

# Development of animal models for schizophrenia

P. Alexander Arguello<sup>1,\*</sup>, Sander Markx<sup>2,\*</sup>, Joseph A. Gogos<sup>1,3</sup> and Maria Karayiorgou<sup>2,‡</sup>

Schizophrenia is a devastating psychiatric disorder that affects around 1% of the population worldwide. The disease is characterized by 'positive symptoms', 'negative symptoms' and cognitive deficits. Over the last 60 years, a large number of family, twin and adoption studies have clearly demonstrated a strong genetic component for schizophrenia, but the mode of inheritance of the disease is complex and, in all likelihood, involves contribution from multiple genes in conjunction with environmental and stochastic factors. Recently, several genome-wide scans have demonstrated that rare alleles contribute significantly to schizophrenia risk. Assessments of rare variants have identified specific and probably causative, disease-associated structural mutations or copy number variants (CNVs, which result from genomic gains or losses). The fact that the effects of such lesions are transparent allows the generation of etiologically valid animal models and the opportunity to explore the molecular, cellular and circuit-level abnormalities underlying the expression of psychopathology. To date, the most common genomic structural rearrangements that are unequivocally associated with the development of schizophrenia, are de novo microdeletions of the 22q11.2 locus. Fortunately, the human 22q11.2 locus is conserved within the syntenic region of mouse chromosome 16, which harbors nearly all orthologues of the human genes. This has made it possible to engineer genetically faithful, and thus etiologically valid, animal models of this schizophrenia susceptibility locus.

## Schizophrenia: a clinical overview

Schizophrenia is a severe psychiatric disorder that has a lifetime prevalence of around 1% in most of the populations studied (Karayiorgou and Gogos, 1997), and which has been estimated to be the seventh most costly medical illness to our society (Freedman, 2003). Although patients with schizophrenia can present with several clinical abnormalities, including structural brain pathology (e.g. enlarged third and fourth ventricles; reduced volume of cortical gray matter) and neuropsychological impairments (e.g. deficits in working memory) (Lewis and Lieberman, 2000), none of these are consistently present in all patients who suffer from this disease. Because of the absence of any consistent diagnostic biological markers that exist, for example, for

neurodegenerative disorders, such as Alzheimer's disease or Parkinson's disease, schizophrenia is defined as a clinical syndrome. The disease is characterized by 'positive symptoms' including hallucinations, delusions and thought disorders; 'negative symptoms' such as blunted emotions, poverty of speech, avolition and asociality; and cognitive deficits including impairments in attention, executive function and working memory. Although assessment of cognitive symptoms can predict functional outcome, only the positive and negative symptom domains are captured by operational definitions in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000). However, as a heterogeneous syndrome, schizophrenia lacks any single defining symptom or sign, and no bio-

chemical or physiological test is available for the disorder (Karayiorgou and Gogos, 1997). Furthermore, there is a considerable overlap of diagnostic categories; for example, positive symptoms can be part of at least three different diagnoses – schizophrenia, bipolar disorder and psychotic depression. Although these diagnoses are highly reproducible and clinically useful, they do not necessarily reflect valid, separate constructs on a genetic level. Epidemiological studies indicate a complex pattern of high heritability that interacts with epigenetic, stochastic and environmental factors. Although some genetic variants appear to increase the risk across several diagnostic entities, others only influence the risk for a subset of conditions (i.e. endophenotypes or intermediate phenotypes) (Burmeister et al., 2008). It appears likely that when sufficient, replicated genetic findings have become established, they will reshape the way in which schizophrenia is clinically conceptualized. From a treatment standpoint, antipsychotics target some of the symptoms that patients with schizophrenia suffer from, but often with suboptimal results, and many patients develop side effects that cause them to become non-compliant with their medication (Lieberman et al., 2005). Furthermore, except for possibly clozapine, none of the treatment modalities appear to be effective for the negative symptoms, which to a large extent determine functional outcome for many of the patients (Webber and Marder, 2008). This all points to the imperative need for a better understanding of the pathogenesis of schizophrenia, so that more optimal medications can be developed on the basis of hypothesis-driven research.

## Genetic architecture of schizophrenia

Schizophrenia, like other common psychiatric and non-psychiatric diseases, is multifactorial in nature with contributions from multiple susceptibility genes in conjunction with epigenetic, stochastic and

<sup>1</sup>Departments of Neuroscience, <sup>2</sup>Psychiatry, and <sup>3</sup>Physiology and Cellular Biophysics, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

\*These authors contributed equally to this work

‡Author for correspondence (mk2758@columbia.edu)

### Case study

V.C. is a 24-year-old, previously healthy man, who was brought to the psychiatric emergency room (ER) by his father because he was convinced that he could hear the voice of demons at night, telling him that they were planning to hurt him. During the previous year, V.C. had become increasingly withdrawn and had stopped going out with friends and family. In addition, V.C. started paying less attention to his personal hygiene and his parents noticed that he was becoming increasingly paranoid. His father reported that, 5 months ago, V.C. started talking about being followed in the street and that he felt that people were watching him through hidden cameras in his apartment. During the 3 months leading up to his presentation in the ER, V.C. also noticed that people on television and on magazine covers were looking at him directly and were talking to him. Moreover, V.C. mentioned to his family that he felt that he could read other people's thoughts. His father reported that V.C.'s maternal uncle also has a history of paranoia and hearing voices. In the ER, V.C. appeared disheveled and was noticeably suspicious towards the medical staff. V.C. endorsed hearing voices of demons and acknowledged that he felt that cameras in the apartment were watching him. Furthermore, he denied any medical history or a history of substance use, and was not receiving any medication. V.C. also denied any symptoms that were indicative of depression, hypomania or mania. Laboratory results all came back negative and a computed tomography (CT) scan of his head revealed no abnormalities. The patient was admitted to an inpatient psychiatric unit, where he was started on 2.5 mg of aripiprazole. His dosage was gradually increased to 10 mg and, over the course of a 4-week period, his symptoms gradually decreased. By the time of discharge, V.C. was no longer hearing voices and was no longer experiencing paranoid ideas. When asked about his previous ideas of being watched and followed, he stated that he still believed that people might be out to hurt him, but no longer appeared preoccupied by this.

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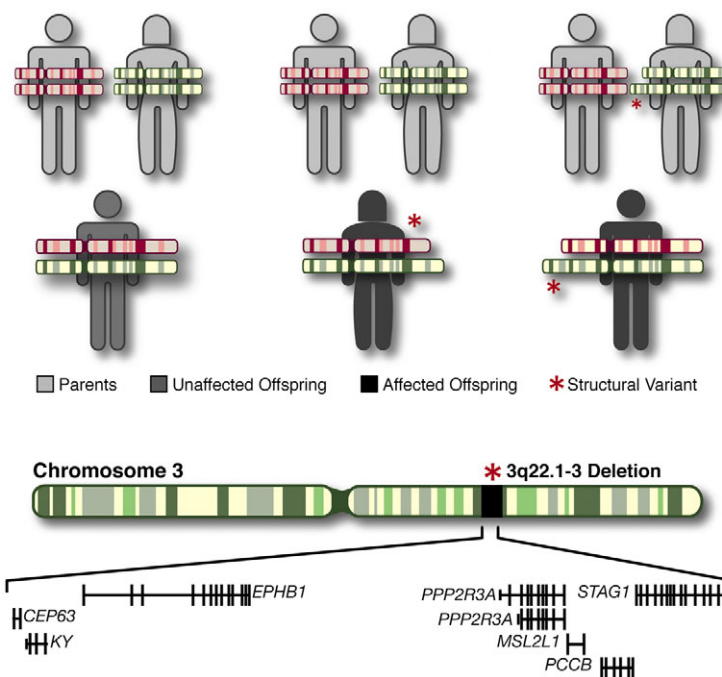
environmental factors (Karayiorgou and Gogos, 1997). The genetic architecture underlying disease susceptibility is characterized by both the frequency and penetrance of risk alleles. The common disease-common allele (CDCA) hypothesis emphasizes the importance of relatively common alleles, each with a small effect, acting together to increase disease risk. The common disease-rare allele (CDRA) hypothesis instead emphasizes the impact of individually rare, yet highly penetrant, alleles. It is likely that both common and rare alleles contribute to the risk of psychiatric disorders. Although the relative impact of each remains unknown, recent studies have provided strong evidence supporting the importance of rare structural mutations/variants in schizophrenia vulnerability.

In particular, recent rapid developments in microarray technologies have led to the discovery of extensive copy number variation (CNV) in the human genome (Lafrate et al., 2004; Sebat et al., 2004) and allow for extensive analysis of the association between such structural genetic variants and complex diseases, like schizophrenia. CNVs are segments of DNA of varying size for which copy number differences have been established by a comparison of two or more genomes (Feuk et al., 2006), and which often encompass one or more genes (Redon et al., 2006). CNVs can be either de novo (formed in the parental germline) or inher-

ited from an affected or unaffected parent (Fig. 1). It has been demonstrated that rare structural mutations leading to an altered copy number of dosage-sensitive genes can lead to the development of neuropsychiatric disorders, such as autism and schizophrenia (Lee and Lupski, 2006; Beckmann et al.,

2007). Recently, several large-scale genome-wide scans have successfully identified several schizophrenia-associated CNVs, including a number of recurrent variants (Table 1), which appear to be rare but, typically, highly penetrant (Xu et al., 2008; Xu et al., 2009; International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Walsh et al., 2008).

Of all the CNVs, the most extensively studied are the de novo 22q11.2 microdeletions. (Karayiorgou et al., 1995). 22q11.2 microdeletions are relatively common and are associated with a high schizophrenia risk, approximately 25-31 times that of the general population (Pulver et al., 1994; Murphy et al., 1999). Conversely, 22q11.2 microdeletions account for up to 1-2% of nonfamilial (sporadic) cases of schizophrenia (Karayiorgou et al., 1995; Xu et al., 2008). This strong bidirectional association remains to be demonstrated for other potentially pathogenic CNVs (such as the ones shown in Table 1). Thus, to date, microdeletions of 22q11.2 are the only known recurrent CNVs that are unequivocally associated with schizophrenia, and therefore make the mouse model of this CNV an attractive approach to study the disease.



**Fig. 1. Structural mutations (CNVs) and their mode of inheritance.** Top panel: structural mutations can be either de novo (generated in the parental germline) (middle) or inherited from affected or unaffected parents (right). Bottom panel: a typical CNV (microdeletion) including several genes identified in the Xu et al. study (Xu et al., 2008).

**Creating valid models for schizophrenia in mice**

Models are approximations of phenomena of interest that are more tractable for experimental investigation. To be useful, animal models of psychiatric disorders need not fully recapitulate the disease, which, given the human uniqueness of these disorders, is actually impossible. In creating mice models of schizophrenia, two main factors must be considered: the genetic and clinical data upon which the model is based, and the methods for characterizing the model (Arguello and Gogos, 2006).

The search for genetic variants that influence complex traits, such as the risk for psychiatric disorders, is often plagued with inconsistent findings and equivocal reports (Shi et al., 2009; Stefansson et al., 2009). In that respect, rare variants offer important advantages in terms of modeling in mice compared with more common and less penetrant variants. Importantly, the potential insight into disease etiology gained from rare variants is greater because their statistical association is more consistent and their functional effects are more transparent. This enables models that faithfully recapitulate the disease-associated allele to be engineered genetically. This genetic fidelity is essential because any given gene product can participate in numerous biological pathways, and modeling the exact risk allele is more likely to affect those pathways that are relevant to disease pathogenesis. Ultimately, a comparison of models of different rare alleles holds the most promise for identifying disease mechanisms. One example of this is the balanced translocation affecting the *DISC1* gene that was found in a large Scottish pedigree affected with high rates of psychiatric illness, which was subsequently modeled in mice (Koike et al., 2006).

**Clinical terms**

**Endophenotype or intermediate phenotype** – a biomarker of an illness that is heritable and found to co-segregate with family members of subjects with the illness

**Copy number variation (CNV)** – segments of DNA of varying size for which copy number differences have been established by a comparison of two or more genomes

**Microdeletion** – a CNV where a segment of DNA is deleted

**Hypomania** – a clinical psychiatric state, where patients experience moderately severe symptoms of decreased need for sleep, increased goal-directed activity, flight of ideas, pressure to keep talking, grandiosity, and increased involvement in high-risk behaviors

**Mania** – a clinical psychiatric state, where patients experience severe symptoms of decreased need for sleep, increased goal-directed activity, flight of ideas, pressure to keep talking, grandiosity, and increased involvement in high-risk behaviors

Another case in point is the 22q11.2 microdeletion, which we discuss further below. Nearly all human orthologous genes are located in the syntenic region of mouse chromosome 16, which allowed the generation of a mouse allele with high fidelity to the disease-associated human allele using the Cre/lox technology (Fig. 2).

**Phenotyping animal models**

A considerable body of evidence from neuropathological, imaging and genetic studies indicate that schizophrenia pathology exists at a molecular, cellular and neuronal circuit level, and that mouse models should be designed in accordance with this. Thus, despite its complexity, schizophrenia can be deconstructed into these individual phenotypic components that can then be analyzed in animal models (Arguello and Gogos,

**Clinical and basic research opportunities**

- Identification of consistent biological markers that can be used to diagnose schizophrenia
- Determination of the relative contributions of genes, epigenetic, stochastic and environmental factors that influence a person’s susceptibility to schizophrenia
- Genetically engineered mouse models that recapitulate the genetic attributes of human disease: mice with rare genetic variant forms of disease that can be used to uncover new potential targets for therapy

2006). Clearly, the psychotic features of schizophrenia, such as the auditory hallucinations and delusions, are challenging, if not impossible, to measure in animal models. Nevertheless, hyperactivity in response to stress or novelty, as well as hypersensitivity to psychostimulants, have been suggested as potentially useful correlates that can be modeled in rodents. However, the basic foundations of perception, attention and memory are present in mice and these can, unlike thought content, be readily measured through objective behavioral tests. In particular, the ability to accurately characterize cognitive function is crucial given that cognitive deficits are more enduring, more predictive of functional outcome, and less responsive to treatment than other symptoms. Furthermore, precise tests of cognitive operations can identify specific underlying neural circuits and processes that can then be more finely characterized at molecular and cellular levels. It is likely that evaluating cognition in animal models will not only lead to a better understanding of disease mechanisms but will also aid in the discovery of novel targets for therapeutic intervention.

**Table 1. Recurrent CNVs enriched in schizophrenia cohorts**

CNV locus	Size	References
1q21.1	>1 Mb Del	ISC, 2008; Stefansson et al., 2008
2p16.3	18-420 kb Del/Dup	Rujescu et al., 2009
15q11.2	470 kb Del	Stefansson et al., 2008
15q13.3	~1.5 Mb Del	ISC, 2008; Stefansson et al., 2008
16p11.2	600 kb Dup	McCarthy et al., 2009
17p12	~1.4 Mb Del	Kirov et al., 2009
22q11.2*	3 Mb Del (~90% of cases) 1.5 Mb Del (<10% of cases) Smaller atypical deletions	Karayorgou et al., 1995; Xu et al., 2008; ISC, 2008; Stefansson et al., 2008

\*Bidirectional association; deletion carriers have a high schizophrenia risk, ~25-31 times that of the general population. Del, deletion; Dup, duplication; ISC, International Schizophrenia Consortium.

There are diverse behavioral paradigms for assessing cognition in models. Memory systems in animals, like in humans, are organized across the temporal domain with both short and long forms. Conditioned fear is a type of long-term memory (LTM) that is critically dependent on the hippocampus and amygdala. Mice with a hemizygous deletion spanning all (*Df(16)A<sup>+/-</sup>*) (Stark et al., 2008), or part (*Df1/+*) (Paylor et al., 2001), of the orthologous genes within the 1.5-Mb region exhibit impaired conditioned fear. Working memory (WM) is a special case of short-term memory and is more labile and transient than LTM. It depends on the orchestration of neural activity across

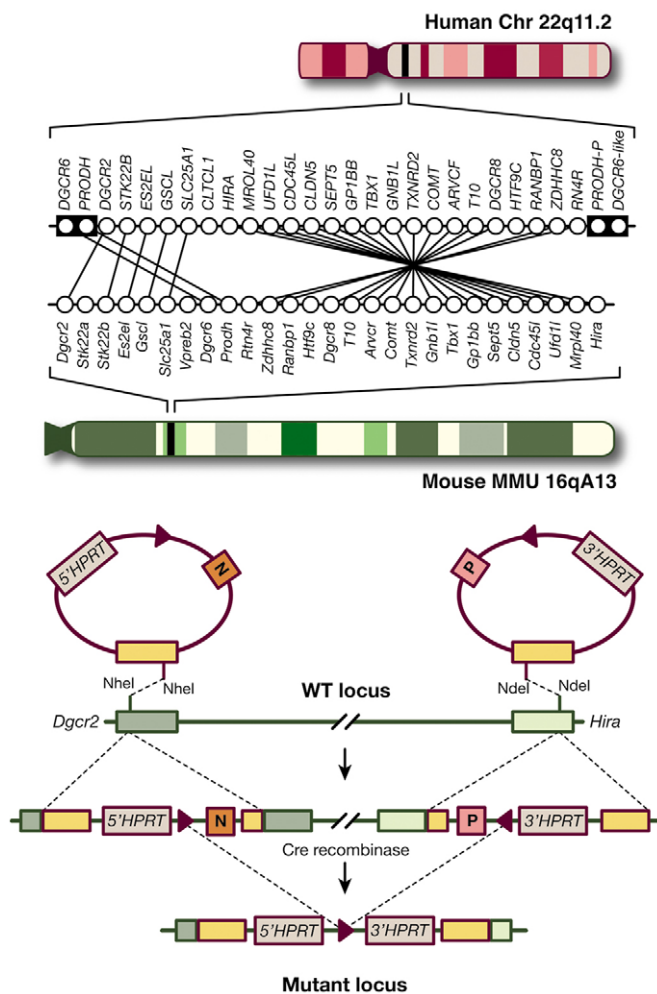
brain regions by the prefrontal cortex. Mice that are hemizygous for the orthologous 22q11.2 deletion seem to have deficits in WM in addition to the LTM deficits described above. These mice are impaired in the acquisition of a task requiring them to alternate between arms in a maze following a brief delay. Interestingly, this deficit arises in part from a deficiency of one gene within the deletion, *Dgcr8*, a microRNA processor that, when absent, causes changes in microRNA levels and impairs dendritic development; heterozygous deletion of just *Dgcr8* impairs acquisition of a similar WM task (Stark et al., 2008). The combined reduction in the levels of two other 22q11.2

genes, catechol-*O*-methyltransferase (*Comt*, encoding an intracellular enzyme that plays a significant role in modulating dopamine clearance in the cortex) and proline dehydrogenase (*Prodh*, encoding an enzyme that metabolizes the neuromodulator L-proline), and their epistatic interaction in modulating cortical dopaminergic transmission, also contributes to the WM deficits that emerge as a result of the 22q11.2 microdeletion (Paterlini et al., 2005). Taken together, this suggests that behavioral deficits associated with the 22q11.2 microdeletion result from the combined effects of genes acting individually and interactively. A promising area of future research is investigating how these cognitive deficits are related to the changes in dendritic complexity, excitatory synapses and dopamine transmission that are found in *Df(A)* deletion mice (Mukai et al., 2008; Paterlini et al., 2005; Stark et al., 2008).

Other groups have shown that several genes within the 1.5-Mb region differentially affect pre-pulse inhibition (PPI), a measure of pre-attentive processing where a brief, low intensity acoustic stimulus (the 'pre-pulse') inhibits the startle reflex caused by a loud stimulus (Powell et al., 2009). PPI is affected in a number of patients with schizophrenia and other psychiatric diseases (Powell et al., 2009). Although PPI is not diagnostically specific or predictive of clinical outcome, it is a relatively robust and widely used assay in phenotyping animal models of schizophrenia, and can be administered to animals in a fashion almost identical to humans. A heterozygous deficiency in a subset of 22q11.2 genes (*Gnb1l*, *Dgcr8* and *Tbx1*) has been shown to result in reduced PPI levels (Long et al., 2006; Paylor et al., 2006; Stark et al., 2008). Notably, an engineered mouse strain that is deficient for seven other genes spanning around 150 kb of the 1.5-Mb deletion syntenic region (Kimber et al., 1999) has an increased PPI, suggesting that other genes within this region have opposing influences and that PPI deficits emerging as a result of the 22q11.2 microdeletion are the result of interplay between both positive and negative contributions from genes residing in this locus.

### Schizophrenia: future directions

Advances in understanding the causes and treatment for schizophrenia require the integration of human genetic findings and



**Fig. 2. Modeling structural mutations in mice.** Top panel: schematic diagram showing the human chromosome 22q11.2 region and the syntenic mouse region. Almost all of the functional human genes in this segment are represented in the mouse, organized in a slightly different order. The minimal 1.5 Mb deletion is mediated by the low copy repeat sequences LCR-A and LCR-B (illustrated as black boxes in the human chromosome). *PRODH-P* and *DGCR6-like* (also known as *DGCR6L*) indicate pseudogenes. *Dgcr2* and *Hira* are the two end points of the depicted targeted deletion generated in mouse chromosome 16. Bottom panel: Cre-induced recombination between *loxP* sites in cis leads to the generation of a functional HPRT minigene and a 1.3-Mb deficiency in mice.

animal models. As the resolution and efficiency for identifying structural mutations or other types of rare mutations increases, and as disease phenotypes are better defined, more advanced mouse models will lead to a better understanding of this complex disease.

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#### COMPETING INTERESTS

The authors declare no competing financial interests.

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