) has been identified as a potential susceptibility gene for schizophrenia, and defects in the expression of erbB3, one of the NRG1 receptors, have been shown to occur in the prefrontal cortex of schizophrenic patients, suggesting that NRG1-erbB signaling is involved in the pathogenesis of schizophrenia. These findings open new approaches to defining the molecular and cellular basis of schizophrenia in more mechanistic terms.

Schizophrenia is a severe psychiatric disorder, which typically produces life-long disability. Once considered to be a neurodegenerative disorder, schizophrenia is now most commonly viewed as a disorder of development (for review, see ref. 1). This view is supported by a lack of neurodegenerative processes during much of the course of the disease, and by the fact that affected individuals show cognitive and social impairment even before the first episode of the disease[2]. The prevailing hypotheses postulate either an early developmental defect that develops into schizophrenia when normal maturational events occur during adolescence or early adulthood, or defects in late developmental events such as myelination or sexual maturation. Concordance rates are 41–65% in monozygotic twins, compared to 0–28% in dizygotic twins, leading to heritability estimates as high as 85% (ref. 3). Although it is clear that there are strong genetic factors, there is also evidence that environmental factors contribute significantly to schizophrenia[3]. Numerous loci at different chromosomes have been linked to the disease, indicating that several genes underlie susceptibility to schizophrenia[4], but the identification of these genes has been very difficult. New techniques, including large-scale surveying of gene expression in brains of people with schizophrenia and genome-wide linkage analysis in isolated populations, have implicated the neuregulins and their receptors. While *NRG1* is not the only candidate gene that predisposes an individual to schizophrenia, the extensive knowledge of the biological roles of the NRG1-erbB pathway provides an opportunity to gain new insight into the molecular and cellular mechanisms of the disease.

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Published online: 25 May 2004; doi:10.1038/nn1258

Neuregulins and their receptors

The neuregulins constitute a family of proteins that signal through erbB2 (also known as HER2), erbB3 (HER3) and erbB4 (HER4) receptor tyrosine kinases, members of the EGF receptor family (for review, see ref. 5). Through alternative splicing, the *NRG1* gene produces numerous *NRG1* isoforms, all having an EGF-like domain that is sufficient for receptor binding and activation. Early studies demonstrated that NRG1 expression is highest in the brain[6]. Initially, NRG1 was shown to regulate the expression of acetylcholine receptors in skeletal muscle and induce the proliferation of Schwann cells[7,8]. Subsequently, NRG1 has been implicated in key neurodevelopmental processes in the central nervous system, including neuronal migration and specification[9–12], hormonal control of puberty[13], regulation of acetylcholine[14], $GABA_A$ and glutamate receptor expression[15–18] and oligodendrocyte development[19–25]. Interestingly, these developmental processes are thought to be involved, directly or indirectly, in schizophrenia[14,17,26–46].

Altered expression of a neuregulin receptor in schizophrenia

The first evidence that NRG1-erbB signaling is altered in schizophrenia came from comparisons of gene expression profiles in the prefrontal cortex of people with chronic schizophrenia and control patients, which revealed a significant reduction in the level of *erbB3* expression (schizophrenia, 58% of control)[32]. This decrease was confirmed by quantitative and differential-display RT-PCR analysis[37]. Because the lower level of *erbB3* expression was accompanied by reduced expression of oligodendrocyte-specific genes, these results could be interpreted in two ways: (i) alterations in erbB signaling lead to deficiencies in oligodendrocytes or (ii) alterations in *erbB3* expression are secondary to the defects in oligodendrocytes observed in schizophrenia.

Genetic evidence for neuregulin abnormalities in schizophrenia

The hypothesis that defects in NRG1-erbB signaling contribute directly to schizophrenia was strengthened by recent genetic studies linking the *NRG1* gene and the disease. A genome-wide scan, which

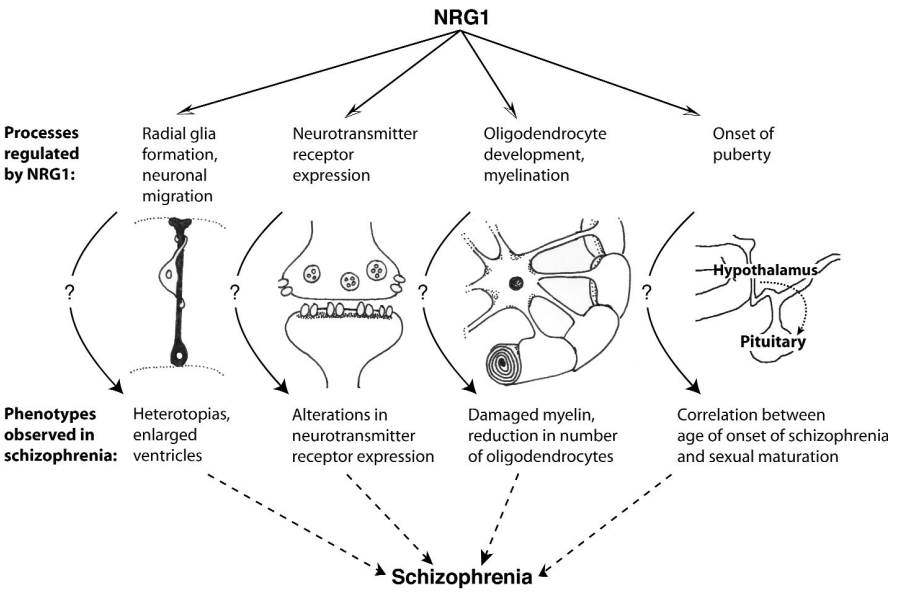

Figure 1 Potential relationships between NRG1 function and schizophrenia phenotypes. NRG1 has been implicated in cortical development by regulating radial glia morphology and neuronal migration, in synapse formation and function by regulating the expression of glutamate, GABA and ACh receptors, in myelination by regulating oligodendrocyte proliferation and differentiation, and in the control of the onset of puberty through the induction of LHRH release in the hypothalamus. All these developmental processes have been proposed to be altered or involved in schizophrenia. Thus, defects in NRG1 function can potentially contribute to the disease by altering one or more of these processes. The arrows with question marks indicate the current hypothetical nature of these possible links between NRG1 function and schizophrenia.

took advantage of the extensive pedigree information and relative genetic isolation of the Icelandic population, identified the *NRG1* gene as a susceptibility locus for schizophrenia[17]. This first study identified an "at-risk haplotype" that is present at a frequency of 15.4% in the affected individuals, as compared to 7.5% in controls (relative risk ratio, 2.1). In a follow-up study in Scottish patients, an estimated risk ratio of 1.8 was observed with the same haplotype[47]. A third and independent study replicated these findings in a large sample of unrelated Welsh patients[48]. The risk ratio in this population was estimated at 1.2, lower than that observed in the Icelandic and Scottish pedigrees[48]. However, meta-analysis[49] combining the three studies revealed a highly significant association between the at-risk haplotype and schizophrenia (odds ratio 1.64, confidence interval = 1.36–1.97, $P = 1.5 \times 10^{-7}$). Finally, studies of two Chinese populations[50,51], showed a similarly strong association between *NRG1* and schizophrenia. One of these studies[51], however, found a different set of markers contributing to the at-risk haplotype. It is worth noting that a more recent study of a Japanese population did not find an association between the *NRG1* gene and schizophrenia[52]. This highlights that fact that *NRG1* is not the only gene underlying susceptibility to schizophrenia and that *NRG1* is unlikely to be implicated in all cases of schizophrenia or in all populations; rather, this disease is very complex with multiple contributing genes. Nevertheless, the replication of the linkage between *NRG1* and schizophrenia in diverse populations provides very strong correlative genetic evidence for the association between the 5′ end of the *NRG1* gene and schizophrenia.

These studies show that the *NRG1* gene may predispose an individual to schizophrenia or that *NRG1* is in linkage disequilibrium with a schizophrenia locus. Since regions near *NRG1* on chromosome 8p are relatively gene-poor, with no identified genes at least 500 kb upstream or downstream of the *NRG1* gene, it is unlikely that these results are due to linkage to a close gene. Another important concern is that no mutations in the *NRG1* gene have been linked to the disease. Rather, the linkage has been associated with polymorphisms resulting in silent changes rather than in amino acid substitutions. Theoretically, these polymorphisms should not alter the bioactivity of the NRG1 protein, raising the possibility that they could affect *NRG1* gene expression. Interestingly, it was recently found that the ratios of three *NRG1* mRNA isoforms are altered in the dorsolateral prefrontal cortex of schizophrenic patients[53]. Further evidence for a role of NRG1 in the disease comes from mice lacking one copy of the *Nrg1* gene, which have behavioral abnormalities related to the features of schizophrenia. These include hyperactivity, which can be reduced by the anti-psychotic drug clozapine, and deficiencies in prepulse inhibition, a measure of sensory gating that is abnormal in schizophrenia[17]. Components of the NRG1 signaling pathway are robustly associated with schizophrenia, but how would altering this pathway increase susceptibility to the disease? Given that NRG1 and its receptors are pleiotropic (that is, they are involved in diverse processes of brain development), changing the expression levels or function of NRGs by altering the specific isoforms expressed could affect the development of the brain in multiple ways. In the next paragraphs we will review the information regarding the possible links between schizophrenia and several developmental processes, and the ways in which NRG1 may contribute to the disease through these processes.

Neuronal migration and cortical connectivity

The evidence for structural alterations in the brains of people with schizophrenia is subtle but convincing (for review, see ref. 54). For example, imaging studies showed enlargement of the lateral ventricles and reduction in some associative cortical areas in affected individuals compared to their healthy monozygotic twins. The cause of these alterations is unclear, but it has been proposed that the initial steps of brain development, such as neuronal migration and differentiation, could be altered. Numerous histological studies of postmortem tissues have demonstrated cytoarchitectural alterations in several areas of the brain implicated in schizophrenia. For example, interstitial neurons (remnants of the subplate) are abnormally distributed in white matter of the prefrontal and temporal cortices of people with schizophrenia[26,28].

NRG1-erbB signaling has been shown to participate in neuronal migration, primarily by promoting radial glia formation and differentiation. Rio and colleagues (1997) showed that NRG1 induces cerebellar astrocytes to adopt a radial glia phenotype *in vitro*, and that erbB signaling in radial glia is necessary for neuronal migration[9]. Anton and colleagues (1997) showed that NRG1-erbB signaling has similar roles in the cerebral cortex, inducing the elongation of cortical radial glia fibers and resulting in an acceleration of neuronal movement[10]. In these cells, blockade of NRG1 signaling resulted in

shorter radial glia and reduced neuronal motility. Thus, NRG1-erbB signaling seems to mediate critical interactions between radial glia and migrating neurons. This signaling pathway may also function in migration that does not depend on radial glia, as erbB4 receptors are expressed on migrating neurons in the rostral migratory stream and ganglionic eminences[11,12].

These lines of evidence suggest that defects in NRG1-erbB signaling during brain development could lead to alterations in neuronal migration. This would result in disruption of cortical connectivity and, subsequently, in behavioral defects. It is important to note that although several studies have shown defects in brain cytoarchitecture in schizophrenia, others failed to reproduce these findings[55]. It is likely that NRG1 is involved in the pathogenesis of the disease in only a subset of patients. Thus, it would be important to analyze the correlation between genotype and migration defects in human cases.

Neurotransmitter receptor expression and signaling

A hypothesis favored by numerous investigators is that alterations in the levels of expression or function of specific neurotransmitter receptors are involved in schizophrenia (for review, see refs. 56,57). Defects in neurotransmitter expression could lead to synaptic dysfunction and, ultimately, to abnormal information processing in the brain. The strongest candidates in this respect are the dopamine, serotonin, glutamate, GABA and acetylcholine receptors. Of particular interest here are the last three, whose expression is influenced by NRG1.

The link between glutamatergic NMDA receptors and schizophrenia developed, at least in part, from the observation that PCP and ketamine—NMDA receptor blockers—induce a schizophrenia-like state in humans. This led to the glutamate dysfunction model of schizophrenia (for review, see ref. 57). Supporting this, Akbarian and colleagues (1996) found an increase in the relative abundance of the *NR2D* subunit mRNAs and a 22–41% reduction in the levels of *NR2C* subunit mRNAs in layers 1–6 of prefrontal cortex of schizophrenics compared to controls[27]. Similarly, quantitative autoradiography of ^{3}H-MK-801 binding to NMDA receptors demonstrated a 17% increase in binding in layers 2 and 3 of the anterior cingulate cortex[29]. It has been proposed that the changes in the pattern of expression of NMDA receptors may compensate for impaired glutamatergic signaling[57]. Further support for the involvement of NMDA receptors in schizophrenia comes from studies of mice expressing the NR1 subunit at 5–10% of normal levels; these mice showed behaviors related to schizophrenia symptoms[30]. Therefore, although the specific receptor subunits that are involved, the loci of the changes and the physiological consequences of the alterations are not clear, it is evident that alterations in glutamate neurotransmission contribute to schizophrenia.

It has also been proposed that defective GABAergic inhibitory modulation may contribute to the symptoms of schizophrenia. Numerous studies point to complex alterations in GABAergic neurotransmission (for review, see ref. 56). High-resolution autoradiographic analysis of ligand binding showed that $GABA_A$ receptors are upregulated in the cingulate cortex, prefrontal cortex and hippocampus of people with schizophrenia[58]. Nucleic acid analysis of the prefrontal cortex showed increases in the levels of expression of the α1, α2 and α5 $GABA_A$ receptor subunits in affected individuals. Other studies have shown decreases in GABA receptor expression, including a decrease in the short isoform of the $GABA_A$ γ subunit in the dorsolateral prefrontal cortex[31,58]. Whereas some studies using microarray and RT PCR analysis report that genes involved in the synthesis and uptake of GABA are upregulated in people with schizophrenia[32,33], others, using *in situ* hybridization, report decreased expression of GAD67 and the GABA transporter GAT1 in layers 1–5 of the prefrontal cortex[34,35]. Thus, it appears that GABAergic neurotransmission is impaired in schizophrenia but that the alterations are heterogeneous. Individual components of the GABAergic system are differentially affected, such that changes in particular components are observed only in specific regions of the schizophrenic brain and, depending on the molecule and brain region, the change may be positive or negative.

The possible link between acetylcholine nicotinic receptors (AChRs) and schizophrenia is based on genetic and expression studies. The gene for the α7 subunit of the AChR is located in a region of chromosome 15 that has also been mapped as a possible schizophrenia locus. Binding studies have shown reductions in the number of α7-containing AChRs in the hippocampus[44], reticular formation[45] and cortex[46] of people with schizophrenia.

Recent studies have shown that *NRG1* regulates the expression of specific NMDA, $GABA_A$ and ACh receptor subunits. Ozaki and colleagues (1997) showed that NRG1 induced a large increase in the levels of mRNA for the NMDA NR2C subunit in cerebellar slices in culture[15]. Interestingly, this subunit is reduced in the prefrontal cortex of people with schizophrenia[27]. In addition, *NRG1*$^{+/-}$ mice show a significant decrease in the number of functional NMDA receptors in the prefrontal cortex, an area that has been clearly implicated in the disease[17]. The evidence for NRG1 influence on GABAergic neurotransmission is also strong. Rieff and colleagues (1999) showed that NRG1 increases expression of $GABA_A$ receptor β2 subunit mRNA and increases GABA-induced currents in cerebellar granule cells in culture[18]. More recently, NRG1 has been found to decrease the mRNA level of α subunits of $GABA_A$ receptors and the amplitude of miniature inhibitory postsynaptic currents (mIPSCs) in CA1 hippocampal neurons[16]. Thus, alterations in NRG1 expression or function may serve to increase or decrease receptor expression in a regional and receptor subunit–dependent manner. As for nicotinic AChRs, Liu and colleagues (2001) showed that NRG1 induces increases in the number of α-bungarotoxin binding sites and the peak amplitude of the ACh-induced current in a population of large hippocampal GABAergic neurons in culture[14]. Together, these results suggest that defects in NRG1 function may lead to altered excitatory and/or inhibitory neurotransmission, which could have an important impact on information processing, and thus contribute to schizophrenia.

Myelination

Myelination starts during embryonic development and is mostly complete by 2 years of age. However, significant myelination continues to occur until adolescence or early adulthood, a period corresponding to the peak time for onset of schizophrenia. This late myelination is most evident in the frontal and temporal lobes[59]. Recent histological and imaging studies support the idea that white matter changes exist in schizophrenia (for review, see ref. 60). For example, light and electron microscopy show damage in myelin sheath lamellae, a significant decrease in the nuclear area and the volume density of oligodendrocyte mitochondria, as well as signs of apoptosis and necrosis of oligodendrocytes in the prefrontal cortex of people with schizophrenia[36]. A recent stereologic analysis of oligodendrocytes in cortical layer 3 and gyral white matter of area 9 showed 30% fewer oligodendrocytes in people with schizophrenia compared to controls[38,39]. Furthermore, oligodendrocytes exhibited a less clustered arrangement and were reduced by 25% in cortical layer 6 of schizophrenic patients[39]. Magnetic resonance imaging and diffu-

sion tensor magnetic resonance (also known as DTI, an imaging technique to quantify anisotropic diffusion in white matter) have also revealed alterations in white matter development and integrity as well as reduction of myelin content in the temporal and frontal lobes[40–42].

In addition to structural alterations in white matter, microarray analysis has shown downregulation of oligodendrocyte-related mRNA species within the dorsolateral prefrontal cortex of affected compared to non-affected patients[32]. Genes involved in the compaction of myelin, axon-glia interactions and *erbB3* had reduced expression in affected individuals[32]. Other researchers have confirmed and extended this work, finding significant downregulation of genes expressed in precursor and myelinating oligodendrocytes in people affected by schizophrenia. This further supports a role for oligodendrocytes in schizophrenia[37,61].

The evidence for a role of NRG1-erbB signaling in oligodendrocyte development is compelling. Like many other glial cell types, oligodendrocytes express erbB receptors[19] and can, therefore, respond to NRG1. An early study showed that NRG1 is expressed in the subventricular zone at the time of oligodendrocyte differentiation and that NRG1 induces forebrain oligodendrocyte precursors to differentiate *in vitro*[24]. Not surprisingly, spinal cord explants from animals lacking NRG1 do not generate oligodendrocytes[20]. Other *in vitro* studies show that NRG1 induces the proliferation and survival of oligodendrocyte precursors[21,25]. NRG1 may have spatially and temporally distinct roles in oligodendrocyte development. For example, in neurosphere cultures derived from the striatum, inhibition of NRG1 signaling by addition of soluble erbB3 initially decreased proliferation, whereas after adhesion, soluble erbB3 induced differentiation[22]. In addition, neurospheres derived from the spinal cord of erbB3-deficient embryos were capable of producing myelinating oligodendrocytes in an *in vivo* differentiating paradigm in the retina[23]. This suggests that the timing and location of NRG1 signaling, as well as which erbB receptor is activated, are important in oligodendrocyte proliferation, differentiation and maturation.

These studies indicate that NRG1-erbB signaling is involved in oligodendrocyte development and CNS myelination. NRG1 may promote myelination by inducing oligodendrocyte differentiation and myelin formation or by amplifying or promoting the survival of oligodendrocyte precursor cells. Thus, defects in NRG1-erbB signaling could result in alterations of oligodendrocyte development and abnormal myelination.

Hormonal control of puberty

The age at which the first episode of schizophrenia occurs is typically associated with the post-pubertal period, but mild symptoms including deficits in social, motor and cognitive function may be observed at earlier stages[2]. These are periods of dramatic hormonal changes, suggesting that neuroendocrine maturational events may be involved in the pathogenesis of schizophrenia. However, this line of inquiry has been explored to a lesser extent than the ones described above[43]. A role for NRG1-erbB signaling in the neuroendocrine control of puberty and hormonal production and release has been demonstrated in transgenic mice expressing a dominant-negative form of erbB in hypothalamic astrocytes[13]. These mice have a specific delay in the onset of puberty and in reproductive development due to the reduced release of luteinizing hormone-releasing hormone (LHRH) by hypothalamic neurons, an event that initiates puberty. Thus, defects in NRG1 signaling could disrupt the control of hormonal levels during puberty, which would affect not only reproductive development but also neurodevelopmental processes that, when altered, may contribute to schizophrenia.

The cellular basis of schizophrenia

A large number of exquisitely timed steps are required for normal brain development and function; therefore, it is likely that schizophrenia could originate from alterations at more than one developmental stage. How could perturbations in the events described above lead to the disturbed brain function observed in schizophrenia? Altered neuronal migration could lead to misconnectivity of different brain regions such that external stimuli generate inappropriate cognitive responses (**Fig. 1**). The cytoarchitectural abnormalities observed to date are subtle and are unlikely to be the sole cause of schizophrenia. In addition, even though clinical onset of schizophrenia occurs after puberty, direct evidence linking puberty and disease is lacking. Therefore, changes in receptor or transmitter expression and/or reduced axon conductance caused by altered myelination may lead to abnormal neural transmission (**Fig. 1**). A reduction in growth factors, like NRG1, may also weaken synaptic strength and, ultimately, lead to synaptic destabilization and the symptoms of schizophrenia[62]. In fact, these processes are not necessarily independent.

The case for myelination defects in schizophrenia is growing. It is not yet known whether the changes observed in oligodendrocytes and myelination play a direct role in the disease or whether they're a consequence of the elusive, primary deficits. If altered myelination is a causal factor in schizophrenia, then diseases characterized by hypomyelination should have overlapping cognitive symptoms. Indeed, multiple sclerosis (MS), metachromatic leukodystrophy (MLD), Nasu-Hakola disease and bipolar disorder exhibit both disrupted myelination and cognitive changes (for review, see refs. 60,63). The differences in symptoms among these diseases may be accounted for by the location and timing of myelination deficits[60].

How could altered myelination lead to schizophrenia? Hypomyelination is thought to lead to reduced or irregular neural transmission, which could lead to altered perception and emotional states characteristic of schizophrenia. Alternatively, or in addition, changes in myelination could unmask a previously acquired genetic or environmental deficit in brain architecture or connectivity by reducing signal transduction. One hypothesis points to hypoconnectivity in the schizophrenic brain, which results from increased synapse elimination during adolescence[64]. Gray matter deficits observed in affected individuals are also found in their first-degree relatives without the concomitant decrease in white matter[65], suggesting that the reduction in neuropil observed in people with schizophrenia is compensated for by normal myelination in their siblings.

The pronounced alterations in neurotransmitter systems must also be taken into account in any discussion of schizophrenia. Evidence suggests that NRG1 signaling can directly influence glutamatergic, GABA and cholinergic systems in the brain. Alternatively, the brain may adapt to hypomyelination by altering synaptic release or expression of receptors and other pre- and postsynaptic molecules. In fact, specific receptors and related proteins at the postsynaptic density have been found to be upregulated in people with schizophrenia (see above and ref. 29).

Conclusions

The hypotheses regarding the cellular and molecular basis of schizophrenia are numerous, and in many cases contradictory. The evidence that defects in NRG1-erbB signaling contribute to this disease provides an opportunity to focus research efforts on specific aspects of schizophrenia. Most critical at this time will be (i) to determine which characteristics of the *NRG1* gene contribute to the disease and (ii) to further study variants of NRG1, as well as erbB receptors, for association with schizophrenia. It would also be worthwhile to study the

genetic interaction between these loci for schizophrenia susceptibility. We have outlined several means by which alterations in NRG1-erbB signaling may contribute to the development of schizophrenia. Defects in all of these developmental processes may be involved, but we particularly favor a role for alterations in NRG1-erbB signaling that lead to oligodendrocyte abnormalities that contribute to the disorder. The expression profiling studies implicated several oligodendrocyte-related genes in the disorder and suggested a cellular pathology in schizophrenia. Follow-up studies demonstrated reduced numbers of these cells in schizophrenia. Furthermore, the ultrastructural studies and imaging studies support a decisive abnormality in oligodendrocytes. Postulating a cellular abnormality in schizophrenia should lead to detailed analysis of oligondendrocytes at various stages of the disorder and may ultimately implicate factors promoting oligodendrocyte survival as protective in schizophrenia.

In summary, further examination of the NRG1-erbB pathway by genetic and molecular methods, and by the use of animal models, may lead to a deeper understanding of the roles of these molecules in normal development and in the pathogenesis of this devastating disease.

ACKNOWLEDGMENTS

Supported by the National Institute of Neurological Disorders and Stroke (R01 NS35884 to G.C.) and a Conte Center Grant (National Institute of Mental Health P50 MH066392 to J.D.B.). We thank J.N. Hirschhorn for help with meta-analysis of the genetic data and A. Rosenbaum for help with the illustration.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Published online at http://www.nature.com/natureneuroscience/

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