Schizophrenia: genes at last?

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Genetic epidemiological studies suggest that individual variation in susceptibility to schizophrenia is largely genetic, reflecting alleles of moderate to small effect in multiple genes. Molecular genetic studies have identified several potential regions of linkage and two associated chromosomal abnormalities, and evidence is accumulating in favour of several positional candidate genes. Currently, the positional candidate genes for which we consider the evidence to be strong are those encoding dysbindin \((DTNBP1)\) and neuregulin 1 \((NRG1)\). For other genes, disrupted in schizophrenia 1 \((DISC1)\), D-amino-acid oxidase \((DAO)\), D-amino-acid oxidase activator \((DAOA, formerl known as G72)\) and regulator of G-protein signalling 4 \((RGS4)\), the data are promising but not yet compelling. The identification of these, and other susceptibility genes, will open up new avenues for research aimed at understanding the pathogenesis of schizophrenia, and will catalyse a re-appraisal of the classification of psychiatric disorders.

Introduction

Schizophrenia is a severe psychiatric disorder with a lifetime risk of \(~1\%\). The disorder is characterized by psychotic symptoms in particular delusions and hallucinations, reduced interest and drive, altered emotional reactivity and disorganised behaviour. Often relatively subtle cognitive and behavioural signs are present from early childhood, but the characteristic features generally have their onset in the late teens and early twenties. Although outcomes are variable, even with treatment, the typical course is one of relapses followed by only partial remission, and a marked reduction in social and occupational function such that sufferers are often the most vulnerable, isolated and disadvantaged individuals in society.

Genetic epidemiology

Schizophrenia has been the subject of numerous family, twin and adoption studies that show conclusively that risk of illness is increased among the relatives of affected individuals and that this is largely the result of genetic factors [1]. However, although heritability (Box 1) is high, \(~80\%\), concordance in mono-zygotic twins is typically \(~50\%\), pointing to the importance of environmental factors. Genetic epidemiology also tells us that, similar to other common disorders, schizophrenia has a mode of transmission that is complex and compatible with a multi-locus model [2,3]. However, the number of susceptibility loci, the disease risk conferred by each locus, the extent of genetic heterogeneity and the degree of interaction among loci all remain unknown. Risch [4] has calculated that the data are incompatible with the existence of a single locus conferring a relative risk in siblings \((\lambda_s; see Glossary)\) of \(>3\) and, unless extreme epistasis exists, models with two or three loci of \(\lambda_s \leq 2\) are more plausible.

Defining the phenotype for genetic research

Schizophrenia displays considerable heterogeneity of symptoms, course and outcome. Although it has not yet been possible to distinguish aetiologically distinct subgroups, it is possible that the disorder, as defined by current diagnostic criteria, includes several different disease processes. However, structured and semi-structured interviews together with explicit operational diagnostic criteria permit the reliable diagnosis of a syndrome with high heritability, which should in principle be

Box 1. Heritability

Heritability is a central concept in quantitative genetics. The heritability of a quantitative phenotype is the proportion of phenotypic variance that is accounted for by genetic effects; for a phenotype that is present or absent it is the proportion of variance in liability (based on the liability-threshold model) that is accounted for by genetic effects.

The broad sense heritability \((h^2)\) is the proportion of total phenotypic variance \((V_p)\) (or variance in liability) accounted for by total genetic variance \((V_G)\) (i.e. additive and non-additive genetic effects) \((V_g)\): \(h^2 = V_g/V_p\). The narrow sense heritability \((h^2)\) refers only to additive genetic variance \((V_A)\): \(h^2 = V_A/V_p\).

Heritability refers to variance in a population; it has no straightforward meaning for an individual. Also, even in the face of constant disease allele frequencies, heritability estimates can vary over time for a single population, or between populations at the same point in time because of differences in exposure to environmental agents. Moreover, when genes interact with environmental factors that are shared by family members to increase risk of disease, this interaction tends to be attributed to heritability in most genetic epidemiological studies. This is because the correlation in the effect of the environmental exposure on pairs of individuals will depend on the degree of genetic relatedness. Thus, high heritability does not exclude an important role for environmental factors, but it suggests that if such factors exist they are likely to be sufficiently common as to affect multiple members of a family and require interaction with the genotype before exerting an effect on the phenotype. Interestingly, MZ twins reared apart have about the same concordance rates as co-twins reared together [79]. This suggests that an environmental agent of importance to susceptibility would have to be sufficiently ubiquitous for both co-twins to be exposed, despite being reared in different locations or to operate pre-natally or early in life. An example of a disease with high heritability in which an interaction between genotype and a ubiquitous environmental agent is important is phenylketonuria [80].
schizoaffective disorder, and schizotypal personality disorder to include a spectrum of disorders including uncertainties concerning the range of clinical phenotypes possibility genes (Box 2).

Several endophenotypes for schizophrenia have been relationship to other psychotic disorders, especially studies have made some progress in our general understanding of schizophrenia (e.g.[9,10]). However, it is not neither achieved stringent ‘genome-wide’ levels of significance nor replicated pre-existing findings (reviewed in [11]). These disappointing findings are probably attributable to a combination of small genetic effects, inadequate sample sizes (with typical samples being between 20 and tractable to molecular genetic studies. Thus, in the absence of validated ways of defining sub-groups, most groups have chosen to search for genes using schizophrenia as a phenotype.

One way of refining the phenotype for molecular genetic studies is to define intermediate phenotypes or endophenotypes: traits that are intermediate between susceptibility genes and the clinical phenotype (Box 2). Several endophenotypes for schizophrenia have been proposed based on electrophysiology, pharmacology, psychology or neuro-imaging, but as yet their use has not resulted in replicated data implicating specific susceptibility genes (Box 2).

Phenotypic classification is further complicated by uncertainties concerning the range of clinical phenotypes to which genetic susceptibility to schizophrenia can lead. It clearly extends beyond the core diagnosis of schizophrenia to include a spectrum of disorders including schizoaffective disorder, and schizotypal personality disorder [5,6] but the limits of this spectrum and its relationship to other psychotic disorders, especially bipolar disorder, remain uncertain [7,8]. One of the earliest benefits from the identification of susceptibility genes for schizophrenia is that, as we discuss below, it has permitted exploration of the genetic validity of the schizophrenia phenotype and its relationship to other diagnostic groups.

Are there clues for genetics from epidemiology, pathophysiology and neurobiology?

Epidemiological, pharmacological and neurobiological studies have made some progress in our general understanding of schizophrenia (e.g.[9,10]). However, it is not possible confidently to implicate specific pathophysiological processes or to nominate compelling candidate genes from the currently rather vague concepts of altered neurodevelopment, synaptic dysfunction and aberrant neuronal connectivity that have been proposed. The more specific hypotheses based on abnormalities in neurotransmission, especially dopaminergic and glutamnergic, are possibly relevant to some of the overt clinical manifestations of the disorder but, with few exceptions, candidate gene association studies based solely on these hypotheses have met with disappointing results. This, together with the evidence for high heritability, has encouraged several groups to apply positional genetic approaches for the simple reason that these do not depend on knowledge of disease pathophysiology.

Linkage

Until recently, the results of linkage studies in schizophrenia were disappointing. Early hopes of finding mendelian forms did not materialize, and most studies neither achieved stringent ‘genome-wide’ levels of significance nor replicated pre-existing findings (reviewed in [11]). These disappointing findings are probably attributable to a combination of small genetic effects, inadequate sample sizes (with typical samples being between 20 and

Box 2. Endophenotypes

Endophenotypes, or intermediate phenotypes, are measurable variables which lie on the pathway between genotype and disease [81]. Unlike the clinical phenotype, they are not readily observable and usually require the use of special processes or instruments for their detection. Examples in medical diseases with complex genetics such as diabetes, hypercholesterolemia or hypertension include such measures as the glucose tolerance test, measurements of serum cholesterol levels and blood pressure measurements, respectively. In neuropsychiatric diseases, an endophenotype might be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature. The assumption is that endophenotypes will have a closer relationship to the underlying disease genotype and thereby be less complex genetically. Gottesman and Gould [81] have suggested the following criteria to judge the validity of potential endophenotypes:

(i) The endophenotype is associated with illness in the population.
(ii) The endophenotype is heritable.
(iii) The endophenotype is primarily state-independent (i.e. manifests in an individual whether or not illness is active).
(iv) The endophenotype and illness should co-segregate in multiply affected families.
(v) The endophenotype found in affected family members is found in unaffected family members at a greater rate than in the general population.

Several potential endophenotypes have been suggested for schizophrenia. These include sensory-motor gating deficits [e.g. deficits in pre-pulse inhibition (PPI)], various event-related potentials measured by electroencephalography (EEG), eye-tracking dysfunction and impairments in working-memory. As yet none of these has been used successfully to identify replicated susceptibility genes for schizophrenia, although some, as yet unsubstantiated, claims have been made (see [81]).

Another attraction of endophenotypes in schizophrenia is that they offer the potential for developing animal models. PPI can be demonstrated in rodents and PPI deficits have attracted interest as a partial model for schizophrenia [81].

There are several problems with the use of endophenotypes in schizophrenia. First, there is little convincing data that the genetic architecture of the endophenotypes is substantially simpler than that of the illness. Second, the requirement for special methods for endophenotype detection means that it is difficult to collect samples of sufficient size for genetics research. Third, there is often considerable inter-laboratory variation in the detailed measures used and little consensus on the most appropriate methods to employ.

Glossary

Odds ratio (OR): is approximately to the ‘relative-risk’ and is a measure of the increased risk conferred by possession of a risk factor. If possession of a risk factor is associated with a two-fold increased risk of a disorder relative to the population risk, the risk factor is said to have a relative risk of two.

Schizotypal personality disorder: is found in the relatives of people with schizophrenia, and probably constitutes a milder form of schizophrenic illness. It is characterized by non-psychotic symptoms, such as poor social relationships, anxiety in social situations and limited emotional responses. Less frequently, mild forms of thought-disorder, suspiciousness, magical thinking, illusions and perceptual aberrations are also present.
100 families and only two full genome scans being reported in samples of >300 sib-pair equivalents) and the use of marker maps of insufficient density to fully extract the genetic information from them. Because sample sizes have been small, the general failure to replicate is also, at least in retrospect, not particularly surprising, given that larger samples are required to replicate true linkages than to obtain initial evidence for linkage [12] and because positive studies often tend to overestimate effect sizes [13,14]. In human populations, replication studies (in the strict sense of a second study reproducing exactly the experimental conditions of the first) are impossible because samples almost certainly differ in genetic architecture because of ethnicity, ascertainment, variation in exposure to environmental risks and, where there are multiple disease loci, sampling variance [14,15]. In spite of these difficulties, as the data from >20 genome-wide studies have accumulated, and sample sizes increased, some consistent patterns have emerged (Figure 1).

In an attempt to deal with the issues of power, two meta-analyses of schizophrenia linkage have recently been undertaken [16,17]. The study of Lewis and colleagues [17] is the more systematic of the two, being based on data collected using identical methods across many studies both published and unpublished, whereas Badner and Gershon [16] relied on published data that had been analysed using different methods. Unsurprisingly, the results obtained are somewhat different although there are regions of overlap. The study of Badner and Gershon [16] supported the existence of susceptibility genes on chromosomes 8p, 13q and 22q, whereas that of Lewis and colleagues [17] most strongly favoured 2q, but also found that the number of loci meeting the aggregate criteria for significance was much greater than the number of loci expected by chance ($P<0.001$). Support was also obtained for regions on chromosomes 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q and 14p. Thus the 8p and 22q regions were supported by both meta-analyses but nine regions were supported by only one. Furthermore, the region most strongly supported by the Lewis et al. [17] analysis (on chromosome 2q), is not one that has received strong support previously; but it is now clearly worthy of further investigation.

The linkage data therefore support the predictions made by Risch [4] on the basis of genetic epidemiological findings: it is highly unlikely that there exists a locus of effect size $l_s > 3$. However, there is evidence implicating several regions, which is consistent with the existence of susceptibility alleles of moderate effect (population $l_s 1.2–3$), and possibly loci of larger effect that can be identified in specific samples of large multiply affected families. Of course the proof that a positive linkage is correct comes when the disease gene, or genes, is identified, and several of the linked regions are currently undergoing detailed analysis with, as we shall see, encouraging results. Another way of resolving uncertainty

![Figure 1](https://www.sciencedirect.com)

**Figure 1.** Locations of linkage findings and genes discussed in this paper. Linkages that reached genome-wide significance on their own (red) or those that have received strong support from more than one sample (blue) are shown. The red arrows refer to the location of chromosomal abnormalities associated with schizophrenia. The yellow arrows and circles show the locations of the genes discussed in the main text.
is to study larger samples (e.g. 800–1000 nuclear families) than those studied to date, which should be sufficient to detect susceptibility genes of moderate effect size and might also enable the detection of interactions between loci, relationships between allele sharing at particular loci and aspects of the phenotype, and loci of smaller effect. Given the expense of sample collection, it would also be sensible to extract as much information as possible out of existing samples by combining those samples where the diagnostic information is sufficiently well characterized, and then re-analysing them with higher-density maps of identical markers [18].

Positional candidate genes

The convergence of positive linkage findings has led to several detailed mapping studies of linked regions and some of these have implicated specific genes [19]. The putative susceptibility genes for which the most follow-up data are available are those encoding dysbindin (DHNBP1, also known as dystrobrevin-binding protein 1), neuregulin 1 (NRG1), D-amino-acid oxidase (DAO), D-amino-acid oxidase activator (DAOA, formerly known as G72) and regulator of G-protein signalling 4 (RGS4). In our view, the evidence now strongly implicates DTNBP1 and NRG1, whereas the data for DAO, DAOA and RGS4 are promising but not yet compelling [19]. There are also several other genes for which high profile claims have been made including CAPON (encoding the C-terminal PDZ domain ligand of neuronal nitric oxide synthase) [20], PPP3CC (encoding protein phosphatase 3, catalytic subunit) [21] and TRAR4 (encoding trace amine receptor 4) [22], which map to the 1q22, 8p21.3 and 6q23.2 linkage regions, respectively. However, none of the original reports for these genes is alone compelling and there are as yet insufficient follow-up data to make informed judgements.

**Dysbindin**

Evidence implicating DTNBP1 in schizophrenia was first reported by Straub and colleagues [23], who undertook association mapping across the linkage region on chromosome 6p22.3. Support for association rapidly followed from a largely German study [24] and in two large samples, one case control from the UK and Ireland [25] and the other from Bulgarian parent-proband trios [19]. Although there have also been samples in which no association was found [26], significant associations have now been published in ten samples [27,28] including an initially negative Irish sample [29], when one additional marker that defined the risk haplotype in our own UK sample was genotyped in the Irish sample [25]. Thus, the evidence in favour of DTNBP1 as a susceptibility gene for schizophrenia is strong. However, there are inconsistencies in the specific risk alleles and haplotypes between studies, suggesting that, if this is indeed a susceptibility gene, there are either multiple susceptibility and protective alleles [25], or a single susceptibility allele is carried on a remarkable diversity of haplotypes even in closely related populations. As yet, no causative variant has been identified, but the absence of associated non-synonymous coding alleles [25] suggests that disease susceptibility depends on variation affecting mRNA expression. This is indirectly supported by evidence for as yet unknown cis-acting polymorphisms affecting DTNBP1 expression in human brains [30] and, more directly, by two recent studies showing reduced levels of expression of the mRNA [31] and protein [32] in post-mortem brain samples from patients with schizophrenia.

Dysbindin binds to both α- and β-dystrobrevin, which are components of the dystrophin glycoprotein complex [33]. The dystrophin complex is found in the sarcolemma of muscle but is also located in postsynaptic densities in several brain areas, particularly mossy fibre synaptic terminals in the cerebellum and hippocampus. Although its functions are largely unknown, its cellular location initially suggested that variation in DTNBP1 might confer risk of schizophrenia by mediating effects on postsynaptic structure and function [23]. However, Talbot and colleagues [32] have recently shown that the presynaptic dystrobrevin-independent fraction of dysbindin is reduced in schizophrenic brain within certain intrinsic glutamatergic neurones of the hippocampus, and this is associated with increased expression of vesicular glutamate transporter type 1. Moreover, a reduction in glutamate release has been demonstrated in cultured neurons with reduced DTNBP1 expression [27]. These data suggest that variation in DTNBP1 might confer risk by pre-synaptic effects on glutamate trafficking or release.

**Neuregulin 1**

NRG1 was first implicated in schizophrenia in an Icelandic population after association mapping across 8p21–p22 revealed association between schizophrenia and a multi-marker haplotype at the 5′ end of NRG1 [34]. The same Icelandic haplotype was subsequently reported to be associated in a large sample from Scotland [35] and in a UK-wide sample [36] although in this study, the association was only just significant. Other positive findings have emerged from Irish [37], Chinese [38–41] and South African samples [42]. However, some studies have failed to find evidence of association [43–45,42]. Only the first three studies [34,35,37] have implicated the specific Icelandic haplotype, perhaps reflecting differences in the linkage disequilibrium (LD) structure across NRG1 in European and Asian samples (e.g. [40]).

NRG1 encodes many mRNA species and proteins. Despite detailed re-sequencing [34], specific susceptibility variants have not been identified, but the Icelandic haplotype points to the 5′ end of the gene, once again suggesting that altered expression or mRNA splicing is involved. It is even formally possible at this stage that NRG1 is not the susceptibility gene, because the first intron contains another expressed sequence [37] whose function is unknown. However, in so far as it is possible to model schizophrenia in animals, behavioural analyses of NRG1 hypomorphic mice support the view that the association is related to altered NRG1 function or expression [46] – a hypothesis supported by the observation of alteration in the ratios of NRG1 mRNA species in schizophrenic brain [47]. Just as for DTNBP1, the mechanisms by which altered NRG1 function might lead to schizophrenia are unclear. Modulation of glutamatergic mechanisms might be involved [34]; however, NRG1 is thought to encode ~15 proteins
with a diverse range of functions in the brain, including cell–cell signalling, ErBb receptor interactions, axon guidance, synaptogenesis, glial differentiation, myelination and neurotransmission [48]. Any of these could potentially influence susceptibility to schizophrenia.

**Chromosomal abnormalities associated with schizophrenia**

Several associations between schizophrenia and chromosomal abnormalities have been reported [49], but only two provide convincing evidence for the location of a susceptibility gene. Several studies have shown that adults with 22q11 deletion syndrome (also known as DiGeorge syndrome, Velo-cardio-facial syndrome, Sphynxen syndrome and conotruncal anomaly face syndrome) have an increased risk for schizophrenia (reviewed by [50]), with the largest study of adult patients to date (n=50) estimating this at 24% [51]. The deletion cannot account for a high proportion of schizophrenic cases in the general population [52], but reports of linkage to 22q11 (see discussion of meta-analyses above and Figure 1) suggest that variants in genes mapping to this region contribute to more typical cases. Candidates for which positive data have been reported include catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH) and zinc finger- and Asp-His-His-Cys (DHH) domain-containing protein 8 (ZDHHC8), but again a clear pattern of replication has yet to emerge and intensive efforts by several groups to identify susceptibility genes in this region continue [19].

The other major finding based on a chromosomal abnormality comes from an extended Scottish pedigree in which a balanced chromosomal translocation (1;11) (q42;q14.3) showed strong evidence for linkage to a fairly broad phenotype comprising schizophrenia, bipolar disorder and recurrent depression [53]. The translocation was found to disrupt two genes on chromosome 1: DISC1 and DISC2 [53,54]. DISC2 contains no open reading frame and can regulate DISC1 expression by anti-sense RNA [54]. Interestingly, DISC1 and DISC2 are located close to the chromosome 1 markers implicated in two Finnish linkage studies [55,56] (Figure 1). Although the function of DISC1 is not understood in detail, there is evidence that at least some of its functions are compatible with a role in schizophrenia pathogenesis. For example, it appears that one function of DISC1 is related to cytoskeletal regulation, disruption of which might influence neuronal migration, neurite architecture and/or intracellular transport [57,58]. Although interesting hypotheses, it is important to remember that translocations can exert effects on genes other than those directly disrupted, and there are several mechanisms by which a translocation can influence the expression of neighbouring genes. Thus, to implicate DISC1 and/or DISC2 unequivocally in the pathogenesis of schizophrenia, it is necessary to identify mutations or polymorphisms that are associated with schizophrenia in another population and to show that those associations cannot be attributed to LD with neighbouring genes. Four published studies have attempted to find such evidence. Negative studies were reported by the group who originally identified DISC1 and DISC2 [59], and by a group who focused on the 5’ end of the gene in a large Japanese sample [60]. However, positive findings have been reported in a large Finnish sample [61] and in US samples with schizophrenia, schizoaffective disorder and bipolar disorder [62]. The possibility of a direct role of DISC1 in schizophrenia is further suggested by recent findings of enhanced nuclear DISC1 protein expression in schizophrenic brain [63].

**Overlap with findings in bipolar disorder**

Bipolar disorder is a genetically complex disorder [64,65] that is characterized by disturbances in mood ranging from extreme elation (mania) to severe depression often accompanied by hallucinations, delusions and cognitive changes. Traditionally, psychiatric research in general, and the search for predisposing genes in particular, has proceeded under the assumption that schizophrenia and bipolar disorder are separate disease entities. However, a recent twin study [66] has added to previous evidence challenging this assumption [65]. Moreover, genetic linkage studies have identified some chromosome regions that show convergent or overlapping regions of interest in both disorders. These include the regions of 13q, 22q that we discussed earlier, 6q (Figure 1 and reviewed in [65]) and chromosome 18 [16,67]. The chromosomal regions implicated are large and contain many genes so it is not certain that the apparent overlaps reflect the existence of shared genes between the two disorders. We should also remember that it remains possible that any given linkage might be a false positive in at least one of the disorders. However, the hypothesis that loci exist that influence susceptibility across the schizophrenia–bipolar divide has received direct support from a recent genome scan [68] using families ascertained on the basis of a proband with schizoaffective disorder (a form of illness with prominent features of both schizophrenia and bipolar disorder). That study reported significant genome-wide evidence to a locus at 1q42 and suggestive linkage at 22q11. The linkage evidence was contributed equally from ‘schizophrenia’ families (i.e. where other members had predominantly schizophrenia) and ‘bipolar families’ (i.e. where other members had predominantly bipolar disorder). Linkage findings in complex disorders must always be regarded as provisional until the underlying risk loci are identified. Thus, the identification of schizophrenia susceptibility genes has provided a direct means to explore the possible overlap with bipolar disorder. It is therefore of great interest that several recent reports suggest that variation in genes implicated in influencing susceptibility to schizophrenia also influences susceptibility to bipolar disorder. These include G72 (DAOA)/G30 [69–71] DISC1 [62] and NRG1 [72]. If these findings are replicated this will confirm suspicions that schizophrenia and bipolar disorder share pathogenic mechanisms and will challenge current diagnostic practice in which schizophrenia and bipolar disorder are considered to be largely separate disease entities. If schizophrenia and bipolar disorder reflect the same susceptibility variants, then this is consistent with the two conditions having overlapping pathogenic mechanisms that might be manifest in susceptibility to a shared underlying psychopathology and endophenotypes.
Implications of recent findings
In our view, the evidence now strongly implicates DTNBP1 and NRG1 as susceptibility genes for schizophrenia. Data for DISC1, which we have discussed to illustrate the possible utility of cytogenetic abnormalities, and several other genes including DAO, DAOA and RGS4, which we have not discussed, are promising but not yet compelling. However, even in the most convincing cases, the risk haplotypes appear to be associated with small effect sizes [odds ratio (OR)<2.5], and, although this is difficult to determine, do not appear to explain fully the linkage findings that prompted each study. This could suggest that the associated polymorphisms and haplotypes are only in weak LD with the true pathogenic variants, that the linkages reflect variation at more than one susceptibility site in the same gene (or in multiple genes in the area of linkage), or that in some cases, despite the statistical evidence, the associations are spurious. For all of these genes, there have been inconsistencies between studies in the specific alleles and haplotypes that are associated, highlighting the difficulties in determining a clear replication in association studies based on LD and haplotypes [73]. It is by no means certain that support requires the same pattern of association to be obtained nor, conversely, that a negative finding can be regarded as a failure to replicate if only the associated allele or haplotype from the origin study is examined. Detailed follow-up studies, including de novo mutation detection and detailed genotyping in large samples drawn from different populations, with the aim of answering these questions are now required.

For most geneticists, the purpose of disease gene identification is to enhance our understanding of pathogenesis. Thus, it is now important that we identify the specific mechanisms by which the recently implicated genes alter the risk of schizophrenia and the molecular and cognitive processes that link these primary events to psychopathology. Already, it has been noted that several of the genes encode proteins that potentially impact on the function of glutamatergic synapses, which might therefore be the location of the primary abnormality [74–76]. The possible importance of synaptic abnormalities in schizophrenia had already been recognized [77] and the recent genetic data suggest that there is at last convergence of psychiatry. Data for schizophrenia. Scrutinizing the validity of the definition. Arch. Gen. Psychiatry 44, 634–641
Kirov, G. et al. (2004) Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia in 488 parent-offspring trios from Bulgaria. Biol. Psychiatry 55, 971–975 genes; identifying these genes will enable us to test existing, and to generate novel, hypotheses of pathogenesis.

Finally, we can expect that over the coming years molecular genetics will catalyse a re-appraisal of psychiatric nosology and will provide a path to understanding the pathophysiology that will facilitate development of improved treatments. For example, current genetic findings suggest that rather than classifying psychosis as a dichotomy, a more useful formulation might be to conceptualize a spectrum of clinical phenotype with susceptibility conferred by overlapping sets of genes [78]. These developments will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.

References
19 Kirov, G. et al. (2004) Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia in 488 parent-offspring trios from Bulgaria. Biol. Psychiatry 55, 971–975


Hamshere, M.L. et al. Genome-wide linkage scan in schizoaffective disorder: Significant evidence for linkage (LOD = 3.54) at 1q42 close to DISC1, and suggestive evidence at 22q11 and 19q13. Arch. Gen. Psychiatry (in press)


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