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Progress in defining the biological causes of schizophrenia

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Schizophrenia is a common mental illness resulting from a complex interplay of genetic and environmental risk factors. Establishing its primary molecular and cellular aetiopathologies has proved difficult. However, this is a vital step towards the rational development of useful disease biomarkers and new therapeutic strategies. The advent and large-scale application of genomic, transcriptomic, proteomic and metabolomic technologies are generating data sets required to achieve this goal. This discovery phase, typified by its objective and hypothesis-free approach, is described in the first part of the review. The accumulating biological information, when viewed as a whole, reveals a number of biological process and subcellular locations that contribute to schizophrenia causation. The data also show that each technique targets different aspects of central nervous system function in the disease state. In the second part of the review, key schizophrenia candidate genes are discussed more fully. Two higher-order processes – adult neurogenesis and inflammation – that appear to have pathological relevance are also described in detail. Finally, three areas where progress would have a large impact on schizophrenia biology are discussed: deducing the causes of schizophrenia in the individual, explaining the phenomenon of cross-disorder risk factors, and distinguishing causative disease factors from those that are reactive or compensatory.

> One may speculate about some far future in which individuals will routinely undergo 'genic analysis', as nowadays they are routinely vaccinated…Perhaps massive genic analysis of the population will eventually give us the information that will lead to working out the physical basis for mental disease.
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> Isaac Asimov (1962). *The Genetic Code*. The New American Library, Inc.

Schizophrenia is a chronic and severe mental illness defined by the presence of delusions and hallucinations (positive symptoms), apathy and social withdrawal (negative symptoms), and specific cognitive failures (Ref. 1). It is diagnosed through qualitative assessment of patient interview and case notes with reference to an agreed set of classification criteria. The absence of objective biological tests for schizophrenia (e.g. through blood sample analysis or physiological

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readout) is a hindrance to disease prediction, diagnosis, therapeutic assessment and scientific research. The intangibility of the diagnosis results from the difficulties in assessing the living brain in conjunction with the substantial heterogeneities in biological origin and clinical presentation of the disorder.

In this regard, a detailed description of the biology of schizophrenia would be invaluable. Traditionally, such a description has been based on three principal observations. First, there is the pharmacologically defined involvement of specific neurotransmitter receptor systems and their particular anatomical pathways in the brain. The action of amphetamine in inducing or worsening psychotic symptoms suggested that dopaminergic hyperactivity is an important component of illness. Further elucidation of the key dopaminergic tracts in the brain affected by receptor-blocking antipsychotic medication explained both the alleviation of positive symptoms and motor-control side effects. Hypofunction of the glutamatergic neurotransmitter system is also implicated through the action of neurotransmitter receptor antagonists, such as phencyclidine (PCP) and ketamine, together with expression studies that show reduced subunit expression in post-mortem brain samples from individuals diagnosed with schizophrenia (Ref. 2). Second, evidence from brain-imaging approaches has provided evidence for regional brain abnormalities in structure – implicating neurodevelopment – and function associated with illness. Some of these features correlate with genetic risk status, as recently reviewed (Ref. 3). Third, particular cellular pathologies have been described in brains from patients diagnosed with schizophrenia: for example, reduced oligodendrocyte number (Ref. 4) or altered neuronal cytoarchitecture (Ref. 5). Until recently, these 'high-level' observations, although highly informative, have not been matched by an understanding of the underlying genetic and molecular mechanisms.

Schizophrenia is partly genetic (Refs 6, 7, 8, 9) although its 'genetic architecture' (how many and what type of mutations contribute to illness in the individual and population) is still a subject of much debate (Ref. 10). The existence of families with a high density of affected individuals suggests that segregating unitary gene effects can strongly predispose to illness. However, not all diagnosed individuals show such inheritance patterns, indicating that common, small-effect variants in multiple genes that co-occur through random and transitory co-segregation are able to produce a form of the disorder phenotypically indistinguishable from the familial form. Evidence from epidemiology (Ref. 11) and the genomic studies described below suggests that certain genes are risk factors not only for schizophrenia, but also for bipolar disorder (Refs 12, 13) and major depression (Ref. 14), hinting at a degree of biological overlap.

In the eight years since the genetics of schizophrenia was last reviewed in this journal (Ref. 15), research in the field has been transformed in direction and ambition by the advent of 'whole-genome' technologies, revealing the common genetic variation and rare DNA copy number variants (CNVs) that contribute to risk of illness. In parallel, the use of structural and functional brain-imaging, biomarker discovery through transcriptomics and proteomics, and the generation of several mouse disease models are increasing our understanding of how primary biological deficits are translated into clinical outcome (Refs 16, 17, 18, 19, 20, 21). This review sets out the major discoveries from such studies: primarily those at the molecular and cellular end of brain functional hierarchy. Although a broad but shallow approach is inevitable, there is a clear intention to highlight findings spanning research strategies and to discuss those techniques that perhaps do not presently receive the attention that they merit. With this in mind, the review covers paths to discovery, notable gene candidates and emerging processes, and ends with a discussion of three issues facing the field of schizophrenia research. Key reviews have been signposted throughout to allow the reader to explore specific aspects in more detail.

The discovery process

Genome-wide association studies

The genetic information responsible for the development and regulation of the brain is the foundation of its functional operation. This position suggests that genetic studies are the most likely to reveal primary and causative factors predisposing to illness. Case–control association studies reveal the contribution of common genetic variation to risk of disease. The past five years have seen impressive progress

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following the move away from small, gene-specific studies towards the large genome-wide association studies (GWAS). These have been made possible by the sharing of DNA samples within consortia and the technological advances in the massively parallel detection of single-nucleotide polymorphisms (SNPs) that make up the greater part of common variation. The GWAS experimental design makes no subjective assumptions concerning gene candidacy or even genic contribution (the studies include SNPs in gene-poor regions of the genome). This feature – along with the cytogenetic approaches detailed below – will probably do most to benefit the biological understanding of schizophrenia because it has bypassed the subjective and cyclical knowledge that drove many earlier individual genetic and biological studies. Several individual studies and some combined meta-analyses (Refs 22, 23, 24, 25, 26, 27, 28, 29, 30) have been carried out for schizophrenia: the latter intended to boost signal-to-noise ratio resulting from locus and allelic heterogeneity. A current estimate places the genetic contribution of common polymorphic variation to risk of schizophrenia at ~34% (Ref. 25).

Identified genes have been subjected to specific replication studies as well as examination in related conditions such as bipolar disorder and major depression. The major confirmed finding is the association of schizophrenia with a broad swathe of markers on chromosome 6p22.1 (Refs 25, 26, 27). This locus houses the major histocompatibility complex (MHC) consisting, in part, of the human leukocyte antigen genes that mediate the body's monitoring of self and non-self in the context of infection. The potential role of the immune system in the aetiology of psychiatric disorders makes this an important finding and is discussed in more detail later. However, a note of caution must be attached to the finding. The MHC region is highly mutable, subject to strong natural selection and known to influence mammalian mate choice. These are all features known to perturb the Hardy–Weinberg equilibrium of allele frequencies in populations. Careful analysis will be required to ensure that the GWAS signals detected here are specifically attributable to influence on schizophrenia risk. Apart from the MHC genes, the associated region also contains a number of other genes, including *NOTCH4*, a previously identified candidate gene with a neurodevelopmental role (Ref. 31), and a histone gene cluster. We have recently shown that the histone cluster is coordinately regulated by the transcription factor SOX11, which is responsible for neuronal differentiation (Ref. 32), suggesting that chromatin modification might be an alternative biological explanation for the association.

In addition to the MHC region, GWAS studies have highlighted variants strongly linked with a risk of schizophrenia within the following individual genes: *ZNF804A, MYO18B/ADRBK2, AGAP1 (CENTG2), NTRK3, EML5, ERBB4, NRGN, TCF4, CCDC60, RBP1, PTPN21, CMYA5, PLAA, ACSM1, ANK3, SULT6B1, ASTN1, CNTNAP1* and *GABRR1*. Using an additional criterion of independent identification in at least two studies [including those also targeting bipolar disorder (Ref. 12)], the following genes might also be associated: *ASTN2, OPCML, PSD3, RYR3, TMCC2, GRID1, A2BP1, CACNA1C, CNTN5, CRYBB1, EML5, CSMD1, FAM69A, LRP8, PTPRG1, SLIT3, TMEM17* and *VGCNL1/NALCN*. As further GWAS studies and meta-analyses amass (including those from non-Northern European populations) and cross-diagnostic comparisons are made, this list will slowly evolve into a robust set of candidates. A range of statistical methodologies and gene categorisation resources are now being leveraged to translate GWAS data into associated gene functions in order to define key biological processes perturbed in schizophrenia (Ref. 33). One study of gene functions enriched in single schizophrenia GWAS identified glutamate metabolism, apoptosis and inflammation or immunity as major processes (Ref. 34). Another report found significant over-representation of cell adhesion molecules in two schizophrenia GWAS studies and moderate evidence in support of tight junction, cell cycle, glycan synthesis and vesicle transport pathways (Ref. 35).

The extraction of biological pathway information from GWAS data will always be tempered by the fact that common variant frequencies have been modulated by ancient founder effects, selection pressures and the migratory history of human populations. These geographical and pathological filters might limit the ability of GWAS to signpost the full range of genes and processes that underlie schizophrenia.

Copy number variation and other cytogenetic failings

Deviations from diploid copy number in the genome have long been recognised, particularly

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in the context of the duplications and deletions observed in cancer, but the full extent of CNVs in humans has only been appreciated relatively recently (Refs 36, 37, 38). In contrast to common SNPs, common CNVs do not seem to predispose to disease risk (Ref. 39). Therefore, the focus has been to identify rare CNVs enriched in, or specific to, schizophrenia (Refs 40, 41, 42). As a consequence, the chief issue has therefore been how to statistically prove a causative role to a given rare CNV in a numerically limited sample set.

Five properties of the CNVs discovered in schizophrenia are important: (1) CNVs appear mainly randomly throughout the genome. They can be sporadic (clearly observed in autism) or (perhaps subsequently) present as familial forms. Hence, compared with common SNPs, CNVs may define a broader gene contribution to illness given sufficient sample size. (2) Both deletions and duplications have been observed at specific loci in schizophrenia. This implies that copy number deviation, rather than direction of change, is the chief mediator of disease – a finding that holds for other disorders and testifies to the subtleties of evolved gene expression regulation (Ref. 43). (3) Several very large CNVs that simultaneously alter the dosage of multiple genes, including those found at 1q21.1, 2q12, 3q29, 7q36.3, 15q13.3, 16p11.2, 16p13.1, 17q12 and 22q11.2, are repeatedly and consistently over-represented in schizophrenia (Refs 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54). Among these, the 22q11.2 CNV represents a submicroscopic version of the previously described chromosome 22 deletion that underlies velo-cardio-facial syndrome (VCFS)/DiGeorge syndrome, which is the most common genetically defined risk factor for schizophrenia. It will be a considerable challenge to dissect these 'syndromic' CNVs and expose the relative contribution of each constituent gene to the final clinical diagnosis. (4) Certain CNVs (particularly larger ones) initially linked to schizophrenia also contribute to the risk of other diagnoses such as autism spectrum disorder, developmental delay, mental retardation and epilepsy. The most convincing explanation for this observation is that these CNVs perturb brain development: an effect that is compounded by other gene variants [as a 'second hit' (Ref. 55)] or by the environment to define the precise clinical endpoint. The earlier observation of increased frequency and heritability of schizophrenia in individuals diagnosed with mental retardation can also be explained by the same neurodevelopmental model (Ref. 56). (5) The degree to which CNVs contribute to the general risk of bipolar disorder is still uncertain (Refs 39, 57, 58), but appears less than for schizophrenia. However, CNVs are associated with early-onset bipolar disorder, supporting the notion that CNVs are strongly linked to the kind of neurodevelopmental dysfunction that might be a distinguishing feature of schizophrenia.

Small CNVs present an opportunity to identify individual candidate genes. The following is a nonexhaustive list of genes occurring in at least two schizophrenia CNV studies: *A2BP1*, *ACP6*, *BCL9*, *CHD1L*, *CHRNA7*, *CLDN5*, *CNTNAP2*, *DLG2*, *FHIT*, *FLJ39739*, *FMO5*, *GJA5*, *GJA8*, *GNB1L*, *KLF13*, *NRXN1*, *PARK2*, *PRKAB2*, *TRPM1* and *VIPR2*. Additionally, the following genes show overlap between schizophrenia and bipolar disorder CNV studies: *GRM7*, *LARGE*, *PTPRD*, *RTN4R*, *SNAP29*, *SOX5*, *TXNIP*, *UFD1L* and *ZNF74*. Generally, genes within CNVs associated with schizophrenia are statistically over-represented with functions relating to neurodevelopment, synaptic transmission and signal transduction.

An older form of cytogenetic investigation based on microscopic study of patient chromosome rearrangements has been productive in the search for schizophrenia risk genes in individuals and families (Ref. 59). Chromosomal disruption can sometimes be localised within specific genes that immediately become strong candidates for disease causation. A notable example is the study of a t(1;11) translocation disrupting the *DISC1* (disrupted in schizophrenia) gene in a Scottish family (Refs 60, 61, 62, 63). The large family size not only allowed the translocation to be statistically linked with illness but also allowed the detailed phenotypic assessment of family members, including the observation that diagnosis-free obligate carriers of the translocation nevertheless possessed measurable deficits in cognitive endophenotypes (Refs 64, 65). It can be speculated that in these individuals the primary neurodevelopmental deficit is quantifiable but has not been matched by additional genetic or environmental factors required to cross a threshold into illness. Another gene, *PDE4B*, which is disrupted in an independent translocation event associated with schizophrenia, encodes a phosphodiesterase

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enzyme subsequently shown to bind to DISC1, thus providing a good example of functional convergence (Ref. 66).

Other candidate schizophrenia genes identified by the cytogenetic route include a glutamate metabolism pathway enzyme, *PSAT1* (Ref. 67), a kainate-type ionotropic glutamate receptor, *GRIK4/KA1* (Refs 68, 69, 70), a member of the ATP-binding cassette membrane transporter family, *ABCA13* (see the section of rare variants below and Ref. 71), and a brain transcription factor, *NPAS3* (Refs 72, 73, 74). The last of these has also been identified as a moderately significant risk factor for schizophrenia, bipolar disorder and major depression through GWAS analysis (Refs 14, 75).

Rare gene sequence variants in schizophrenia

The field awaits data from the final stage in genome-wide data gathering, the high-throughput sequencing methodologies targeting rare variants in individual patients. A recent study has suggested that rare sequence variants are likely to contain a disproportionate number of nonsynonymous pathological changes, which is a consequence of continuing negative selection pressure in the population (Ref. 76). However, the observation that the sequenced exomes of nominally healthy individuals reported so far all show several rare and apparently disruptive coding variants strongly predicted to cause illness is an indication that caution is warranted (Ref. 77). This reduced penetrance or compensation is likely to make confirmation of rare variants statistically challenging. Until now, the analysis of rare variants associated with schizophrenia has largely been carried out on a gene-by-gene basis with conventional sequencing methodology. *DISC1* (Ref. 78), *ABCA13* (Ref. 71), *KIF17* (Ref. 79) and *PCM1* (Ref. 80) are examples of candidate genes that have been sequenced in case and control populations, leading to the discovery of rare variants. Some of the variants, even those with a clear impact on protein structure and function, have failed replication (Ref. 81). The whole-genome and exome projects for schizophrenia will provide a clearer picture of the overall disease risk from rare variants and reveal the extent of incomplete penetrance.

Transcriptomic studies

In contrast to primary genetic defects, the following three sections concentrate on the assessment of cellular activity and reactivity. Post-mortem gene expression studies have compared gene transcription between brain tissue samples taken from healthy control individuals and those from individuals diagnosed with schizophrenia. Originally, this was undertaken on a hypothesis-driven, gene-by-gene basis: for example, studying glutamate receptor expression changes in the schizophrenic brain (Refs 82, 83, 84). The availability of full-gene-set microarray chips has widened the search to reveal novel diagnostic biomarkers (Refs 85, 86) and the significant contribution of gene ontologies (descriptors of biological function or location) to the pathology and aetiology of disease (Ref. 87).

However, many extraneous factors modify expression profiles, including response to drug treatment, age, gender and physiological state of the individual at death, cell-type complexity of the tissue excised for analysis and preservation of the tissue post mortem. Additionally, there is uncertainty about whether transcriptional changes reflect cause (which itself will be of heterogeneous nature between individuals) or a secondary response to the disease state. With the adoption of large sample sets and best technical or analytical practice, the results from microarray studies have shown some convergence on particular biological processes. These include metabolic regulation, mitochondrial activity, synaptic function, inhibitory neurotransmission, oligodendrocyte and myelination processes, ubiquitin–proteasome function, chaperone function and immune response. These are reviewed in detail elsewhere (Refs 88, 89, 90, 91, 92, 93, 94). Reduced brain expression of *RGS4* (regulator of G-protein signalling 4) is perhaps the most replicated specific transcriptional change in schizophrenia.

The use of tissue samples, such as blood, from living patients is a route to practical biomarker identification. However, this demands that peripheral gene expression profiles reflect those in the brain, and so far there are conflicting reports on this matter (Refs 95, 96, 97, 98). Similarly, many studies have examined gene expression changes in genetic or therapeutic models of schizophrenia in cell lines or transgenic mouse models (Refs 99, 100, 101). These studies tend to yield relatively robust findings and might prove to be a starting point for biological hypotheses that may be confirmed in post-mortem tissue.

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A new addition to microarray studies is the search for changes in the endogenous microRNA species that bind gene regulatory sequences and are thought to coordinate global transcriptional responses. Human post-mortem studies have been recently summarised (Refs 102, 103), and the findings indicate a number of specific miRNAs associated with schizophrenia that implicate, through shared ontology of their targets, neurodevelopmental and neurotransmitter pathways in disease pathology. A role for perturbed miRNA signalling in schizophrenia is further suggested by the presence of the *DGCR8* gene in the 22q11.2 VCFS deletion region: this gene encodes a component of the miRNA processing complex.

Proteomic studies

The schizophrenic proteome has also been explored for its biomarker potential, again focusing on clinically accessible tissue samples such as blood serum and cerebrospinal fluid (CSF) (Refs 104, 105). The studies show good consistency and often overlap with existing genetic findings, as recently reviewed in detail (Ref. 105). Alterations in the abundance of proteins with roles in metabolic function, particularly glycolysis (ENO1, ENO2, ALDOC, PGAM1, TPI1 and LDHB), and the cytoskeleton (INA, NEFL and SEPT3) are particularly frequently associated with schizophrenia (Refs 106, 107, 108, 109, 110). A recent study found that stimulation of peripheral blood mononuclear cells from schizophrenia patients resulted in significant increases in glycolytic enzyme expression in comparison to the same procedure in healthy controls (Ref. 111).

One specific finding merits further discussion: CSF upregulation of the secreted factor VGF has been shown in cases of schizophrenia and depression, even before therapeutic drug use (Refs 112, 113). Independently, VGF has been implicated in metabolic control and appears to mediate the antidepressant actions of exercise by increased hippocampal neurogenesis (Refs 114, 115, 116, 117). We have recently demonstrated that the *VGF* gene is a target of the NPAS3 transcription factor (Ref. 118).

Metabolomic studies

Perhaps the most recently developed tool applied to schizophrenia is based on the large-scale biochemical analysis of tissue from patients or transgenic mouse models, which is usually achieved through a combination of chromatography and high-resolution mass spectrometry (Ref. 119). Improvements in resolution mean that several hundred molecular species can be identified, depending on the precise extraction conditions and separation parameters. Biosynthetic pathway flux, redox balance, cellular energy state, neurotransmitter abundance and membrane composition can all be assessed. Hence, the resulting data are of a different flavour to those described above, providing a snapshot of the homeostatic interactions between genome-directed enzyme expression, disease pathology and environmental factors. The results of metabolomic studies of schizophrenia have been reviewed previously (Refs 120, 121) and frequently include disruptions to three biological processes. First, schizophrenia alters the composition of brain lipids, such as phosphatidylethanolamine and phosphatidylcholine (omega-6 forms, in particular), a state that is reversible with antipsychotic use (Refs 122, 123, 124, 125). This interaction with medication is further indicated by the general and specific changes in lipid pathway transcriptomics induced by a wide spectrum of neuroleptics (Ref. 101). Second, schizophrenia, similarly to other CNS disorders such as Parkinson disease, Alzheimer disease and multiple sclerosis (MS), is associated with metabolic changes consistent with an imbalance in redox state or oxidative stress (Refs 126, 127, 128). Notably, the free-radical scavenger glutathione appears to be reproducibly decreased (Refs 129, 130) and mirrored in the observed genomic deletions of glutathione *S*-transferase genes in schizophrenia (Ref. 131). Third, and perhaps closely related to these defective oxidative processes, are the reported deficiencies in glucose utilisation (Ref. 132) and energy production that point to perturbed anaerobic glycolysis and mitochondrial oxidative respiration (Refs 133, 134). The role of glucose metabolism is especially relevant in the context of the increased risk of metabolic syndrome or type II diabetes in schizophrenia. Although this can often be linked with antipsychotic side effects, there is good evidence for inherent deficits of glucose metabolism in drug-naive patients (Refs 135, 136). Oxidative damage to the mitochondrial genome has been frequently reported in schizophrenia, highlighting this organelle as a focus of pathology (Ref. 137). Additionally, mitochondrial morphology and

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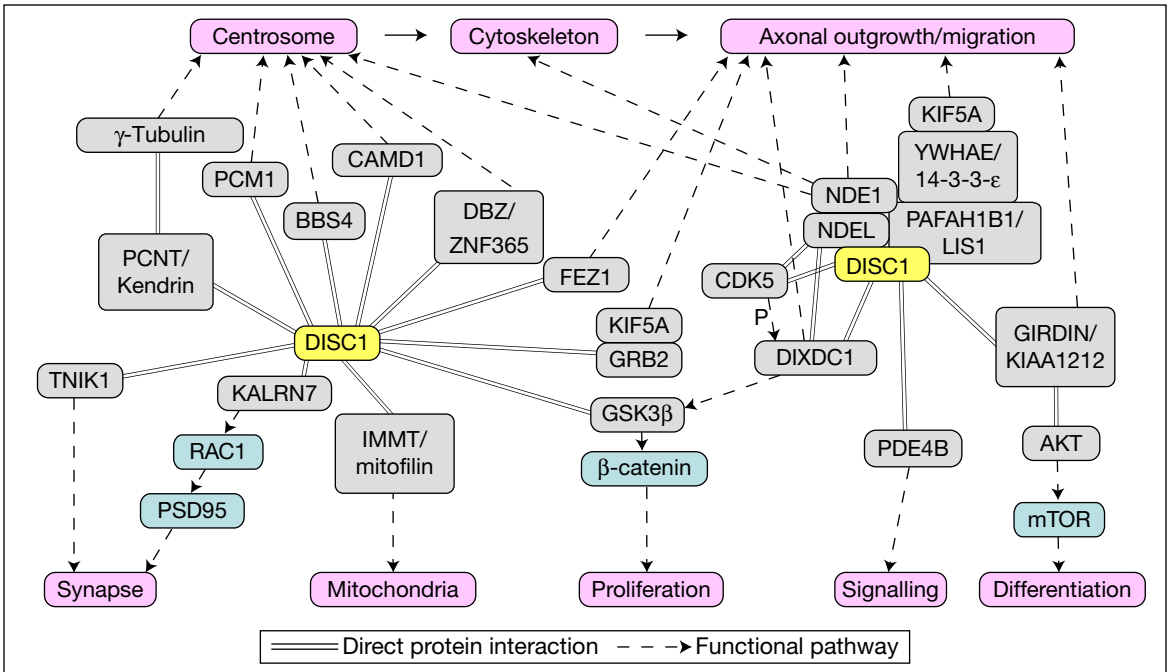

The function of DISC1 has been defined by its protein interactions and has generated deep insight into the molecular basis of neurodevelopmental failures central to the aetiology of schizophrenia

Figure 1. The function of DISC1 has been defined by its protein interactions and has generated deep insights into the molecular basis of neurodevelopmental failures central to the aetiology of schizophrenia. DISC1 (yellow) is shown at two locations in the centre of the diagram and its interactors lead to various outputs located at the top and bottom. In the case of the centrosome, cytoskeleton and axonal growth or migration, all three can be considered different aspects of the same neurodevelopmental pathway. The data (only a subset of the total) have been assembled from general (Refs 147, 148, 149, 150, 151, 152, 153, 154) and specific protein-interaction papers. DISC1 interacts with KALRN/HAPIP (Ref. 155), DBZ/ZNF365A (Ref. 148) (Ref. 147), the NDE1 complex (Refs 156, 157), BBS4 and PCM1 (Ref. 158), PDE4B (Ref. 66), FEZ1 (Ref. 151), CAMD1 (Ref. 159), GIRDIN and AKT (Refs 160, 161), KIF5A and YHWAE/14-3-3-ε (Refs 162, 163, 164), DIXDC1 (Ref. 165) and IMMT/mitofilin (Ref. 140).

subcellular distribution are known to be regulated by DISC1 and its interactors, such as IMMT/mitofilin (Refs 138, 139, 140). The metabolomic approach might help to expand phenotyping of transgenic animal models. We recently demonstrated that *Npas3*-knockout brain tissue has specific disturbances of the NAD^+ redox intermediate, as well as components of the glucose and pentose phosphate metabolic pathways: a finding that was supported by in vitro analysis of the gene targets of this transcription factor (Ref. 118).

Established candidate genes

Specific gene-hunting methods have led to the discovery of several strong candidate schizophrenia genes. Three of these are briefly summarised here: *DTNBP1* (dystrobrevin-binding protein 1/dysbindin) (Ref. 141), *NRG1* (neuregulin) (Ref. 142) and *DISC1* (Ref. 61). Each has spawned a dedicated research field using cell biology and transgenic mouse modelling to link gene function to disease.

Dysbindin is known to interact with component proteins of the biogenesis of lysosome-related organelles complex 1 and dystrophin-associated protein complex (DPC) (Ref. 143). A number of directly interacting proteins in these complexes (e.g. CMYA5) have also been independently linked with risk of schizophrenia. Other candidate disease proteins such as NRXN1 and LARGE are indirectly associated with the DPC.

Neuregulin encodes several isoforms of a growth factor with known roles in both neuronal (inhibitory interneuron) and glial cell

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function. NRG1 isoform type IV has particular relevance to schizophrenia because its promoter lies close to the SNP with strongest genetic association with illness. Neuregulin signals through the ErbB4 receptor that has also been associated with schizophrenia (Refs 144, 145).

In the ten years since the discovery of *DISC1*, work on the gene has moved from confirmation of genetic risk to extrapolation of function by mapping protein interactors (Refs 60, 146) and, finally, onto pathological and behavioural studies in transgenic mouse models. Figure 1 summarises the predominant cellular roles of DISC1 by presenting the several protein interactions that have been described at the nucleus, mitochondrion, centrosome, growth cone and synapse. One particularly important DISC1 function can be summarised as the harnessing of the cytoskeleton for intracellular trafficking, cellular movement and axonal extension, which in turn contributes to structural brain development and clinical manifestations.

Functional paradigms in schizophrenia

Cellular trends

As the number of schizophrenia risk genes or proteins accumulates and resolves, they are assessed for statistically significant over-representation of certain ontologies. This convergence of processes and pathways thus defines likely biological causes of schizophrenia. The genomic dissection of autistic spectrum disorders (ASDs), accelerated by its substantial cytogenetic component, has led the way in this regard, with at least three clear functional asymptotes discovered: that of the structure and function of the synapse, axonal insulation and the mTOR pathway (Refs 166, 167). Figure 2 shows a model neuron together with a subset of the genes or proteins detailed within this review grouped according to their typical functions or subcellular locations. Does it permit new insights beyond the banal fact that synapses, axons and dendrites are all important in schizophrenia aetiology? The concentrated cytoskeletal, mitochondrial and metabolic links might be the most revealing aspects. The first is in line with the action of the DISC1 complex detailed above. Thus, we can place the cytoskeletal processes of intracellular trafficking, as well as the dynamic migration of neurons and axonal extension during development, at the forefront of aetiological processes linked with schizophrenia. The density of proteins involved in glycolysis and mitochondrial function is an indication of the perturbed state of brain energy regulation in schizophrenia. In summary, a variety of techniques persuasively suggest that deficiencies of the synapse, cytoskeleton, cell adhesion, metabolism and oligodendrocyte function are key factors underlying schizophrenia.

The immune system

As studies of schizophrenia transition from the cellular to organism level, several biological processes become apparent, including inflammation and adult neurogenesis. Epidemiological data have long supported an immune component to schizophrenia. The increased risk of schizophrenia due to habitation in an urban environment (Ref. 168) might be explained by increased exposure to infectious disease (Ref. 169). The proposed mechanism is through effects of maternal infection during pregnancy, which impinge on the formation of the fetal brain during critical neurodevelopmental stages. Specific infections, such as the cat-borne *Toxoplasma gondii* parasite, have been repeatedly associated with risk of schizophrenia and linked to behavioural and cognitive performance changes (Refs 170, 171). At the molecular level, there is evidence for increased levels of inflammatory markers (e.g. interleukins) in the brains of those diagnosed with schizophrenia. Interleukin administration during rodent development can induce schizophrenia-like phenotypes (Ref. 172). Targeting these inflammatory processes in schizophrenia [e.g. by reducing prostaglandin E2 production with the nonsteroidal anti-inflammatory drug aspirin (Ref. 173)] appears to be a useful adjunct to conventional antipsychotic treatment.

En masse analysis of GWAS data sets has described a relationship between schizophrenia and bipolar disorder, but clearly distances them both from the core group of common, complex genetic disorders known to share an autoimmune component [e.g. rheumatoid arthritis (RA), Crohn disease (CD), MS and type I or II diabetes (T1D/T2D)] (Ref. 25). Nevertheless, the association between schizophrenia and the MHC region on chromosome 6 suggests that a link might exist.

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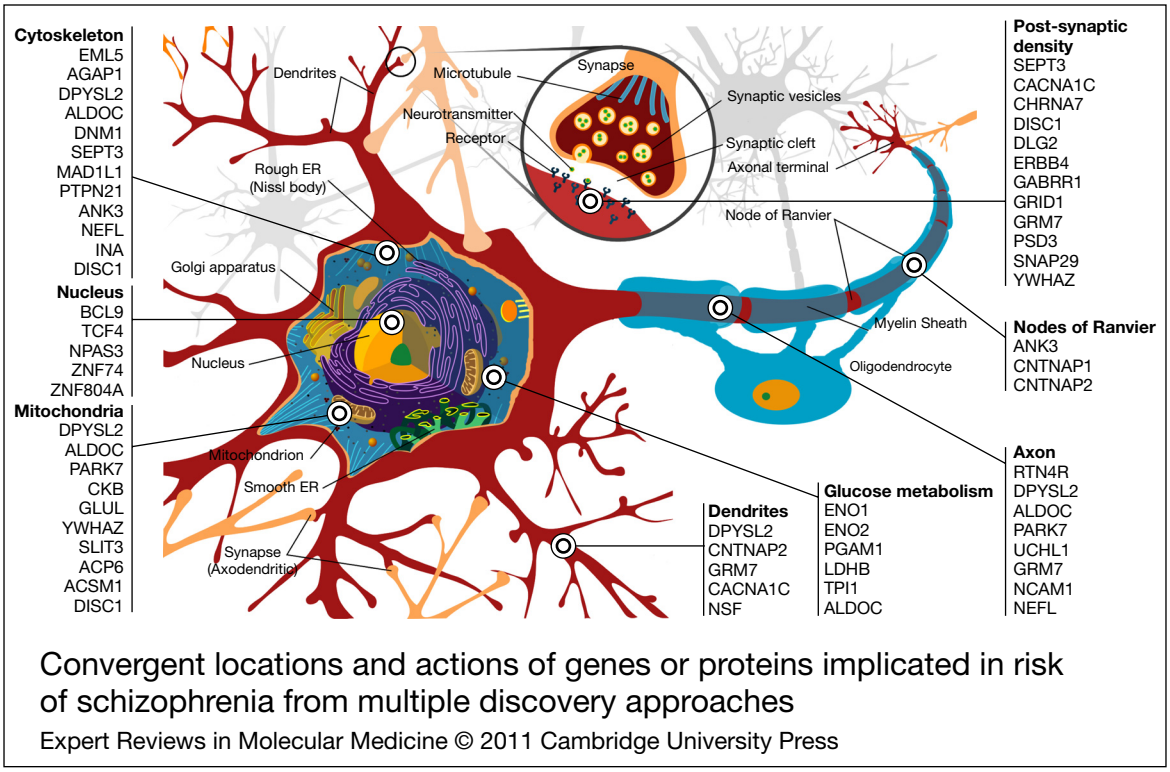

Convergent locations and actions of genes or proteins implicated in risk of schizophrenia from multiple discovery approaches

Figure 2. Convergent locations and actions of genes or proteins implicated in risk of schizophrenia from multiple discovery approaches. Neuron adapted from a Wikimedia Commons image (http://commons.wikimedia.org/wiki/File:Complete_neuron_cell_diagram_en.svg).

A recent analysis of GWAS overlaps among the autoimmune disorders (Ref. 174) identified genes with considerable relevance to schizophrenia. For example, *NRXN1* (a shared risk factor for RA, CD and MS), *TRIM27* (RA, CD and T1D), and, with less statistical significance for overlap, *ZNF804A* (RA, T1D), *CSMD1* (RA, MS) and *ZDHHC8* (RA, T2D) have also been identified in the schizophrenia GWAS and CNV literature.

Immunostimulation of mice with compounds such as lipopolysaccharide or polyI:C has recently been used in an attempt to model such gene–environment interactions. Both postnatal and in utero treatments of polyI:C have been used in mice overexpressing a dominant-negative mutant form of the human DISC1 protein (Refs 175, 176, 177). For both time points, combining immunostimulation and overexpression of mutant DISC1 resulted in significantly greater phenotypic consequences than treatment or overexpression alone. The effects were diverse, ranging from increased anxiety or depression, altered social interaction, behavioural paradigm performance changes, memory deficits, altered interleukin production (IL-1β up, IL-5 down), reduced HPA axis activation in stressful conditions, reduction in DISC1-specific enlargement of lateral ventricles, reduction in parvalbumin-expressing interneuron number and reduced dendritic spine density. These are important hypothesis-driven experiments that expose the breadth of responses to gene–environment interaction but, as yet, do not fully reveal whether these effects are independent (additive risk) or mechanistically synergistic (a role for DISC1 in immunomodulation). In terms of linking DISC1 to immune response, it is intriguing to note that one of its protein interactors, ZNF365 (DBZ/KIAA0844), is also a key candidate for CD (Ref. 178) and breast cancer (Ref. 179), both of which have immune components to their aetiologies.

In addition to proinflammatory pathways, new interest in the actions of the innate and adaptive immune systems in the central nervous system has been sparked by the realisation of the extent

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to which both MHCI and complement cascade proteins such as C3 contribute to synapse pruning during development (e.g. the visual system in the dorsolateral geniculate nucleus) and in neurodegenerative disorders (Ref. 180). This is particularly intriguing when it is considered that excessive synaptic pruning within the adolescent prefrontal cortex might directly precede and contribute to the onset of schizophrenia (Refs 181, 182, 183). The protein CSMD1, discussed above, appears to have a role in complement pathway regulation.

Adult neurogenesis

Structural brain-imaging studies support a neurodevelopmental model of schizophrenia (Ref. 3). This model is physically manifest at the levels of proliferation, differentiation and migration of neurons during the embryonic formation of the cortex and, later, recapitulated as the addition of new granule cells to the dentate gyrus region of the hippocampus in adulthood (Refs 184, 185). At the molecular level, protein interactors such as DISC1, NDE1 and PAFAH1B1, for example, are known to be vital participants in both the embryonic and adult processes. Moreover, both processes involve a defined layer of stem cells located within the subventricular zone or subgranular zone that generate a neuronal progenitor population, which divide to produce daughter cells committed to a neural fate. The process does not begin and end with this proliferation: in adult neurogenesis, only a proportion of the new neurons successfully differentiate, migrate and integrate permanently into the existing neuronal architecture; the remainder apoptose.

Post-mortem studies showing that adult neurogenesis is attenuated in schizophrenia (Ref. 186), together with evidence that it is improved by antipsychotic treatment, have sparked enormous interest as a potential pathology that might also reflect defects in embryonic neurodevelopment (Ref. 185). Dentate gyrus granule cells form one of the component synaptic junctions, mossy fibre synapses, in the hippocampal trisynaptic circuitry that contribute to the long-term activity-dependent synaptic plasticity changes (long-term potentiation, LTP) thought to underlie learning and memory. Therefore, neurogenesis, by effects on LTP, has the potential to contribute to some of the cognitive aspects of schizophrenia, although evidence to support this is currently incomplete (Ref. 187).

The rate of neurogenesis in transgenic mouse models of schizophrenia (as measured by the incorporation of nucleotide analogues into the genomic DNA of dividing cells) provides an attractive means to quantify effects of the single genetic defect and correlate this with behavioural and cognitive deficits. However, adult neurogenesis does not measure up perfectly as a causative pathology in schizophrenia. First, neurogenesis declines steeply with age in rodents and humans, which is at odds with the course of schizophrenia. Second, neurogenic proliferation is a highly reactive phenomenon. Many stimuli seem able to trigger it, including hypoxia, aerobic exercise, environmental stimulation, sex hormones and seizures. Third, it is somewhat disconcerting to see it touted as an important pathology in Alzheimer disease (Ref. 188) and other forms of neurodegeneration (Refs 189, 190, 191, 192). In the light of these conflicting properties, one pragmatic stance might be that levels of adult hippocampal neurogenesis provide a useful barometer of neurodevelopmental competence, general cognitive activity and 'health status' of the brain, rather than a specific risk factor for schizophrenia.

Transgenic mouse models of schizophrenia have been vital in driving the association between neurogenesis and schizophrenia. Several strains with *Disc1* dysfunction have comprehensively dissected the gene's role in embryonic and adult neurogenesis, revealing participation in both the proliferative and migration or maturation stages (Refs 160, 161, 193, 194, 195, 196, 197, 198, 199, 200, 201).

Mice lacking the *Npas3* gene also display cognitive, behavioural and neurodevelopmental phenotypes (including adult neurogenesis deficiency) consistent with a model for human psychiatric illness (Refs 202, 203, 204). A recent paper (Ref. 205) described an in vivo screen for small molecules that could reverse the neurogenesis phenotype in *Npas3* mutant mice. One molecule that achieved this, P7C3, helped determine that the *Npas3* neurogenesis failure was due to increased levels of apoptotic death among newly formed neurons, rather than defective proliferation. Because electroconvulsive stimulation of *Npas3*-knockout mice also restores neurogenesis, it might be

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speculated that Npas3 acts as a survival checkpoint: determining whether new neurons are registering 'activity' consistent with appropriate integration into dentate gyrus circuitry. Intriguingly, the *Npas3*-knockout deficits appear to be a consequence of mitochondrial fragility, in line with the metabolic defects described earlier, making this gene a point of convergence for glucose metabolism and neurodevelopmental risk mechanisms.

Outstanding issues in schizophrenia biology

Recent progress in the study of schizophrenia is beginning to place the disorder within a robust framework of key biological processes. However, three outstanding issues have emerged, and tackling them might greatly facilitate the practical application of this new-found knowledge.

Personal schizophrenia

There is a need to quantify genetic risk at the level of the individual. GWAS identifies common genetic variants contributing to population risk of psychiatric illness. It can be thought of as using a 'horizontal' approach in which averaged allele frequencies are compared between cohorts of cases and healthy controls. This is in contrast to 'vertical' studies such as CNV detection and exome resequencing, which define the genetic status of the individual. The consequence of this distinction is that GWAS variants are not studied in their genomic context, as an additive (or even multiplicative) contribution to an individual's mutational load. The horizontal approach benefits considerably from statistical power, but the vertical approach comes closer to the clinical goal of predictive testing for disease status and effective treatment. With common genetic variation predicted to act by transcriptional regulation, there is now an opportunity to combine genomic and transcriptomic data sets to reveal those 'expression quantitative trait loci' with greatest relevance to schizophrenia aetiology in the individual (Refs 206, 207, 208, 209, 210). Such studies, which have already been applied to DISC1 pathway biology (Ref. 211) and are supported by a very recent proof-of-concept study (Ref. 212), will require the correlation of CNS-relevant expression profiles from several individuals diagnosed with schizophrenia with their genome-wide SNP genotypes. The generation and neuronal differentiation of induced pluripotent stem (iPS) cell lines from patients might provide the appropriate material to make this approach feasible (Refs 213, 214, 215).

Overlapping aetiologies

The estimate of a 50% genetic overlap between schizophrenia and bipolar disorder, and its further biological relationships with ASD, epilepsy and mental retardation, requires reassessment of both simple models of neuropsychiatric disorder classification and single-process aetiologies. It might also force a categorisation of risk factors according to their mode and site of action. If it is found that much of the shared genetic variation is present in the neurodevelopmental gene fraction, then a model based on a 'fragile-brain' endophenotype might be constructive. Such a model would be consistent with the substantial genetic heterogeneity observed because it would just require an initial generalised deficiency in brain function or connectivity. A secondary hit by other genetic factors or the environment would then produce diagnosis-specific pathologies (Figure 3). Applying a crude computer analogy, the neurodevelopmental failures might cause relatively nonspecific defects in hardware, whereas disease-specific processes target specific routines in the software.

Cause and effect in schizophrenia

An important issue is how to define the point of action of any biological process linked with schizophrenia (Figure 3). Are we able to distinguish those biological pathways that are bona fide primary causes of schizophrenia from those that are the downstream reaction to, or homeostatic consequences of, schizophrenia or environmental risk factors? This might be pertinent for diagnosis and treatment. Genetic or molecular factors identified through the methods outlined above might reflect patient-specific responses to a primary deficit just as much as the primary deficit itself, and so an early-life diagnostic test might be better aimed at the latter. Similarly, therapeutic drugs might be best targeted to the root causes or downstream consequences of disease [or both (Ref. 173)]. In such a model, where do current antipsychotics act? As one moves up the

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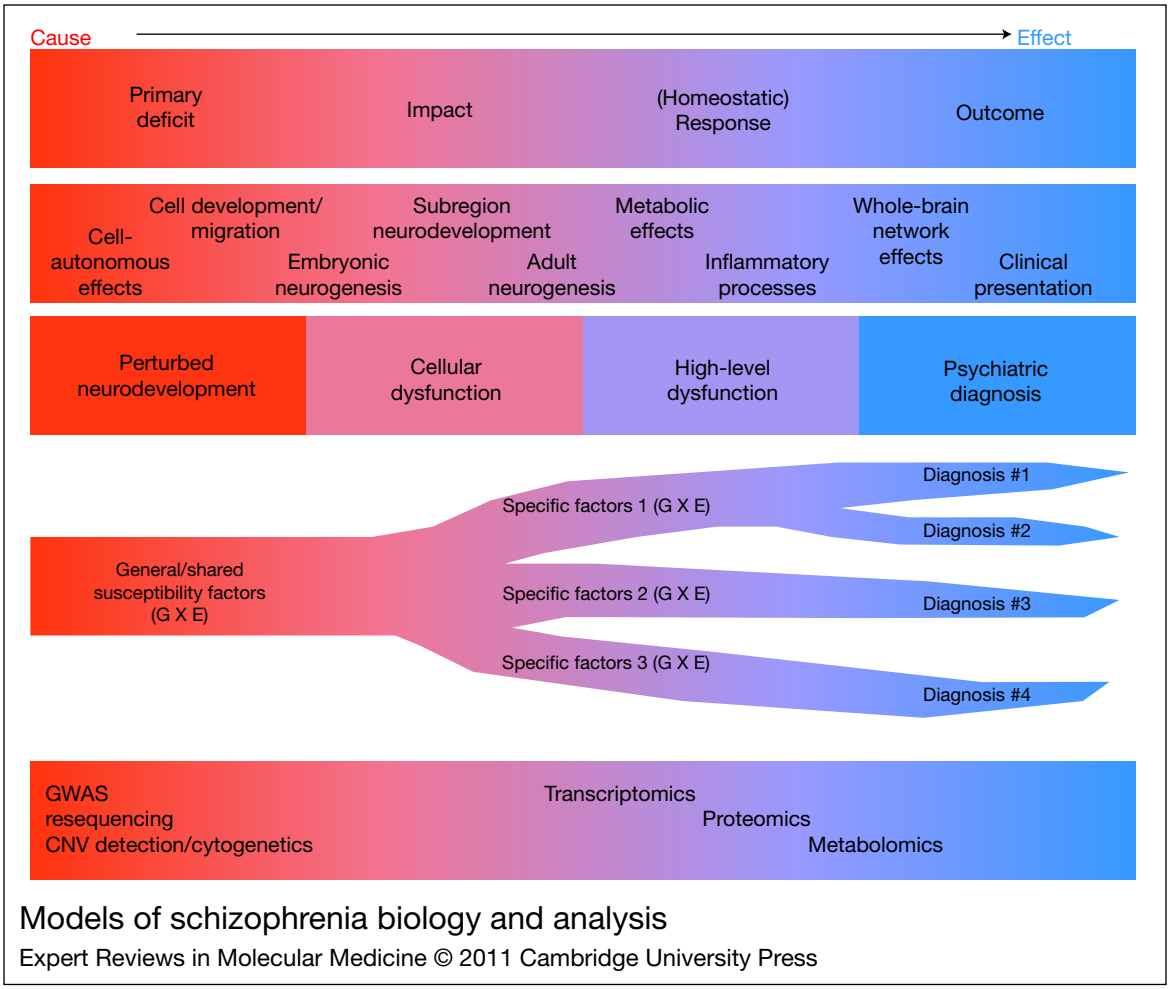

Figure 3. Models of schizophrenia biology and analysis. In this speculative representation, distinctions between biological cause and effect are presented from left to right. These highlight primary deficits and reactionary responses in schizophrenia, the specific stages of biological processes that might be involved, the progression from general mental illness susceptibility to specific diagnoses, and the competence of commonly employed investigative techniques to resolve these aspects. 'G X E' indicates the combined effect of genes and environment on risk.

biological hierarchy from gene to cell to organ and then individual, reactive processes are likely to be more prevalent (Fig. 3). The process of inflammatory response would perhaps fall into the reactive category, whereas cytoskeleton function, for example, might be considered causative. Embryonic neurogenesis would be causative, adult neurogenesis potentially reactive. This distinction would be mirrored in the discovery arena too. Genomic strategies are likely to reflect cause (although there will clearly be a genetic component to reaction) whereas other '-omics' would be increasingly influenced by environment and disease state. The skewed distribution of evidence for metabolic disturbance in the upper part of the hierarchy, as detailed above, suggests that it has more of a reactive or secondary role; however, the *Npas3* findings argue otherwise. Perhaps the detection of cell-autonomous defects, a possible corollary of causation, might be ideally suited to resolve the cause–effect dilemma. Again, the study of patient iPS cells might be invaluable in this regard.

A biological definition of the causes of schizophrenia is now a realistic, albeit challenging, goal. Its potential to influence therapeutic strategies, diagnostic methods and social acceptance of those diagnosed would be considerable, more than justifying the time,

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effort, cost and frustration involved in its formation.

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Further reading, resources and contacts

The Schizophrenia Research Forum contains up-to-date news and views on the progress of basic and clinical research into schizophrenia:
http://www.schizophreniaforum.org/

A website much more directed towards informing those diagnosed with schizophrenia together with their families and carers can be found at
http://www.schizophrenia.com/index.php

Features associated with this article

Figures

Figure 1. The function of DISC1 has been defined by its protein interactions and has generated deep insights into the molecular basis of neurodevelopmental failures central to the aetiology of schizophrenia.

Figure 2. Convergent locations and actions of genes or proteins implicated in risk of schizophrenia from multiple discovery approaches.

Figure 3. Models of schizophrenia biology and analysis.

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