Research report

The molecular genetics of the 22q11-associated schizophrenia

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Abstract

Schizophrenia has a strong genetic component but the mode of inheritance of the disease is complex and in all likelihood involves interaction among multiple genes and also possibly environmental or stochastic factors. A number of studies have shown that the 22q11 deletion syndrome (22q11DS) is a true genetic subtype of schizophrenia and as such may play an extremely important role in deciphering the genetic basis of schizophrenia. Microdeletions of the 22q11 locus are associated with a staggering increased risk to develop schizophrenia. The same locus has also been implicated by some linkage studies. Systematic examination of individual genes from the 1.5 Mb critical region has identified so far the PRODH and ZDHHC8 as strong candidate schizophrenia susceptibility genes from this locus. Discovery of these genes implicates neuromodulatory aminoacids and protein palmitoylation as important for disease development. Other genes, including the gene encoding for COMT, have been implicated by candidate gene approaches. It therefore appears that the 22q11-associated schizophrenia may have the characteristics of a contiguous gene syndrome, where deficiency in more than one gene contributes to the strikingly increased disease risk. Mouse models for individual candidate genes will provide the investigators with the opportunity to start understanding the function of these genes and how they may impact on schizophrenia. Mouse models that carry long-range deletions will likely capture the interactions among the culprit genes and help explain the genetic contribution of this locus to the high risk for schizophrenia. In-depth human and animal model studies of 22q11DS promise to answer critical questions relating to the devastating illness of schizophrenia, whose causes remain largely unknown.
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1. Introduction

Schizophrenia is a severe mental illness, which affects a staggering 1% of the world's population and typically causes severe functional decline, tremendous suffering, and lifelong disability [27]. In the absence of reliable biological markers, schizophrenia is defined as a clinical syndrome. A number of relatively precise operational definitions of the syndrome exist, such as the editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [2] that, when used in conjunction with standardized research interviews, can lead to a reliable, valid, and "heritable" diagnosis of the disease. Case identification usually begins with the observation of psychotic ("positive") symptoms (delusional ideas, hallucinations, and disordered thinking) and bizarre behavior, often with a later emergence of "negative" symptoms, including low levels of emotional arousal, mental activity, and social drive. Furthermore, there is increasing recognition of prominent cognitive impairments, particularly in attention, memory, and executive functions, which perhaps equally contribute to schizophrenia's disability. The age of onset of the full set of diagnostic

symptoms of schizophrenia is around 20 years, but there is substantial evidence to suggest that the negative symptoms and neurocognitive impairments are very often present in childhood, predate the full phenotypic expression of schizophrenia, and persist even after the resolution of the florid psychotic symptoms with traditional pharmacological treatment.

2. The genetic component of schizophrenia

A large number of family, twin, and adoption studies of the last 50 years have demonstrated conclusively that the genetic constitution of an individual plays a large role in determining whether he or she will become schizophrenic [35]. Family studies, for example, have demonstrated that an individual's lifetime risk of developing schizophrenia increases exponentially with the degree of relatedness to an affected individual. Specifically, compared with the ~1% risk of the general population, first cousins of schizophrenics have ~2% risk to develop the disease, siblings of schizophrenics have ~9% risk, and someone with both an affected sibling and a parent has ~16% risk [27]. Gene identification, however, has not been forthcoming primarily because the mode of inheritance of the disease is complex [32] and likely involves interaction among multiple genes and environmental factors. Technological advances such as the development of rapid high-throughput genotyping and availability of dense maps of polymorphisms, as well as progress in genetic analytic methods will facilitate the discovery of genes influencing susceptibility to mental disorders, but it will require large-scale data collection efforts to obtain samples of sufficient power for the detection of susceptibility loci of relatively small effect. In that respect, identification of a genetic subtype for a complex disease can provide a valuable shortcut. Identification of such genetic subtypes has been of paramount importance in deciphering the genetic basis of complex diseases such as Alzheimer's and Parkinson's [53,63]. The 22q11 deletion syndrome represents one such genetic subtype of schizophrenia [4].

3. 22q11 microdeletions and schizophrenia

The chromosome 22q11 deletion syndrome (22q11DS) occurs in one of every 6000 births [7]. 22q11DS presents a variable phenotype that can include specific congenital heart defects, thymic hypoplasia, hypocalcemia, velopharyngeal defects, neurodevelopmental delays, cognitive deficits, and/or behavioral abnormalities, coupled with facial dysmorphologies. Frequently occurring subclusters of these symptoms were previously considered to constitute distinct "syndromes" including the DiGeorge syndrome (DGS) characterized by thymic and parathyroid dysplasia or hypoplasia, the conotruncal anomaly face syndrome (CAFS) characterized by congenital heart defects, and the velo-

cardio-facial syndrome (VCFS) characterized by velopharyngeal defects [59]. More recently, profound neurodevelopmental, cognitive, behavioral, and psychiatric symptoms that often times occur in the absence of any major physical anomaly have been recognized. Indeed, a large percentage of 22q11DS children have marked neurodevelopmental abnormalities beginning in infancy, and it is estimated that 25% will develop schizophrenia in adolescence and adulthood.

One of the first clues that psychiatric symptomatology may be associated with this microdeletion was a report of expressionless face, monotonous speech, and flattened affect among children with the microdeletion [25]. In light of the evidence for suggestive linkage for schizophrenia on chromosome 22 (reviewed in Ref. [32]), patients with 22q11DS were evaluated for psychiatric symptoms or disorders. An initial study and a follow-up replication study both estimated that 25–31% of patients with the 22q11 microdeletion met diagnostic criteria for schizophrenia or schizoaffective disorder [55,48]. More importantly, while deletions of the 22q11 locus occur in the general population at a rate of 0.016% [7], they have been found in 0.3–2% of adult schizophrenic patients [3,33] and in 6% of cases with severe early-onset (before the age of 13 years) schizophrenia [68]. Interestingly, among adult patients, the lowest rate (0.3%) has been reported in a case sample from Japan, whereas a sixfold to sevenfold higher rate was described in two independent Caucasian samples [33,70], suggesting that ethnic differences may underlie the 22q11 schizophrenia susceptibility risk.

In all, these studies suggest that the risk of schizophrenia for a patient with a 22q11 microdeletion may be approximately 25–31 times the general population risk of 1% and that the rate of 22q11 microdeletions in schizophrenia, although relatively low, may be approximately 12–80 times the estimated general population rate. This is the first unequivocal association between a chromosomal abnormality and schizophrenia. In addition, several independent studies reported suggestive linkage results in the 22q11 region [6,62,71]. Furthermore, a series of recent studies suggests that schizophrenic patients carrying the 22q11 deletion bear the hallmark neuropsychological and neuroanatomical features of classical schizophrenia [15,16].

4. Molecular genetic analysis of the 22q11 schizophrenia susceptibility locus

The overwhelming majority of the 22q11 deletions (~87%) are 3 Mb in size, while a smaller percentage of them (~8%) involve the same proximal breakpoint but a different distal breakpoint resulting in a smaller 1.5-Mb deletion (Fig. 1a). All deletions are mediated by low copy repeat sequences [20,61]. At least one schizophrenic patient has been described to carry the smaller 22q11 microdeletion [33]; therefore, the "schizophrenia critical region" has been defined as 1.5 Mb (Fig. 1a). The relatively small size of the
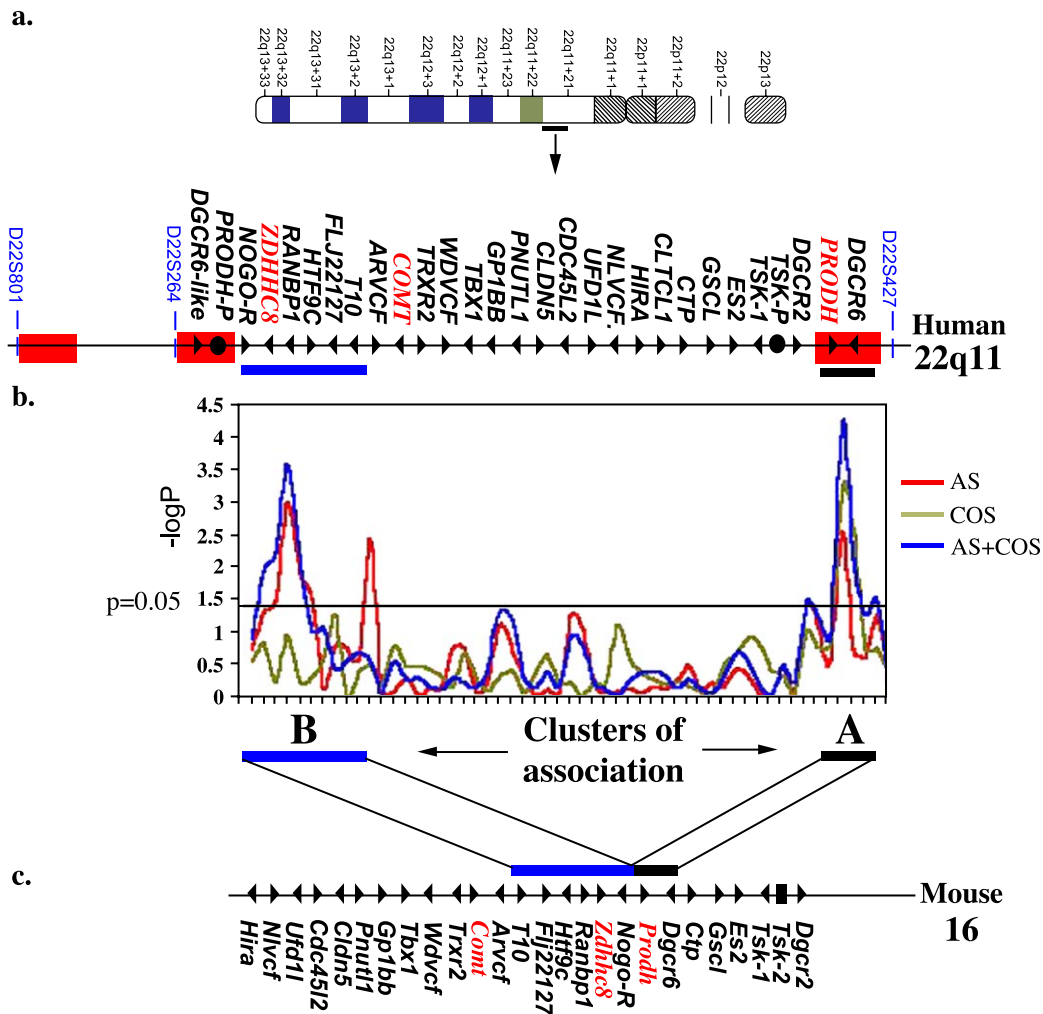
Fig. 1. (a) Map of the human 22q11 locus. Deletions are mediated by low copy repeat (LCR) sequences (illustrated as red boxes). Indicated is the order and transcriptional direction of the known genes between microsatellite markers D22S427 and D22S264. The distance between these markers is ~1.5 Mb and defines the smallest region associated with schizophrenia as shown in previous studies [33]. The distance between markers D22S427 and D22S801 is ~3 Mb. *PRODH-P*, *DGCR6-like*, and *TSK-P* indicate pseudogenes. (b) Haplotypic association *p* values ($-\log_{10}$) across the 22q11 locus [41,40]. Shown are results from two samples: one of adult patients (AS) and one of children (COS) analyzed both separately and as a combined sample. Results from a third replication sample of South African Afrikaner patients are not shown. The two clusters of statistically significant SNP association across the entire 22q11 locus (clusters A and B) are underlined (black and blue bars). Note that although these subregions are located ~1 Mb apart in the human 22q11, visual inspection of their arrangement in the mouse syntenic region on chromosome 16 indicates that they are directly abutted (c). This arrangement might be fortuitous or might signify a need for coordinated regulation of the culprit genes. (c) Mouse synteny. The region of mouse chromosome 16 syntenic to the human interval between markers D22S427 and D22S264 is also shown and is ~1.3 Mb in size.

implicated region is a substantial advantage, if one considers the large regions implicated through linkage studies. The majority of the genes in the region is known (http://genome.ucsc.edu; Fig. 1a), making this locus amenable to molecular genetic analysis.

It seems extremely likely that the 22q11 region harbors genes that alone, or in combination, are causally implicated in schizophrenia. While hemizygous deletion of the approximately 30 genes residing at the 22q11 locus accounts for ~2% of schizophrenia cases, nondeletion variants in one or more individual genes from this locus may make a larger contribution to susceptibility to schizophrenia in the wider population and explain the increased risk for schizophrenia associated with this locus.

This hypothesis would be compatible with the positive linkage findings in the region and with the notion that complex psychiatric disorders are likely to be associated with low penetrance but common, functional variations in a number of susceptibility genes.

5. *PRODH* as a schizophrenia susceptibility gene

Two independent systematic screenings to examine all individual genes in the 22q11 locus in an unbiased manner have taken place [29,40,41]. Two different methodologies were employed: the first screen used a mutational survey of 27 genes in combination with linkage disequilibrium (LD)

studies in family samples (triads) that test for preferential transmission of single nucleotide polymorphisms (SNPs) and multi-SNP haplotypes from parents to affected individuals. A total of 242 schizophrenia patients and their families were examined [40,41]. The second screen searched for genomic rearrangements of 23 genes from the 22q11 locus in 63 unrelated schizophrenic patients and 68 unaffected controls. These authors searched for a small size deletion that would help pinpoint the location of a schizophrenia susceptibility gene from this region [29].

In the SNP-based study of Liu et al. [40,41], two independent peaks of association were identified: one in the proximal end of the locus and one in the distal end of the locus (Fig. 1b), pinpointing the position of two strong candidate schizophrenia susceptibility genes from this region. The proximal peak of association was due to overtransmission of a haplotypic variant of the gene encoding proline dehydrogenase (*PRODH*). The functional consequences of this variant located at the 3′ end of the gene are still unknown. Nevertheless, this finding was recently replicated in two independent family-based samples, including a very large collection of 528 families from China [37], as well as a smaller sample of 93 families from Taiwan [39]. In both cases, the implicated variant is also consistently located at the 3′ end of the gene. Liu et al. [41] also identified rare variants of the gene, affecting highly conserved amino acids (likely generated through gene conversion from the nearby pseudogene) that are enriched to various degrees in samples of individuals with schizophrenia.

The rearrangement screening analysis of Jacquet et al. [29] converged with the aforementioned SNP-based mapping approach of Liu et al. [40,41] identifying in a family with two schizophrenic subjects a heterozygous deletion of the entire *PRODH* gene. This deletion was associated with hyperprolinemia in the two schizophrenic patients. In addition, Jacquet et al. [29] identified the same heterozygous *PRODH* missense mutations described by Liu et al. [41]. Two of them (L441P and L289M) were detected in 3 of 63 schizophrenic patients, but in none of the 68 controls. They were also associated with increased plasma proline levels and segregated with the disease in families. In all, these two independent systematic approaches provided strong support for the *PRODH* gene playing a significant role in schizophrenia susceptibility.

There are at least two ways that decreased activity of PRODH can disturb neuronal function and contribute to schizophrenia susceptibility. First, L-proline itself may serve as a direct modulator of glutamatergic transmission in the brain, a role suggested primarily by the selective expression of a brain-specific high-affinity proline transporter (SLC6A7) in a subset of glutamatergic synapses [23,56] and supported by neurochemical and electrophysiological studies [18,49]. In preliminary in vitro studies, L-proline was shown to modulate aspects of glutamate-dependent synaptic plasticity. Concentrations of proline typical of human CSF (3 μM) have been shown to potentiate trans-

mission at Schaffer collateral–commissural synapses on CA1 pyramidal cells of the rat hippocampus. Proline-induced potentiation far outlasted the period of proline application and required the activation of NMDA receptors. Proline enhanced Schaffer collateral–commissural synaptic transmission, even when the connections between areas CA1 and CA3 had been interrupted. These results suggest that normal levels of endogenous extracellular proline regulate the basal function of some glutamate synapses by maintaining them in a partially potentiated state. Further analysis tested the hypothesis that proline enhances excitatory synaptic transmission by increasing glutamate release. Concentrations of proline normally found in human CSF affect glutamate release very little, indicating that the proline-induced potentiation of Schaffer collateral–commissural synaptic transmission probably involves a postsynaptic, rather than a presynaptic, mechanism. The postsynaptic targets of L-proline still remain largely unknown.

Early studies using dorsal horn neurons grown in culture [28] provided some initial evidence that L-proline is a weak agonist of strychnine-sensitive glycine receptors and both NMDA and non-NMDA glutamate receptors, but further work is necessary to identify unequivocal L-proline targets. It is of interest to note that Chumakov et al. [17], in their recent study on the genetic basis of the 13q32–34 schizophrenia susceptibility locus, both directly and indirectly implicate another amino acid oxidase, namely the D-amino acid oxidase (DAAO). DAAO is expressed in human brain where it oxidizes D-serine, an allosteric activator of NMDA glutamate receptor. Therefore, the studies of Liu et al. [41] and Chumakov et al. [17] are the first to demonstrate genetically an important role for neuromodulatory amino acids in the development of schizophrenia.

Second, recent work by two independent groups using transformed cell lines has implicated *PRODH* in the initiation of apoptosis [19,45]. The gene was identified as a downstream target of the *p53* gene and further analysis directly implicated *PRODH* and the proline/P5C pathway in p53-induced growth suppression and apoptosis. Most importantly, it has been shown that proline oxidation supports the generation of reactive oxygen species (ROS) by donating reducing potential to an electron transport chain. For example, in cells conditionally expressing *PRODH*, the addition of proline increases ROS generation in a concentration-dependent manner. These data suggest that increased proline concentration may trigger an apoptotic death program through oxidative stress, but if and how this property relates to the schizophrenia-associated risk is unknown.

6. *ZDHHC8* as a schizophrenia susceptibility gene

The second segment of association with schizophrenia in the study of Liu et al. [40] lies at the distal part of the 22q11

locus and includes five neighboring SNPs distributed within a haplotypic block of 80 kb and having alleles with nominally significant association results [40]. In the absence of a clear causative variant, LD studies alone could not exclude any of the six genes residing in this haplotypic block. The preponderance of statistical evidence, however, strongly implicated the *ZDHHC8* gene (previously annotated as *KIAA1292*) as the prime candidate from this region. Specifically, every tested variation within the *ZDHHC8* gene unit demonstrated a significant association with schizophrenia in two independent family samples tested. In addition, only *ZDHHC8* SNPs were exclusively present in risk haplotypes from this region [40]. Finally, one of the *ZDHHC8* SNPs, rs175174, located in intron 4, showed the highest significance in all 72 SNPs examined from the entire 22q11 locus (including the SNPs from the *PRODH* gene). Most recently, it was shown that the genotype at SNP rs175174 affects the rate of intron 4 retention of the *ZDHHC8* gene and therefore the ratio of an intron 4-containing unspliced form over the fully spliced form [47]. Specifically, the presence of the risk allele rs175174-A results in the production of relatively higher levels of the unspliced form that is predicted to encode for an inactive truncated protein. This result renders substantial further support that the *ZDHHC8* gene is a schizophrenia susceptibility gene from this locus. The precise effect of this gene on schizophrenia, in general, awaits analysis in additional family samples. However, based on its predicted function as well as on the phenotype of a mouse model for the gene (see below), it is almost certain that *ZDHHC8* contributes to the behavioral deficits associated with the 22q11DS.

ZDHHC8 is predicted to have four transmembrane (TM) domains and a cysteine-rich domain that includes a DHHC motif and a Cys4 zinc finger-like metal binding site. This region is largely part of the loop between adjacent TM2 and TM3. Homology searches identified more than 20 ZDHHC members in the human genome. Similar domains in open reading frames deduced from several species have been previously described. Two yeast ZDHHC proteins, ERF2 and AKR1, are TM palmitoyltransferases [42,57] and it is likely that other members of the family, including ZDHHC8, are also palmitoyltransferases with yet unidentified substrates.

Palmitoylation is a posttranslational modification of proteins with the lipid palmitate. Palmitate is a 16-carbon saturated fatty acid that is attached to proteins posttranslationally. This modification is labile and reversible, and it increases protein hydrophobicity, facilitating protein interactions with lipid bilayers, and influencing protein sorting and function. Recent work (reviewed in Ref. [21]) has shown that palmitate reversibly modifies numerous classes of neuronal proteins, including proteins important for neuronal development, neurotransmitter receptors, and synaptic scaffolding proteins indicating that protein palmitoylation may play an important role in synaptic transmission. The enzymes that mediate the palmitoylation of

cellular proteins remain largely unknown. Whether ZDHHC8 is part of a family of enzymes that mediate the addition and removal of protein palmitate is under investigation. Indeed, one member of this family was recently shown to palmitoylate the gamma2 subunit of GABA(A) receptor [34]. *ZDHHC8* is widely expressed in the adult human brain [47]. Analysis of expression in the adult mouse brain demonstrated higher expression levels in the cortex and hippocampus, areas presumed to play an important role in the pathophysiology of schizophrenia.

In summary, systematic approaches designed to identify schizophrenia susceptibility genes from the 22q11 region have implicated so far the genes encoding *PRODH* [29,41] and *ZDHHC8* [40,47]. Other genes in the 22q11 region have also been implicated primarily by candidate gene approaches, including the gene encoding for catechol-*O*-methyltransferase (COMT) [14,64] (an association signal at the 3′ end of the *COMT* gene was originally described in the study of Liu et al. [41], but it was not reproduced in additional samples). COMT metabolizes released dopamine and variation in COMT activity may have effects specific to the prefrontal cortex. This regionally selective effect of COMT may be because, in contrast to striatum, in the prefrontal cortex, the dopamine transporter is expressed in low abundance and not within synapses. The contribution of COMT, if any, to schizophrenia in general appears to be complex. Both high and low activity of this enzyme may be contributing to the disease risk, depending on the context (i.e., presence of other mutations/variants). In addition, the gene appears to have a functionally complex allelic architecture with some alleles (Val158Met) determining the stability of the protein and others determining the level of expression [10]. One way that COMT deficiency may be contributing to the schizophrenia risk specifically associated with 22q11 microdeletions is discussed below.

7. Mouse models

Mouse models for schizophrenia susceptibility genes are likely to help us understand how these genes contribute to the pathophysiology of schizophrenia. Furthermore, mouse models may help us address potential interactions between these genes. One has to express reasonable skepticism as to how accurately mouse models can capture such a complex human disorder as schizophrenia. It is impossible to model in mice disease manifestations such as auditory and visual hallucinations, paranoia, or delusions. On the other hand, modeling certain endophenotypes, such as sensory gating deficits and cognitive impairments that may contribute to schizophrenia susceptibility, could be particularly useful, especially if the choice of the mouse strains under study is guided by and solely based upon reliable, well-designed human genetic studies.

For example, several studies collectively suggest that prominent sensory gating deficits and cognitive impair-

ments, particularly in attention and executive functions, may contribute to schizophrenia susceptibility. These phenotypic indicators (endophenotypes) probably reflect discrete components of pathophysiological processes, mediating between particular sets of predisposing genes and clinical diagnosis. They are often present in childhood, predating the full phenotypic expression of the disease; and are also evident in clinically unaffected, first-degree relatives of schizophrenic patients. Most notable examples of schizophrenia-related endophenotypes are sensorimotor gating, working memory, and attention, all of which can be modeled relatively accurately in mice.

Sensorimotor gating refers to the forebrain influence on the automatic brainstem startle response [9]. It is usually evaluated from the degree of inhibition of the startle response by an acoustic prepulse. The prepulse tone precedes by 100 ms a much stronger, abrupt acoustic startling stimulus (prepulse inhibition, or PPI). Sensorimotor gating is a major central processing mechanism that is affected in many patients with schizophrenia and some of their first-degree, clinically unaffected relatives. It should be noted that PPI deficits are not specific to schizophrenia, but are present in other disorders characterized symptomatically by a loss of gating in sensory, motor, or cognitive domains (such as Obsessive compulsive disorder, Huntington's disease, nocturnal enuresis and attention deficit disorder, Tourette syndrome, and nonepileptic seizures) (reviewed in Ref. [9]). One largely untested hypothesis is that deficits in sensorimotor gating are related to the inability of schizophrenic patients to automatically filter or "gate" irrelevant thoughts and sensory stimuli from intruding into conscious awareness [8,52]. Mice demonstrate a robust and reliable PPI [50]. Indeed, one of the most attractive features of PPI is that it is one of a few neuropsychological measures in which humans and rodents can be evaluated in a similar fashion.

Working memory and attention are characteristically impaired in patients with schizophrenia, irrespective of their level of intelligence [12,22]. Deficits in tests probing working memory and attention have been observed in patients during both active and remitted phases of illness and both before and during treatment with antipsychotic drugs, as well as in a portion of their nonschizophrenic, first-degree relatives [11,12,58]. Therefore, problems in these cognitive domains seem to be at the very core of the dysfunction in this disease [26]. Working memory can be assessed with at least two different assays that require memory retention over brief delays, the Delayed Alternation Task [67] and the Latent Inhibition (LI) Assay [69]. Disruption of LI has been proposed as a possible model of the cognitive abnormality that underlies the psychotic symptoms of acute schizophrenia [31,44].

More importantly than behavior-based analytical assays, mouse models can afford us the possibility to conduct a thorough and detailed evaluation of cellular and molecular neuropathology, which is either off-limits or confounded by drug treatment in humans. For example, one can use a reliable genetic mouse model to study gray matter reduction; to assess the number of neurons, neuronal apoptosis, dendritic and synaptic morphology, and physiology; as well as to evaluate the status of the myelinated white matter and measure the total brain content of selected neurotransmitters. Moreover, mouse models also afford us the possibility to quantify brain mRNA transcripts using microarray technology [13,38,43]. This methodology can lead to identification of changes in gene expression in response to the specific gene disruptions carried by the mouse models. Such analysis can allow identification of individual genes, gene pathways, and cellular processes that either serve as direct targets, or interact with the disrupted pathways, to increase susceptibility to schizophrenia.

The robust association between a well-defined genetic lesion (22q11 microdeletion) and a dramatic increase in the risk to develop schizophrenia, coupled with our precise knowledge of the human/mouse sequence and chromosomal synteny at this locus (Fig. 1a and c), presents a unique opportunity to use a mouse model to understand the biological basis of the increased psychosis risk associated with this genetic lesion. Because more than one gene from this region seems to be contributing to the ~30-fold increase in risk, a mouse model of the entire schizophrenia-associated microdeletion is likely to capture the interactions among the culprit genes and therefore be a relatively accurate model of the disease.

8. Long-range deletion models

The syntenic region of the human 22q11 locus lies on mouse chromosome 16. All human genes (except for one) are represented in the mouse, although the order of the genes is different (Fig. 1a and c; Ref. [54]). We and others (Ref. [51]; Stark et al., unpublished) have modeled the 22q11 deletion in the mouse using gene targeting and chromosomal engineering approaches [46]. Initial ascertainment of the deleted mice assessed different domains of central nervous system functioning using tests such as PPI and the Pavlovian conditioned fear test, which assesses learning and memory. Additionally, simple tests of sensory/motor function, exploratory activity, anxiety-related traits, and analgesia-related responses were evaluated. Mice carrying long-range deletions showed deficits in sensorimotor gating, as well as in learning and memory. Indeed, the response of these mice in the Pavlovian conditioned fear test suggests that they have difficulty remembering the types of cues associated with a complex training environment for long (24 h), but not short (1 h), periods. Deleted mice successfully learn and remember that a single auditory cue was paired with a footshock, suggesting that the conditioned fear impairment is selective and similar in nature to deficits observed in rodents with hippocampal damage [36,1].

The finding of learning and sensorimotor gating deficits is particularly significant because premorbid children with 22q11DS show similar deficits. Children with 22q11 deletions demonstrate problems with complex forms of learning that require problem solving, planning, and abstract thinking [5,72]. In addition, an ongoing longitudinal study of 22q11DS children and their healthy siblings, where, among others, paradigms for PPI are administered annually, revealed severe deficits in this domain. Specifically, as compared to sibling controls, children with 22q11DS showed 20% less PPI; secondary analyses suggested that this decrement did not reflect developmental delay [65]. Interestingly, in the same longitudinal study, comparison of the Attention Network Tests (ANT) index scores showed that children with 22q11DS had less efficient scores on measures of executive attention, indicating less efficient processing in uncued conditions [66]. In light of these findings, it would be interesting to examine working memory and attention indices in the long-range deletion mouse model.

9. Individual candidate gene models

Mouse models for individual candidate genes from this region are also likely to facilitate understanding of the function of these genes and how they may impact on schizophrenia. A mutation introducing a premature termination (E453X) and reducing enzymatic activity in the mouse orthologue of the human *PRODH* gene in the Pro/Re hyperprolinemic mouse strain has been previously described [24]. Measurements of serum and brain proline levels revealed an increase in L-proline levels in mice homozygous for this mutation. Levels of L-proline in the homozygous mutant mice range from 300 to 600 μmol/l (compared to less than 100 μmol/l in wild-type littermate control mice). These levels are comparable to those observed in some individuals with the 22q11 microdeletion or in heterozygous carriers of *PRODH* rare variants, but are well below the levels observed in patients with hyperprolinemia type I—a rare condition often accompanied by epilepsy and mental retardation [30]. Therefore, both in terms of the nature of the mutation and the ensuing increases in L-proline levels, this mutant strain represents an accurate model not only of a susceptibility gene but also of a susceptibility allele.

Prodh-deficient mice have regional neurochemical alterations in the brain accompanied by a deficit in sensorimotor gating [24]. Interestingly, the amount by which PPI is reduced in mutant versus wild-type animals is greater in mice that carry long-range deletions (~15% reduction) than in the *Prodh* mutants (~8% reduction) [51,24] at similar startle/prepulse sound levels. However, mice carrying long-range deletions as originally described have normal serum proline levels [51], suggesting that: (a) they are incomplete models of the schizophrenia-associated genetic lesion, and (b) reduced dosage of other gene(s) in the region results in sensorimotor gating deficits (one caveat with this interpre-

tation is that the more relevant brain L-proline levels have not been reported for the long-range deletion mice).

Transcriptional profiling in the brain of a mouse model for a schizophrenia susceptibility allele might provide an unbiased evaluation of the transcriptional programs affected by the disruption of the gene, reflecting either downstream effects of the mutation or compensatory changes. Initial small-scale transcriptional profiling in the cortex of *Prodh*-deficient mice identified fewer than 10 genes as being differentially expressed (Paterlini et al., unpublished). Most notably, the list of upregulated genes included the *COMT* gene, which also maps within the 22q11 locus and is a candidate schizophrenia susceptibility gene. Follow-up behavioral analysis of these mice revealed a pronounced hyperresponsivity to dopamine, which is unmasked under challenge with amphetamine and is modulated by the level of COMT activity. In that respect, it is worth noting that dopaminergic hypersensitivity in schizophrenia is well established based primarily on the therapeutic effect of dopamine receptor antagonists [60]. Therefore, the transcriptional profiling analysis revealed a previously unsuspected interaction between *PRODH* and *COMT* that can, in principle, modulate the risk and/or the expression of the 22q11-associated psychiatric phenotypes. If, indeed, *COMT* upregulation is one of the mechanisms employed to control cortical dopaminergic hypersensitivity, then schizophrenic patients with a 22q11 deletion are at a particular disadvantage because they are deficient for both genes and perhaps unable to compensate efficiently through *COMT* for the cortical dopaminergic hyperactivity induced by *PRODH* deficiency.

A knockout mouse model for the *Zdhhc8* gene was also recently described [47]. Knockout mice had normal gross brain morphology but presented dosage-dependent behavioral deficits. Specifically, female homozygous mutant mice were found to have significantly lower levels of PPI compared to wild-type littermate controls, as well as profound deficits in indices of fearfulness. Interestingly, homozygous mutant mice also appeared to be somewhat less sensitive to stimulation of locomotor activity induced by the psychomimetic dizocilpine (MK801), suggesting that *ZDHHC8* is affecting behavior at least partly through interference with glutamatergic transmission [47]. This is supported by recent studies indicating that ZDHHC8 may be a palmitoyltransferase for key glutamate signaling molecules (Mukai and Gogos, unpublished). Further behavioral studies modeling additional schizophrenia endophenotypes, as well as neurochemical and gene profiling analysis of *Zdhhc8*-deficient mice, will be necessary to address whether and how deficiency of *ZDHHC8* fits into the emerging picture of genetic interactions outlined above.

10. Conclusion

In all, both genetic association and animal model studies imply that the 22q11-associated schizophrenia may have

the characteristics of a contiguous gene syndrome: deficiency in more than one gene contributes both by impairing synaptic function and by failing to compensate for such impairment. Such synergistic interaction among two physically linked genes, which disrupts neuronal homeostatic plasticity, could in principle lead to the high disease risk associated with this locus and/or modulate the expression of the phenotype.

During the past 2 years, an increasing number of variants in individual genes were identified as contributing to schizophrenia susceptibility. However, in every case: (a) the increase of the risk associated with each variant is small (twofold at most), and, (b) in most cases, the effect of the variant on the expression and function of the gene is unknown. This immensely complicates efforts to generate disease-related mouse models of these susceptibility genes. The deleted region on the long arm of chromosome 22 is an obvious exception. In-depth studies of 22q11DS will allow investigators to answer critical questions relating to the devastating illness of schizophrenia, whose causes remain largely unknown. The identification and functional analysis of genes from this locus contributing to schizophrenia will undoubtedly lead to the design of highly effective targeted treatments, which will have fewer side effects and therefore increased patient compliance and more positive long-term disease outcomes.

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