EIF2B and Oligodendrocyte Survival: Where Nature and Nurture Meet in Bipolar Disorder and Schizophrenia?

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Bipolar disorder and schizophrenia share common chromosomal susceptibility loci and many risk-promoting genes. Oligodendrocyte cell loss and hypomyelination are common to both diseases. A number of environmental risk factors including famine, viral infection, and prenatal or childhood stress may also predispose to schizophrenia or bipolar disorder. In cells, related stressors (starvation, viruses, cytokines, oxidative, and endoplasmic reticulum stress) activate a series of eIF2-alpha kinases, which arrest protein synthesis via the eventual inhibition, by phosphorylated eIF2-alpha, of the translation initiation factor eIF2B. Growth factors increase protein synthesis via eIF2B activation and counterbalance this system. The control of protein synthesis by eIF2-alpha kinases is also engaged by long-term potentiation (LTP) and repressed by long-term depression, mediated by N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors. Many genes reportedly associated with both schizophrenia and bipolar disorder code for proteins within or associated with this network. These include NMDA (GRIN1, GRIN2A, GRIN2B) and metabotropic (GRM3, GRM4) glutamate receptors, growth factors (BDNF, NRGI), and many of their downstream signaling components or accomplices (AKTI, DAO, DAOA, DISC1, DTNBP1, DPYSL2, IMPA2, NCAM1, NOS1, NOSIAP, PIK3C3, PIP5K2A, PDLIM5, RGS4, YWHAH). They also include multiple gene products related to the control of the stress-responsive eIF2-alpha kinases (IL1B, IL1RN, MTHFR, TNF, ND4, NDUFV2, XBP1). Oligodendrocytes are particularly sensitive to defects in the eIF2B complex, mutations in which are responsible for vanishing white matter disease. The convergence of natural and genetic risk factors on this area in bipolar disorder and schizophrenia may help to explain the apparent vulnerability of this cell type in these conditions. This convergence may also help to reconcile certain arguments related to the importance of nature and nurture in the etiology of these psychiatric disorders. Both may affect common stress-related signaling pathways that dictate oligodendrocyte viability and synaptic plasticity.

Key words: famine/virus/oxidative stress/endoplasmic reticulum stress/schizophrenia/bipolar disorder/oligodendrocyte/eIF2-alpha/eIF2B/translation initiation/protein synthesis/polygenic

Introduction

Famine, viral infection, heavy metals, and maternal stress during pregnancy or early development have all been suggested as risk factors in schizophrenia, as well as in bipolar disorder.1–3 Both conditions are characterized by oligodendrocyte cell loss and hypomyelination.4–6 It has been suggested, in the case of famine, that such stress may result in genotoxic effects, related to folate deficiency, resulting in germ line mutations in important developmental and other genes that might predispose to psychiatric disorders.7 However, the link between such types of stress and schizophrenia/bipolar disorder might also be related to the effects of such stressors on any, or several, of a series of extant polymorphic genes already known to be associated with these diseases (table 1) and to the signaling networks that they control. Certain genes associated with schizophrenia can be grouped into families related to pathology and form a clearly defined signaling cascade related to N-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) and plasticity. Defects in this pathway may underpin a particular endophenotype in schizophrenia, related to impaired glutamatergic function, memory disturbances, and synaptic dendritic poverty.8

As suggested below, a further set of genes, implicated either in bipolar disorder of schizophrenia, or both, are implicated in a well-characterized pathway that controls protein translation and synthesis. This pathway is activated by growth factors and NMDA receptors and inhibited by the environmental stress factors associated with bipolar disorder or schizophrenia. Genes associated with bipolar disorder and/or schizophrenia encode for many of its component proteins. This network converges on the eukaryotic translation initiation factor eIF2B. While one would not expect a process as universal as

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translation initiation to affect any particular cell type, mutations in any of 5 eIF2B subunit genes are responsible für vanishing white matter disease which provokes severe loss of oligodendrocytes and astrocytes in early life. Thus, the activation of this stress kinase pathway by diverse stressors implicated in the subsequent development of schizophrenia or bipolar disorder converges onto a system, laced with risk-promoting genes, that somehow dictates the fate of cells that die in these diseases.

As a working hypothesis, one might imagine that polymorphic susceptibility genes create a suboptimal functioning of a pathway designed to cope with stress. This pathway influences oligodendrocyte function and the diverse genetic variants render these cells more vulnerable to the effects of the predisposing stressful influences in these psychiatric disorders.

### Methods

Genes associated with schizophrenia or bipolar disorder were collected by literature survey (table 1). The survey aimed to include all genes for which positive association has been reported and is based on the conclusion of the original authors. It should be appreciated that conflicting

| Table 1. A Selection of Genes Reported to be Associated with Schizophrenia and/or Bipolar Disorder |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Bipolar Disorder**                            | **Schizophrenia**                               | **Bipolar Disorder and Schizophrenia**          |
| Growth factors, tyrosine kinase receptors, and phosphoinositide kinase/AKT signaling: including factors that stimulate the AKT pathway | BCR, DUSP6, FAT, GSK3B, GNAZ, PIK4CA, PLCG1, SYNJ1, TCF4, CALCA, CCL2, IL2RB, P2RX7 | ALK, CHI3L1, CNTF, EGF, ERBB4, IL10, IL10RA, NRG3, NTF3 |
| Glutamate-related, NMDA receptors and elements of the postsynaptic density | CIT | DIO1, DIO4, DISC1, DTPBP1, DPYS2L, GRD1, GRIN1, GRIN2A, GRIN2B, GRIN4, GRM3, GRM4, NOS1, NOSIAP, SYNGR1, YWHAH |
| Protein sorting and transport, glycosylation, endoplasmic reticulum stress, and protein degradation | ALG9, HIP1R, HSPA5, KIF13A, NAPG, SYBL1, WFS1 | ATXN1, HSPA1B, KIF2A, KPNA3, RANBP5, UFD1L |
| Oxidative stress, glutathione and quinone related | NOS3, G6PD | ABCB1, GCLM, GSTM1, HP, NQO2, PTGS2, S100B, SLC1A2, SOD2, TYR, TP53, UCP2, UCP4 |
| Oligodendrocyte related | AGA, CNP, GNPAT, MAG, MOG, NOTCH4, OLG2, PAX6, PLP1, QK1 | MLC1 |
| Protect oligodendrocytes | CNR1, GRM5, NRG3, ERBB4, IL2, IL10, S100B, SLC1A1, glutathione | DRD2, DRD3, IL1RN, NRG1 |
| Toxic to oligodendrocytes | Dopamine, GRIA1, GRIA4, GRIK3, GRIK4, LTA, PLA2G4, TP53 | IL1B, TNF |
| Circadian | ARNTL, RFX4 | CLOCK, PER3, TIMELESS |
| Dopaminergic | DRD1 | COMT, DRD2, DRD3, MAOA, SLC6A3, SLC1A1, TH |
| Serotonergic | TPH2 | HTR2A, HTR5A, HTR6, SLC6A4 |
| Miscellaneous | See Web site | See Web site |

Note: NMDA, N-methyl-D-aspartate; For a more extensive list, reasons for classification, and references, see http://www.polygenicpathways.co.uk.
Stress-Activated Pathways Inhibit Protein Synthesis and Activate ATF4

Viral infection, glucose or amino acid deprivation, heat shock, heavy metals, as well as oxidative and endoplasmic reticulum stress, activate a common signaling network, whose principal goals are to shut down protein synthesis and to activate defense mechanisms in an attempt to combat these stresses or, if unsuccessful, to activate apoptotic cascades (figure 1). Different types of stress activate specific eIF2-alpha kinases (commonly known as HRI [activated by heme deficiency, nitric oxide (NOS1B, NOS3B) and oxidative stress], GCN2 (activated by amino acid starvation), PKR (activated by growth factor deprivation, inflammatory cytokines [TNFβS, IL1BS], bacterial toxins, or viral DNA stress), and PERK (activated by endoplasmic reticulum stress). Each phosphorylates the eukaryotic translation initiation factor eIF2-alpha. Phosphorylated eIF2-alpha inhibits the activity of eukaryotic translation factor eIF2-beta (E1F2B1–E1F2B5), resulting in the arrest of the translation of RNA to protein and a subsequent decline in protein synthesis.8,10–13

This stress-activated pathway also influences the transcription factor, ATF4, which is activated by phosphorylated eIF2-alpha.14 ATF4 controls the transcription of PTGS2S and GCH1B as well as a series of stress-related defense or apoptosis-related pathways via its interactions with transcription factors nrf1 and nrf215,16(NF2E2L1, NFE2L2), HERPUD1,17 and chop/gadd153 (DDIT3).18 These downstream outputs of ATF4 either combat the effects of the stressors (eg, by activating the glutathione defense system or protein folding or degradation networks) or activate apoptotic death programmes if the stress is insurmountable (see http://www.polygenicpathways.co.uk/eIF2.htm for a more detailed summary).

NFE2L2 controls the expression of many enzymes related to the glutathione and quinone defense system. It also controls the transcription of several genes associated with bipolar disorder or schizophrenia including BDNFBS, CHGBS, GABRA1B, GABBR1S, GCLMS, GSTMI1S, G6PDβ, HMB5BS, NQO2S, and SYN2S. HERPUD1 controls endoplasmic reticulum calcium homeostasis and mitochondrial function19 and also plays a role in the endoplasmic reticulum–associated degradation pathway (ERAD) that detects and remove misfolded or degraded proteins.20 Such proteins are transported back to the cytosol for degradation by the ubiquitin–proteasomal system.21 DIT3 controls the expression of genes related to apoptosis, free radical control (SOD2S), cell proliferation, adhesion, and protein processing (proteasomal elements).22,23

This system is counterbalanced by the phosphoinositide kinase/AKT transcriptional pathway, which is activated by growth factors24 and by low-level NMDA receptor activation.25 eIF2B is phosphorylated and inhibited by glycogen synthase kinase 3 beta (GSK3BS) and the inhibition of GSK3B by activation of the growth factor/ AKTBS cascade removes this repression, allowing an increase in translation initiation and protein synthesis, an end point of growth factor effect.

This signaling network, as well as being related to environmental factors influencing the risk of psychiatric disease, is riddled with bipolar or schizophrenia-associated polymorphic genes whose products form components of these pathways, interact with, or are controlled by its component elements. This is illustrated in figure 1 and table 1.

Components of growth factor phosphoinositide-related signaling pathways include growth factors, cytokines, and tyrosine kinase receptors BDNFBS, CNTFS, EGFS, GFRA1S, IL10S, IL10RA5S, NTR3S, NRG1BS, NRG3S, and ERBB4S, many of which are involved in the control of oligodendrocyte growth and development, inter alia. All these stimulate the phosphoinositide kinase/AKT survival pathway, as do CH3L1S, NCAM1BS, and P2RX7S. The phosphoinositide kinase-signaling network is represented by PIK3CB, PIK4CB, PI5PK2AS, PLCG1S, SYN1S, AKT1BS, GSK3BS, IMPA2BS, and TCF4BS. The protein products of other susceptibility genes (BCRBS, DUSP6B, FATBS, GNAZBS, PPP2R2CBS, RGS4BS) bind to components of this pathway. Others bind to or are activated by phosphoinositol-phosphate derivatives of its components (HIP1RS, KCNQ2BS, WFS1BS) or are downstream targets of phosphorylation by GSK3BS (DYSPL2BS, KCNQ2BS, TIMELESSBS) or of the transcription factor TCF4BS (THBS) (see Web site for details).

Bipolar disorder has been associated with a number of genes involved in protein sorting (NAPGBS, HIP1RS, SYBL1BS), glycosylation (ALG9BS), or endoplasmic reticulum calcium homeostasis (WFS1BS). Defects in these processes lead to endoplasmic reticulum stress and activation of the unfolded protein response.27 HSPA5BS and XPB1BS play a key role in the coordination of these pathways.28,29
The endoplasmic reticulum stress pathway is also activated by oxidative stress \(^{10}\) or by homocysteine, \(^{30}\) and oxidative stress pathways also lead into the eIF2-alpha pathway via the heme responsive kinase HRI (EIF2AK1). Elevated serum homocysteine levels have been observed in both bipolar disorder and schizophrenia, \(^{31}\) and a crucial gene involved in folate and homocysteine metabolism has been described as a common risk factor (\(\text{MTHFRBS}\)). Oxidative stress has been implicated in both bipolar disorder \(^{32}\) and schizophrenia, \(^{8}\) and a number of related genes have been associated with either (\(\text{G6PD}^B, \text{NOS3}^B, \text{GCLM}^S, \text{GSTM}^S, \text{NQO2}^S, \text{PTGS2}^S, \)).
SI00B, SLC1A2, SOD2, TYR, TP53, UCP2, UCP4] or both conditions (COMT, NOS1, ND4, NDUFY2).

Circadian Genes and the Control of Protein Synthesis

The processes regulated by these pathways are under circadian control in the brain. During periods of wakefulness, genes related to plasticity acquisition and potentiation, including BDNF, are upregulated as are the glutamate-related genes GRIN2A, genes related to mitochondrial energy metabolism, and genes related to the stress response (CHOP, PERK, and molecular chaperones, including HSPA5). During sleep, genes involved in plasticity consolidation, membrane trafficking, cholesterol biosynthesis (a key process in myelination), protein translation, and GABAergic transmission are switched on. In global terms, protein translation and synthesis, the fulcrum of the growth factor and stress-activated pathways, appears to be switched off during wakefulness and turned on during sleep. The circadian genes associated with schizophrenia or bipolar disorder (PER3, TIMELESS, CLOCK, ARNTL) may thus also feed into this signaling network although the point of control remains to be determined.

NMDA Receptors, Glutathione, and oligodendrocytes

Both schizophrenia and bipolar disorder have also been associated with a number of genes related to glutamatergic and in particular NMDA receptor signaling. DAO, GRIN1, GRIN2A, GRIN2B, GRIN2D, PPP3CC, NOS1, NOS1AP. NMDA receptor activation phosphorlates and activates AKT in neurons, and this effect can be related to the survival-promoting effects of low-level NMDA receptor activation. While NMDA receptors exist on oligodendrocytes, their ability to activate this pathway or their potential cytoprotective effect have not been examined in this cell type. The purinergic receptor P2RX7 has been shown to activate the AKT pathway in astrocytes. It remains to be seen whether NMDA receptor activation affects protein translation in oligodendrocytes.

One of the key outputs of the ATF4 cascade is the control of glutathione-related defense mechanisms. Oligodendrocytes are particularly sensitive to the toxic effects of glutathione depletion, and the control of glutathione-related processes by this network may provide an additional means of dictating oligodendrocyte vulnerability in response to these types of stress. A number of schizophrenia susceptibility genes are related to the glutathione/quinone defense system (COMT, GCLM, GSTM1, NQO2, SLC1A2), while G6PD is responsible for the regeneration of reduced glutathione following its oxidation. As NMDA receptor activation increases the release of the reduced form of glutathione, the proposed hypofunction of this glutamatergic signaling network in adulthood might also influence the ability of oligodendrocytes to cope with these types of stress. A number of genes associated with schizophrenia or bipolar disorder (AGA, CNBP, MAG, MLC1, MOG, NOTCH4, NRG1, OLIG2, PAX6, PLP1, QKI) are specifically concerned with oligodendrocyte function while others dictate oligodendrocyte viability in some way (see table 1). These factors may provide additional means of influencing oligodendrocyte function.

DISC1

DISC1, which is localized in both neurons and white matter, appears to occupy a privileged position as a transduction hub within this network via its interaction with ATF4 and ATF5. Other binding partners of DISC1 include the phosphatase TENC1, a negative regulator of PI3K/AKT signaling and an inhibitor of cell survival and proliferation. DISC1 also binds to the citron kinase CIT, which is also associated with the NMDA receptor subunit GRIN1 as well as to a number of other glutamate receptor scaffold proteins (AKAP9, ACTN2, GRIPAP1, HAPIP, SPTAN1) that are associated with GRIN1, GRIN2A, or GRIN2B. DISC1 also binds to N-acetylglicosaminyltransferase III (GlcNAc-TIII) an enzyme in the same glycosylation pathway as ALGy (see Kegg pathway: http://www.kegg.com/dbget-bin/show_pathway?hsa00510+79796). DISC1 has also been shown to bind to the eukaryotic translation initiation factor 3 (EIF3S3). Translation initiation factor 3 (EIF3) is a multisubunit complex containing at least 12 subunits, including EIF3S3. It binds to the 40S ribosomal subunit, promotes the binding of methionyl-tRNAi and mRNA, and interacts with several other initiation factors to form the 40S initiation complex. The overexpression of DISC1 results in the formation of cytoplasmic stress granules. These stress granules are observed in response to the diverse cellular stresses leading to eIF2-alpha phosphorylation. DISC1 also binds to the protein products of several other genes implicated in schizophrenia or bipolar disorder including DYSPLS, FEZ1, NDE1, MLC1, and PDE4B (see Web site) and would thus appear to be an extremely important hub gene interacting with a variety of networks implicated in psychiatric disorders.

Environmental Stressors and Oligodendrocytes

The convergence of these signaling networks on a translation initiation factor (eIF2B) that, for unknown reasons, plays an important role in oligodendrocyte viability, only indirectly supports a role for this network in dictating the fate of these cells in bipolar disorder and schizophrenia. Other evidence suggests that the type of stressors associated with these diseases appear to target this cell type. Hypomyelination, in vivo, can be induced by prolonged postnatal starvation, the measles rubella
All cell types are sensitive to oxidative stress, but oligodendrocyte progenitors and developing oligodendrocytes in premature infants appear to be particularly sensitive to this type of stressor. Developing oligodendrocytes are also particularly sensitive to glutathione depletion, a situation observed in the frontal cortex in schizophrenia. Thus, a number of environmental stressors that may predispose to psychiatric disorders do appear to exert toxic effects on this cell population.

In vanishing white matter disease, environmental stressors (fright, fever, or minor head trauma) also markedly affect the progression of the disease, resulting in rapid neurological deterioration, suggesting that when eIF2B activity is compromised, there may be maladaptive responses to stress. Indeed, defects in eIF2B in vanishing white matter disease result in an increased stress response (ATF4 induction) in fibroblasts in response to endoplasmic reticulum stress. The increase in eIF2-alpha phosphorylation produced by heat shock is also decreased in lymphocyte cell lines isolated from these patients, and the unfolded protein response (PERK, CHOP, ATF4) is activated in both astrocytes and oligodendrocytes in postmortem brain tissue. These observations suggest that eIF2B malfunction must somehow control elements of the eIF2-alpha–signaling network, as well as protein translation, although how this is achieved remains to be determined.

Risk Factors in Adulthood

In both bipolar disorder and schizophrenia, the environmental stressors associated with disease occur early in life, many years before the development of the disease in adulthood. The age-at-onset for psychosis in schizophrenia correlates, in men and women, with the onset of puberty and in women with the menopause suggesting that sex-steroidal hormonal influences may also be involved in the later etiology of the disease. The progression of bipolar disorder has also been related to postpartum and menopausal events. Hormonal influences, particularly the hypothalamic-pituitary-adrenal stress axis also exert an influence on the development of bipolar disorder in adulthood. Many of these hormonal influences also affect oligodendrocyte function. For example, testosterone amplifies, while 17-beta oestradiol attenuates cytotoxic-induced oligodendrocyte cell death in vitro. Progesterone also promotes myelination in the peripheral and central nervous system. In adult rats, the prolonged administration of corticosterone has been shown to inhibit the proliferation of oligodendrocyte progenitors. Adrenaline, noradrenaline, and dopamine all exert toxic effects on oligodendrocytes, and these effects are accompanied by a reduction in glutathione levels and prevented by the hydrogen peroxide metabolizing enzyme, catalase, or by the glutathione precursor N-acetylcysteine. In adults, Interferon therapy has been associated with bipolar symptoms and psychiatric disturbances. Interferon alpha and beta can promote remyelination acutely but can exert toxic effects on oligodendrocytes in murine models of multiple sclerosis, while interferon gamma, and IL1B can all exert toxic effects on this cell type. Each of these activates the eIF2-alpha kinase (EIF2AK2).

Thus, hormonal influences, stressors in adulthood, or other compromised signaling networks may also target oligodendrocyte viability in some way, as might further bouts of infection resulting in the production of cytotoxic cytokines (TNF, IL1B). These effects may be particularly deleterious if these cells have been somehow weakened by earlier events. Hormones and cytokines may well affect many other processes implicated in schizophrenia and bipolar disorder, but their ability to modify oligodendrocyte function represents a common area of overlap that merits further consideration.

Protein Synthesis and Synaptic Plasticity

Increased protein synthesis is necessary for the plastic changes associated with LTP, mediated by NMDA receptors (GRIN2A, GRIN2B, GRIN2D). The eIF2-alpha kinase pathway is also involved in LTP, and a number of members of the translation initiation complex as well as translation elongation factors are localized within the postsynaptic density, suggesting that the apparatus necessary for dendritic protein synthesis is locally available. LTP decreases eIF2-alpha phosphorylation, allowing this increase in protein synthesis. Conversely, long-term depression, mediated by metabotropic glutamate receptors (GRM3, GRM5), increases eIF2-alpha phosphorylation. eIF2-alpha phosphorylation activates ATF4, a repressor of LTP. Hippocampal LTP is also markedly attenuated by knockout of the eIF2-alpha kinase GCP2 (EIF2AK4). Many of the genes implicated in schizophrenia, including NMDA receptors and growth factors, can be linked to a signaling cascade implicated in the phenomenon of LTP. Thus, this protein translation signaling network may serve a dual function in regulating 2 aspects of schizophrenia pathology, synaptic plasticity, and oligodendrocyte viability.

Evidence for Disruption of These Pathways in Schizophrenia and Bipolar Disorder

The Stanley Medical Research Institute has published an online database containing the results of a number of microarray studies of bipolar disorder, schizophrenia, and depression. Contributors to these studies included the groups of C. A. Altar, S. Bahn, H. Chen, S. E.
Dobrin, A. Fienberg, T. Kato, P. Sklar, M. Vawter, L. T. Young, and M. Elashoff whose work is collectively referenced here and within the database (http://216.55.162.172/index.html).

Gene families from these data sets were classified, by this group, in relation to Gene Ontology biological processes and function and Kegg pathways. These data are summarized in table 2. While the overall profile differs for schizophrenia and bipolar disorder, a large proportion of the gene families commonly dysregulated in schizophrenia and bipolar disorder relate to processes concerned with cell growth, protein synthesis, transport, and degradation. Expression changes for genes involved in protein biosynthesis and phosphoinositide signaling were also heavily represented in a microarray study of biopsied olfactory neuroepithelium isolated from bipolar disorder patients. Many of these processes, including protein transport and degradation, heat-shock protein and chaperone activity, ubiquitinylation and proteasomal activity, and glutathione metabolism relate specifically to the various downstream transcription factor outputs of ATF4. For example, HERPUD1 is involved in protein processing and degradation, DDIT3 is involved in the control of protein processing, cell growth, apoptosis, and glutathione homeostasis, while NFE2L1 and NFE2L2 regulate genes coding for glutathione biosynthesis, as well as the expression of a number of genes implicated in schizophrenia or bipolar disorder. XBP1 is concerned with the regulation of heat-shock proteins and chaperones and with protein degradation mediated by the ERAD pathway (see Web site and above). Although each disease specifically affects other processes, a common area of overlap, in these gene expression studies, relates specifically to the outputs of this growth factor/stress-activated kinase pathway.

The reactivity of this network also appears to be affected in peripheral cells. Leukocytes respond to bacteria or viruses by increasing the production of interferons (an effect mediated by the eIF2-alpha kinase, PKR). This response is attenuated in leukocytes isolated from schizophrenic patients.

Conclusion and Speculation

Identical twin studies have shown that the concordance rates in schizophrenia (48%) or bipolar disorder (40–70%) are less than 100%. Monozygotic twins share the same genome and there may thus be no universal causative gene for these disorders. Although many genes have been associated with these diseases, there is extreme disparity between the individual gene association results. While there is general agreement that DISC1 is a very important risk factor, carriers of the DISC1 translocation can also be asymptomatic. Nevertheless, genes play an important role in modifying the risk of developing these diseases, even though each susceptibility variant may also exist in the normal population. Similarly, while famine, viral infection, or other stressors in early life have been reported to increase the risk of bipolar disorder and schizophrenia, clearly, not all individuals subject to these stresses develop these conditions. Thus, one could argue that neither genes, nor the environment, per se, cause psychiatric diseases.

However, the environmental risk factors activate a key stress-related pathway, composed of, regulated by, or regulating many of these susceptibility genes. Microarray experiments also suggest that the outputs of this network are disrupted in both these conditions. This pathway is important in dictating the vulnerability of oligodendrocytes and also plays a key role in long-term synaptic plasticity. Oligodendrocyte loss, hypomyelination, and altered synaptic plasticity are all components of the pathology of bipolar disorder and schizophrenia. In other polygenic diseases (e.g., bladder cancer), the degree of risk afforded by susceptibility genes is magnified by the presence of other polymorphic genes in the same signaling network. Similar integrative effects are likely to operate in schizophrenia and bipolar disorder (see Carter for discussion). Such effects might also be envisaged for gene-environment interactions, particularly when the signaling networks affected by the environment and the susceptibility genes so clearly overlap. Indeed, the association of APOE with schizophrenia in the Chinese population is influenced by dates of birth corresponding to periods of famine. In bipolar disorder, additive risk-promoting effects have also been observed between the COMT polymorphism and herpes simplex viral infection. The pathological effect of any particular gene variant may thus depend not only on the presence of other polymorphic genes in a particular pathway but also on the presence of environmental influences that may also compromise the same signaling network.

Because the environmental risk factors activate a pathway largely composed of susceptibility genes, there are compelling reasons to suggest that the environmental factors may in fact be causative but only in individuals where this stress-signaling network has been compromised by polymorphic susceptibility gene variants. This has important implications because certain of these causes are preventable or avoidable. For example, vaccination against rubella or influenza prior to pregnancy might be a simple but effective means of reducing the incidence of these psychiatric conditions, a possibility that does not seem to have been addressed in the medical literature. Oligodendrocyte cell loss may also be preventable, both during development and in adulthood. Glutathione (or its precursor N-acetylcysteine) in particular has been shown to protect these cells from a variety of toxic insults. N-acetylcysteine also prevents the oligodendrocyte cell loss in rat pups whose mothers were treated with lipopolysaccharide during gestation. The glutathione defense system is a major output of the growth factor/stress...
kinase-signaling network, and a means of targeting this system may well have beneficial effects in both bipolar disorder and schizophrenia.

Susceptibility gene variants are present from the moment of conception, while the stressors associated with these diseases occur early in life. If these combine to compromise eIF2b function, then the suggested downstream consequences of this effect, oligodendrocyte malfunction and modified synaptic plasticity, might be considered as early prime events in the pathology of both bipolar disorder and schizophrenia. It is thus worth considering whether oligodendrocyte dysfunction in early life is a precipitating factor responsible for other features of these disorders.

In mice or rats, maternal immune activation with the viral mimic and cytokine releaser polyribosinic-polyribocytidilic acid (POLY-IC) produces behavioral changes in the adult offspring. These include increased behavioral sensitivity to the NMDA antagonist MK-801, hyperactivity, and cognitive disturbances. Dopamine turnover is increased in the striatum and the behavioral effects were sensitive to neuroleptics. Although viral infection, which is modeled by POLY-IC, does target oligodendrocytes (see above), their role was not examined in these experiments. Interestingly, mice with combined knockout of fibroblast growth factor receptor (FGFR2) and the oligodendrocyte-specific cyclic nucleotide phosphodiesterase (CNP1S) display pronounced hyperactivity that is blocked by neuroleptics or tyrosine hydroxylase inhibition. Thus, it would appear that modifications in oligodendrocyte function are able to affect dopaminergic activity, the keystone of psychosis. While the role of oligodendrocytes in myelination has been extensively studied, their potential role in synaptic plasticity or neurotransmitter function has been relatively overlooked, a subject that merits further investigation.

In the clinical context, psychosis is common in other demyelinating diseases, eg, metachromatic leukodystrophy. Psychiatric symptoms mimicking those of bipolar disorder and schizophrenia are also prevalent in multiple sclerosis patients. Perhaps, a reclassification of bipolar disorder and schizophrenia as mild leukodystrophies might be a useful conceptual framework for research.

Other genes (eg, those specific to either condition; see table 1 and Web site) signaling pathways and subpathologies are likely to be involved in distinguishing bipolar disorder and schizophrenia. However, the key role of the oligodendrocyte in both conditions merits closer attention, particularly in relation to future potential therapies and prevention. Nature and nurture both play a role in psychiatric disorders, although the weight of each has had its vigorous proponents and opponents. The signaling network described above suggests that both may impinge on a common signaling pathway, composed of psychiatric susceptibility genes (nature) and influenced by diverse environmental stressors (nurture).

Table 2. A summary of the Highest Ranked Gene Families Whose Expression Is Dysregulated in Microarray Studies of Bipolar Disorder and Schizophrenia

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<th>GO molecular function: top 10</th>
<th>Bipolar Disorder</th>
<th>Schizophrenia</th>
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<td>RNA binding, protein transporter*, ligase activity, GTP binding, MHC class-II receptor activity, chaperone activity*, translation initiation factor activity*, ATP-binding, ubiquitin-conjugating enzyme activity*, and single-stranded DNA binding</td>
<td>MHC class-II receptor activity, protein transporter*, voltage-gated ion channel, oxidoeductase, hyaluronic acid binding, heat-shock protein*, transporter activity, MAP kinase phosphatase, metal ion binding, and DAG/CPT activity</td>
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**Note:** ATP, adenosine triphosphate; CPT, carnitine palmitoyltransferase; DAG, diacylglycerol; GO, gene ontology; GTP, guanosine triphosphate; MAP, mitogen-activated protein; MHC, major histocompatibility cells; TCA, tricarboxylic acid. The full data set can be viewed at the Stanley Consortium online Genomics database https://216.55.162.172/index.html. Processes common to both conditions are in bold. Families involved in growth, AKT signaling, protein processing, transport, and degradation and oxidative stress are marked by an asterisk.
A convergence point of this system (eIF2B) appears to be specifically involved in determining oligodendrocyte viability, and further characterization of this network may help in our understanding of this particular sub-pathology of schizophrenia and bipolar disorder. Targeting this system may also lead to the development of radically different and effective treatment and prevention strategies.

References


