Biological Psychiatry: Celebrating 50 Years

Can Animal Models of Copy Number Variants That Predispose to Schizophrenia Elucidate Underlying Biology?

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ABSTRACT

The diagnosis of schizophrenia rests on clinical criteria that cannot be assessed in animal models. Together with absence of a clear underlying pathology and understanding of what causes schizophrenia, this has hindered development of informative animal models. However, recent large-scale genomic studies have identified copy number variants (CNVs) that confer high risk of schizophrenia and have opened a new avenue for generation of relevant animal models. Eight recurrent CNVs have reproducibly been shown to increase the risk of schizophrenia by severalfold: 22q11.2(del), 15q13.3(del), 1q21(del), 1q21(dup), NRXN1(del), 3q29(del), 7q11.23(dup), and 16p11.2(dup). Five of these CNVs have been modeled in animals, mainly mice, but also rats, flies, and zebrafish, and have been shown to recapitulate behavioral and electrophysiological aspects of schizophrenia. Here, we provide an overview of the schizophrenia-related phenotypes found in animal models of schizophrenia high-risk CNVs. We also discuss strengths and limitations of the CNV models, and how they can advance our biological understanding of mechanisms that can lead to schizophrenia and can be used to develop new and better treatments for schizophrenia.

Keywords: CNV, Copy number variant, Genetic animal model, Genetics, Schizophrenia, Schizophrenia-related phenotype

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Schizophrenia patients suffer from positive symptoms, disorganized symptoms, delusions, negative symptoms, and impaired cognition (1–3). Positive symptoms include hallucinations and paranoia, whereas negative symptoms include social withdrawal and avolition (1–3). Despite substantial research efforts, there has been limited progress in understanding the pathophysiology of the disorder and in developing better treatments. One of the main reasons for the limited progress has arguably been the lack of good animal models (4). The heritability of schizophrenia has been estimated to be around 80% (1). However, the genetic architecture of the disorder is highly complex, and 145 independent loci have been significantly associated with schizophrenia in genome-wide association studies of common single nucleotide polymorphisms (SNPs) (5). Individually, each variant has very limited effect size, with odds ratios (ORs) below 1.2. Moreover, most of the variants are in noncoding regions, having only indirect effects on protein expression and splicing, making it less evident what variant to introduce in an animal model.

Another important component of the genetic architecture of schizophrenia is copy number variants (CNVs), i.e., deletions and duplications of chromosomal regions (6). Contrary to common low-risk SNPs, the schizophrenia-associated CNVs are rare and generally confer high risk of disease (OR, 3–58). Eight CNVs have been clearly associated with schizophrenia, and 2.5% to 5% of patients carry at least one of these (7–15) (Table 1). Importantly, common low-risk SNPs as well as rare high-risk CNVs have pleiotropic effects also conferring risk of other neuropsychiatric disorders (16,17) (Table 1).

Five of these schizophrenia-associated CNVs have been modeled in mice, rats, flies, and fish (Figure 1 and Table 2). Some of these models have previously been reviewed with a focus on autism-related phenotypes (18,19). Here, we focus on schizophrenia-related phenotypes, such as cognitive impairment, sensorimotor gating, and phenotypes possibly related to negative and positive symptoms, in animal models of CNVs associated with schizophrenia. Findings are summarized in Table 2.

CLINICAL MANIFESTATIONS

CNVs associated with schizophrenia also carry increased risk for neurodevelopmental disorders such as autism spectrum disorder, developmental delay, intellectual disability, epilepsy, and attention-deficit/hyperactivity disorder (14,20,21). Particularly, the overlap with intellectual disability and autism is pronounced, as all schizophrenia-associated CNVs predispose to these conditions (Table 1). Furthermore, many carriers of these CNVs have dysmorphic

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Table 1. Genetic and Clinical Overview

CNV	Position in Mb	Number of Protein-Coding Genes	RefSeq Gene Names	miRNAs	SCZ Odds Ratio	Neuropsychiatric Disorders	Reference(s)
1q21.1 del	chr1:146,57–147,39	8	*PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*	NA	8	ASD, ADHD, E/S, DD/ID, A	(25)
1q21.1 dup	chr1:146,57–147,39	8	*PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*	NA	3	ASD, ADHD, DD/ID, A	(25)
NRXN1 del	chr2:50,15–51,26	1	*NRXN1*	NA	9	ASD, E/S, DD/ID	(108,109)
3q29 del	chr3:195,75–197,36	21	*TFRC*, *ZDHH19*, *SLC51A*, *PCYT1A*, *TCTEX1D2*, *TM4SF19*, *UBXN7*, *RNF168*, *SMCO1*, *WDR53*, *FBXO45*, *NRROS*, *CEP19*, *PIGX*, *PAK2*, *SENP5*, *NCBP2*, *PIGZ*, *MELTF*, *DLG1*, *BDH1*	MIR4797	58	ASD, E/S, DD/ID, A, BD, D	(26)
7q11.23 dup	chr7:72,74–74,14	23	*TRIM50*, *FKBP6*, *FZD9*, *BAZ1B*, *BCL7B*, *MLXIPL*, *VPS37D*, *DNAJC30*, *WBSCR22*, *STX1A*, *ABHD11*, *CLDN3*, *CLDN4*, *WBSCR27*, *WBSCR28*, *ELN*, *LIMK1*, *EIF4H*, *LAT2*, *RFC2*, *CLIP2*, *GTF2IRD1*, *GTF1I*	MIR590	11	ASD, ADHD, E/S, DD/ID, A	(22,110–112)
15q13.3 del	chr15:31,13–32,48	6	*FAN1*, *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A*, *CHRNA7*	MIR211	8	ASD, ADHD, E/S, DD/ID	(113)
16p11.2 dup	chr16:29,65–30,20	26	*SPN*, *QPRT*, *C16orf54*, *ZG16*, *KIF22*, *MAZ*, *PRRT2*, *PAGR1*, *MVP*, *CDIPT*, *SEZ6L2*, *ASPHD1*, *KCTD13*, *TMEM219*, *TAOK2*, *HIRIP3*, *INO80E*, *DOC2A*, *FAM57B*, *ALDOA*, *PPP4C*, *TBX6*, *YPEL3*, *GOPD3*, *MAPK3*, *CORO1A*	NA	12	ASD, E/S, DD/ID	(114)
22q11.2 del	chr22:19,02–20,26	27	*DGCR2*, *DGCR11*, *DGCR14*, *TSSK2*, *GSC2*, *SLC25A1*, *CLTCL1*, *HIRA*, *MRPL40*, *UFD1L*, *CDC45*, *CLDN5*, *SEPT5*, *GP1BB*, *TBX1*, *GNB1L*, *c22orf29*, *TXNRD2*, *COMT*, *ARVCF*, *TANGO2*, *DGCR8*, *TRMT2A*, *RANBP1*, *ZDHHC8*, *CCDC188*, *RTN4R*	MIR4761, MIR185, MIR3618, MIR1306, MIR1266	>28	ASD, ADHD, E/S, DD/ID, BD, D	(64,78)

Chromosomal coordinates and odds ratios from Rees *et al.* (7) (NCBI37/hg19). Reference Sequence (RefSeq) genes within CNV regions are obtained from the UCSC genome browser. Neuropsychiatric disorders: other neuropsychiatric disorders reported in carriers.

A, anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CNV, copy number variant; D, depression; DD/ID, developmental delay/intellectual disability; del, deletion; dup, duplication; E/S, epilepsy/seizures; miRNA, microRNA; NA, not applicable; SCZ, schizophrenia.

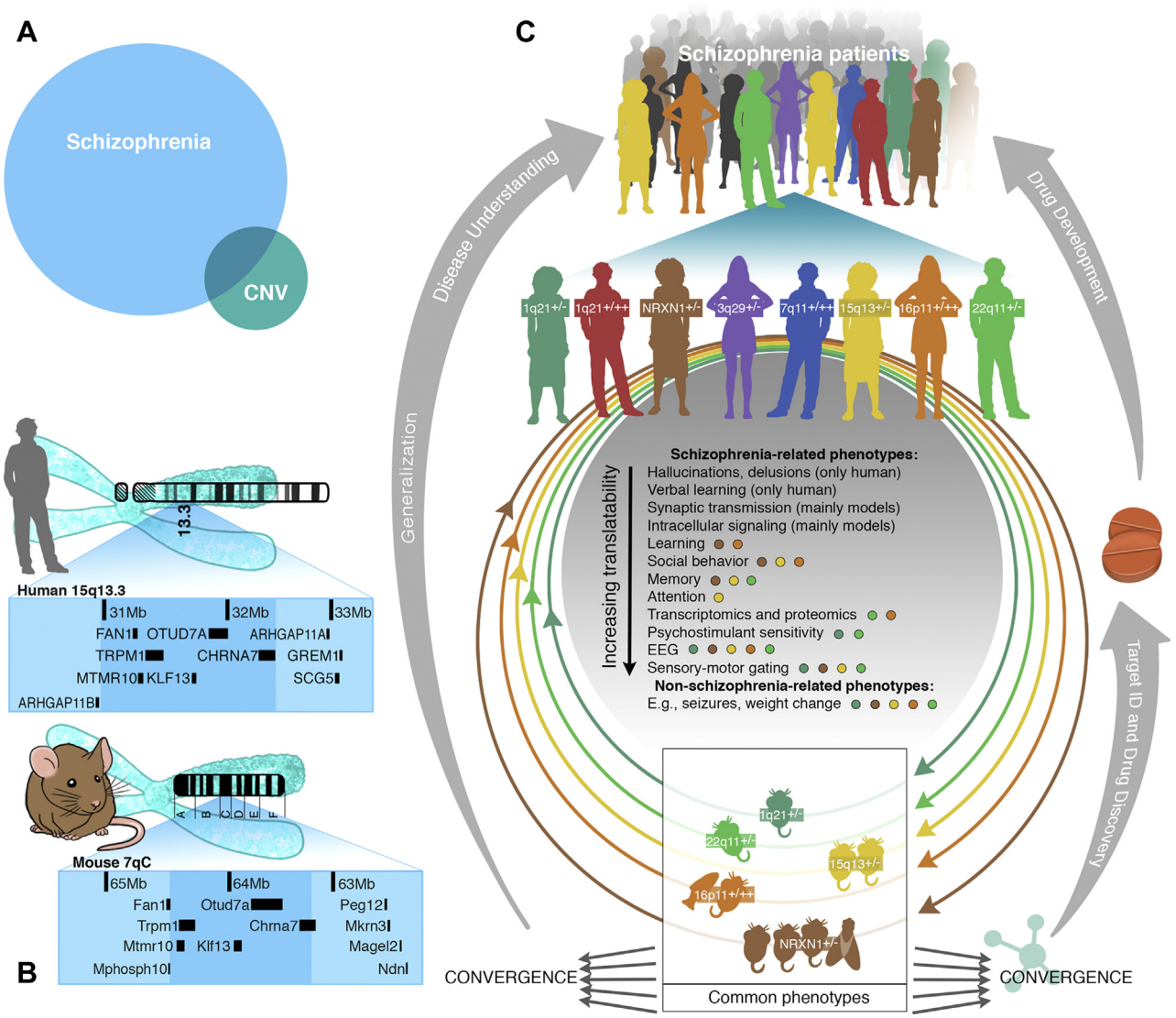

Figure 1. **(A)** Copy number variant (CNV) syndromes and schizophrenia. A subset of schizophrenia patients, 2% to 5%, carry schizophrenia-associated CNVs. Each of these CNVs give rise to syndromes, in which up to 30% develop schizophrenia. **(B)** Chromosomal homology. The human 15q13.3 region exemplifies how most of these CNV regions are conserved in the mouse and other animals facilitating model generation. **(C)** Translational work in CNV animal models can drive disease understanding and drug development. Each of the CNV syndromes is characterized by a specific set of phenotypes, which can be tested in the corresponding animal models (downward colored curved arrows). In turn, characterization of the CNV animal models may uncover phenotypes that can be tested in the carriers of the corresponding CNV (upward colored curved arrows). This process allows assessment of translational validity and mechanistic alterations of individual CNV models. The potential for assessing translatability varies for different phenotypes (subjectively ranked in central circle). The feasibility of measuring phenotypes across species is a major component of this ranking. Specifically, synaptic transmission and intracellular signaling are difficult to measure in humans, while verbal learning, hallucinations, and delusions cannot be measured in animals. Translational phenotypes that have been observed in CNV models are marked with colored dots corresponding to the color codes used above the box (see Table 2 and the text for details). Phenotypes shared by several of the CNV models can potentially identify underlying biology that is relevant to a broader population of schizophrenia patients (generalization, left gray arrow), though it is important to consider whether they relate to schizophrenia or other phenotypes associated with the CNVs. Furthermore, molecular mechanisms underlying common phenotypes of the CNV animals can lead to identification of new drug targets and ultimately new drugs for schizophrenia (right gray arrows). EEG, electroencephalogram.

features, congenital heart disease, and recurrent infections (22–26), indicating that the CNVs affect the development of multiple organ systems. However, selection bias is a large problem in most published clinical studies with detailed description of CNV carriers, as the subjects examined are often selected from patients referred for genetic testing owing to suspicion of genetic disorders. Thus, the prevalence of phenotypes that have not been tested in large systematic genome-wide association studies may be overestimated. An overview of the clinical phenotypes associated with the schizophrenia-associated CNVs is shown in Table 1 and Supplemental Table 1.

Table 2. CNV Animal Models

CNV	Gene Dosage	Phenotypes Related to Schizophrenia Domains: Cognitive Impairments	Sensory Gating	Negative Symptoms	Positive Symptoms	Neurophysiology or Neuroanatomy	Species (Background Strain)	Replication	Reference(s)	Single-Gene Deletion Models[a]
1q21.1 del	+/−	↔Learning ↔Memory	↔PPI (baseline) ↓PPI (psychostimulants)[b]	↔Social interaction	↑Psychostimulant sensitivity[b]	↑Spontaneously active DA neurons ↑Irregular and bursty firing DA neurons	Mouse (C57BL/6N)	Same model	(27)	*Prkab2*, *Fmo5*, *Gja5*, *Gja8*
NRXN1 del	+/−	↔Working memory ↓Object discrimination memory (♀)	↔PPI	↓Social interest (36) ↔Social interest (37) ↔Nest building (NS ↓)	—	—	Mouse (C57BL/6NCrl)	—	(36,37)	—
	−/−	↔Working memory	—	↑Social interest ↓Nest building	—	—	Mouse (C57BL/6NCrl)	—	(37)	
	−/−	↔ Spatial learning ↑Motor learning	↓PPI	↓Maternal care ↓Nest building	—	↓Excitatory synaptic transmission	Mouse (129X1/SvJ×C57BL/6)	—	(33)	
	−/−	↓Instrumental learning (♂) ↓Spatial learning (♂)	↔PPI	—	—	—	Rat (Sprague Dawley)	—	(35)	
	−/−	↓Associative learning	—	—	—	↓Synapses	Fly	—	(34)	
15q13.3 del	+/−	↓Attention ↓Working memory ↔Learning	↔PPI (nonsignificant ↓)	↔Social interest (NS ↑) ↓Nest building	↔Psychostimulant sensitivity	↑Baseline γ-activity ↓Evoked γ-activity ↑Connectivity between brain regions	Mouse (C57BL/6N)	—	(41–43,107)	*Chrna7*$^{+/-}$ and *Chrna7*$^{-/-}$
	−/−	↓Memory	↓PPI[b]	↑Social interest ↓Nest building	—	—	Mouse (C57BL/6N)	Same model	(42)	
	+/−	—	—	↔Social interest ↓Social interaction	—	↑Baseline γ-activity ↓Evoked γ-activity	Mouse (C57BL/6N)	—	(40)	
16p11.2 dup	+/++	—	—	↔Social interaction	—	↑Neuronal arborization	Mouse (129X1/SvJ×C57BL/6)	—	(54,56,57)	All genes in zebrafish (59)
	+/++	↑Memory[b]	—	↔Social interaction	—	↓Excitatory synaptic transmission ↓LTP induction	Mouse (C57BL/6N)	Different background strain	(55)	
	+/++	↑Memory[b]	—	↓Social interaction	—	—	Mouse (C57BL/6N×C3B)	—	(55)	

Table 2. Continued

CNV	Gene Dosage	Phenotypes Related to Schizophrenia Domains: Cognitive Impairments	Sensory Gating	Negative Symptoms	Positive Symptoms	Neurophysiology or Neuroanatomy	Species (Background Strain)	Replication	Reference(s)	Single-Gene Deletion Models[a]
22q11.2 del[c]	+/−	↔/↓Memory (depending on test type) ↓Executive function	↓PPI[b]	—	—	—	Mouse (C57BL/6N)	Across independent models and research groups	(63,67,115,116)	*Prodh*, *Hira*, *Cldn5*, *Sept5*, *Tbx1*, *Gnb1l*, *Comt*, *Dgcr8*, *Zdhhc8*, *Rtn4r*
	+/−	↔/↓Memory (depending on test type) ↔/↓Working memory	↓PPI[b]	—	—	↓Hippocampal-prefrontal synchrony	Mouse (C57BL/6J)	Across independent models and research groups	(62,66,116,117)	
	+/−	↔/↑Memory (depending on test) ↔/↑/↓Working memory (depending on test) ↔/↑Executive function (depending on test) ↔/↑Attention (depending on test)	↓PPI[b]	—	↑Psychostimulant sensitivity	↑Loudness dependent auditory evoked potential	Mouse (C57BL/6N)	Across independent models and research groups	(68,72)	

Upward arrow (↑) indicates increase, downward arrow (↓) indicates decrease, horizontal arrow (↔) indicates no change, and em dash (—) indicates no published data.
♀, only in female animals; ♂, only in male animals; DA, dopamine; LTP, long-term potentiation; NS, nonsignificant; PPI, prepulse inhibition.
[a]Only models tested for at least one schizophrenia-relevant assay are included.
[b]Phenotypes replicated in the same model or an independent model.
[c]Most of the genetic and clinical data in humans is of carriers of the 3-Mb deletion on 22q11, while mouse models carry a deletion homologous to the 1.5-Mb deletion in humans (63).

THE 1q21.1 DELETION

The 1q21.1 deletion spans eight protein-coding genes and has a schizophrenia OR of 8 (7). A mouse model of this microdeletion has recently been generated and characterized with focus on schizophrenia-related phenotypes (27). The main phenotypes of this model are altered response to psychostimulants and altered dopamine transmission.

Psychostimulants such as *N*-methyl-D-aspartate receptor antagonists and amphetamine can exacerbate positive symptoms in schizophrenia patients (28–30). Consequently, increased response to psychostimulants in animal models is hypothesized to be relevant to positive symptoms. The 1q21$^{+/-}$ mice exhibit increased locomotor response to amphetamine but not to phencyclidine, an *N*-methyl-D-aspartate receptor antagonist. Furthermore, the 1q21$^{+/-}$ mice display normal prepulse inhibition (PPI) but increased sensitivity to disruption of PPI by amphetamine and phencyclidine (27). These findings suggest altered dopaminergic signaling and were followed up by mechanistic exploration of dopamine transmission. Electrophysiological recordings demonstrated more spontaneously active dopaminergic neurons in 1q21$^{+/-}$ mice as well as higher proportion of bursty neurons. No alterations were observed in assays of cognition and social behavior (27).

In summary, the 1q21$^{+/-}$ mice have quite selective alterations of dopaminergic transmission and may be a useful model for positive symptoms of schizophrenia.

THE *NRXN1* DELETION

Hemizygous deletions within the *NRXN1* gene on chromosome 2p16.3 have a schizophrenia OR of 9 and are the only well-documented schizophrenia-associated CNV in which only a single gene is affected (7,13). The *NRXN1* gene encodes the synapse adhesion molecules neurexin-1α and -1β. The two isoforms arise from alternative promotors (31). The *NRXN1* deletion that predispose to schizophrenia spans exons of the α, but not the β, isoform (32).

Behavioral studies of *Nrxn-1*α hemizygous (+/−) and homozygous (−/−) deletion mice, rats, and flies have demonstrated several schizophrenia-relevant phenotypes [reviewed in Reichelt *et al.* (32)] (Table 2).

In accordance with a prominent role of neurexins in synapse formation, *Nrxn-1*$\alpha^{-/-}$ mice display reduced excitatory synaptic transmission in hippocampal slices (33). Furthermore, *Nrxn-1*α knockout in flies results in fewer synapses (34). *Nrxn-1*α knockout in flies and rats results in learning deficits (34,35), which are analogous to cognitive deficits in schizophrenia. In one type of memory test, the passive avoidance test, female *Nrxn-1*$\alpha^{+/-}$ mice were reported to be slightly impaired (36). However, in most reports on *Nrxn-1*α deletion mice, no memory impairments were seen (32,36,37).

Impaired PPI of the startle response was observed in *Nrxn-1*$\alpha^{-/-}$ mice on a mixed SV129×C57BL/6 background, potentially mimicking sensorimotor gating impairments of schizophrenia (33,38). This finding was not replicated in a subsequent study in which the *Nrxn-1*$\alpha^{+/-}$ and *Nrxn-1*$\alpha^{-/-}$ mice had been backcrossed to a pure C57BL/6 background (36). *Nrxn-1*$\alpha^{-/-}$ rats display normal PPI (35).

Nrxn-1α deletion mice exhibit phenotypes that may be relevant to negative symptoms of schizophrenia. Initial studies of *Nrxn-1*$\alpha^{-/-}$ mice described a subtle deficit in care of pups by female *Nrxn-1*$\alpha^{-/-}$ mice (39). This was followed by findings of impaired nest building in *Nrxn-1*$\alpha^{-/-}$ mice (33,37). Furthermore, *Nrxn-1*$\alpha^{+/-}$ mice appear to have decreased interest in unfamiliar mice (36), while *Nrxn-1*$\alpha^{-/-}$ mice display increased social interest in unfamiliar mice (37).

The inconsistent results in memory tests, social interest, and sensorimotor gating may be explained by differences in species, background strain, and laboratory protocols.

THE 15q13.3 DELETION

The hemizygous 15q13.3 microdeletion of six protein-coding genes has a schizophrenia OR of 8 (7). Two 15q13.3$^{+/-}$ mouse models have been generated and characterized by independent research groups (40,41). The two models were generated on the same background strain, C57BL/6, and span the same six protein-coding genes as the human deletion (Table 2). Recently, 15q13.3$^{-/-}$ mice have also been characterized (42). Overall, the homozygous knockout mice appear to display similar, but stronger, phenotypes compared with the mice with hemizygous deletion. 15q13 deletion mice have been broadly profiled in schizophrenia-related assays, and collectively, these models show phenotypes related to cognitive impairments, negative symptoms, and electrophysiological changes like those seen in schizophrenia patients (Table 2).

Only some cognitive domains are affected in 15q13$^{+/-}$ mice. They show attentional deficit measured by decreased accuracy at short stimulus durations in the five-choice serial reaction time task (43). In the Morris water maze and novel object recognition task, 15q13$^{+/-}$ mice exhibit slightly decreased performance, indicating a memory deficit, whereas the mice show normal performance in several learning tasks (41,43). PPI is impaired in 15q13$^{-/-}$ mice, but there is no significant difference between 15q13$^{+/-}$ mice and wild-type mice (41,42).

Like the *Nrxn-1*α deletion mice, 15q13 deletion mice display phenotypes potentially related to negative symptoms of schizophrenia. Nest building is gene dosage–dependently impaired in 15q13 deletion mice, and social behavior is altered (40–42). 15q13$^{+/-}$ mice, however, do not seem to recapitulate positive symptom–related phenotypes because no relevant basal ganglia alterations such as increased sensitivity to psychostimulants were observed (41).

Characterization of the 15q13 mouse models revealed several schizophrenia-related electroencephalographic phenotypes including increased baseline activity and decreased auditory evoked gamma activity (30–80 Hz) (40,41). On the single-unit level, 15q13$^{+/-}$ mice have decreased interneuron firing and increased latency to fire in both interneurons and pyramidal neurons (43,44). The gamma-aminobutyric acid type A receptor antagonist gabazine, administered locally in the prefrontal cortex, increases pyramidal activity in wild-type mice, but not in 15q13$^{+/-}$ mice (43). The reduced firing probability of fast-spiking interneurons (FSIs) could be partially normalized by a modulator of the voltage-dependent potassium channel Kv3.1, a key regulator of FSI activity (44). Taken together, these phenotypes resemble electroencephalographic observations in schizophrenia patients and point to an FSI dysfunction in the 15q13$^{+/-}$ mice. In addition, a reduction in parvalbumin-immunoreactive neurons in the anterior cingulate

cortex of 15q13$^{+/-}$ mice has been reported (45). Parvalbumin is a marker of FSIs, and this finding further supports a FSI dysfunction in the 15q13$^{+/-}$ mice.

The 15q13.3 gene *CHRNA7*, encoding the nicotinic acetylcholine α7 receptor, is often proposed to be the key driver of schizophrenia liability in the 15q13.3 microdeletion (46–49), but this hypothesis is only partially supported by the mouse models. A recent study showed that a positive allosteric modulator of *Chrna7* could reverse a hyperconnectivity between brain regions in 15q13$^{+/-}$ mice. However, deletion of *Chrna7* alone results in very subtle phenotypes and does not recapitulate the phenotypes observed in 15q13$^{+/-}$ and 15q13$^{-/-}$ mice, indicating that other genes in the region contribute to the phenotypes (42,50–53).

THE 16p11.2 DUPLICATION

Hemizygous 16p11.2 duplication of 26 protein-coding genes has a schizophrenia OR of 11 (7). Mouse and zebrafish models of the human 16p11.2 duplication syndrome have been tested for a limited number of schizophrenia-related phenotypes (Table 2). Overall, few behavioral but several mechanistic phenotypes have been reported.

Two mouse models of the 16p11 duplication (16p11$^{+/++}$) have been generated by independent research groups (54,55). One of the models have been tested for a number of phenotypes, on two background strains, demonstrating that some of the phenotypes are dependent on background strain (55). The phenotypes tested include social interaction and memory, but not response to psychostimulants or sensorimotor gating. 16p11$^{+/++}$ mice on a mixed C57BL/6× C3B background, but not on a pure C57BL/6 background, display decreased social interaction (55). Social interaction has not been tested in the other 16p11 model (54,56,57). No cognitive deficits have been reported for 16p11$^{+/++}$ mice; rather, a potential improvement in object recognition memory has been reported (55).

Transcriptomic profiling of 16p11$^{+/++}$ mice using RNA sequencing found enrichment of transcriptional changes in genes involved in cilium morphogenesis (57). Subsequently, morphological studies showed that cilia length is reduced in CA1 region of the hippocampus in 16p11$^{+/++}$ mice (58).

On the cellular level, dendritic arborization was found to be increased in cultured cortical pyramidal neurons from 16p11$^{+/++}$ mice. Network analysis of affected genes from five CNVs (1q21.1, *NRXN1*, 15q13.2, 16p11.2, and 22q11.2) associated with schizophrenia identified *MAPK3*, one of the genes in the 16p11.2 region, as the most connected gene in the network. Therefore, the authors hypothesized that *MAPK3* was driving the cellular 16p11.2 phenotype and subsequently demonstrated reversal of dendritic arborization by a *MAPK3/ERK1* inhibitor (56).

In zebrafish, all 26 genes of the 16p11.2 region has been individually overexpressed. This study revealed that overexpression of human *KCTD13* can induce the microcephaly and neuroanatomical phenotypes associated with the 16p11.2 microduplication syndrome (59). Furthermore, *KCTD13* overexpression led to apoptosis and cell proliferation defects. Collectively, these studies suggest that both *KCTD13* and *MAPK3* are important drivers of the 16p11.2 phenotypes.

THE 22q11.2 DELETION

The 22q11.2 deletion was the first CNV shown to be associated with schizophrenia (8). It has the highest OR for schizophrenia (>28) and is also the most studied CNV associated with schizophrenia. The 22q11.2 deletion syndrome, which is also known as velocardiofacial syndrome or DiGeorge syndrome, has been modeled extensively in mice, and these models have been reviewed several times, so here we will only give a brief updated summary of the schizophrenia-related characterization and refer to existing reviews for detailed description of the models (60–65).

Both a long 2.5-Mb deletion of 45 protein-coding genes and a shorter 1.5-Mb deletion of 27 protein-coding genes at 22q11.2 have been associated with schizophrenia (Supplemental Table 1) (7,13,63). Most cases (~85%) carry the 2.5-Mb deletion, while a minority (~15%) carry the 1.5-Mb deletion (63). Although the OR for the 1.5-Mb deletion has recently been estimated as >28 (7), it is not yet clear if the risk is as high as for carriers of the 2.5-Mb deletion, which has recently been estimated as 68 (13) (Supplemental Table 1). A deletion corresponding to the 1.5-Mb deletion on human 22q11.1 has been introduced in mice by three independent research groups (66–68). In addition, several mouse models have been generated with smaller deletions and of single genes in the region (62,63,69,70). As most studies of the 22q11.2 deletion syndrome are of carriers with the longer 2.5-Mb deletion, it might be a limitation of the mouse models that they model the shorter 1.5-Mb deletion (71).

Findings related to cognitive performance of 22q11$^{+/-}$ mice are inconsistent across studies. Deficits in learning and memory were observed in the first 22q11$^{+/-}$ mouse lines published, mimicking aspects of the cognitive impairments seen in schizophrenia (63,66). However, extensive profiling of another 22q11$^{+/-}$ mouse model did not reproduce the cognitive impairments previously reported (72). Because the mouse models were all generated on C57BL/6 background, J or N substrain, this discrepancy is unlikely to be due to differences in background strains (Table 2) (66–68), but rather more likely to be due to differences in methods and conditions.

Profound PPI deficits have been demonstrated in all 22q11$^{+/-}$ models (62,66,68,73). PPI deficits are common in schizophrenia patients (38) and have also been found in children with 22q11.2 deletion without schizophrenia (74).

The evaluation of behaviors related to negative symptoms of schizophrenia is limited. Mice, deficient of a single gene in the region, *Sept5*, spent less time on active social behavior, but no test have been reported for the 1.5-Mb deletion models (75) (Table 2).

22q11$^{+/-}$ mice have increased response to the *N*-methyl-D-aspartate antagonists ketamine and phencyclidine (68,76), indicating biological changes relevant to positive symptoms of schizophrenia.

Electrophysiological studies have shown neural circuit dysfunction and altered synaptic plasticity in 22q11$^{+/-}$ models. Specifically, they show deficient hippocampal-prefrontal synchrony and altered short- and long-term plasticity [reviewed in Sigurdsson (77)].

Several studies have tried to dissect the implication of individual genes for the phenotypes, and *Comt*, *Prodh*, *Tbx1*, *Dgcr8*, and *Zdhhc8* hemizygous or homozygous knockout

mice have been shown to induce some phenotypes of the deletion syndrome [reviewed in Drew *et al.* (62) and Hiroi *et al.* (78)], but it is still not clear which gene(s) is responsible for the increased risk of schizophrenia. It seems likely that several genes in the region are involved.

For 22q11$^{+/-}$ mice, data linking specific genes and phenotypes are emerging. One example is that 22q11$^{+/-}$ mice and mice with hemizygous deletion of the 22q11 gene *Dgcr8* were shown to have increased expression of the sarco(endo)plasmic reticulum Ca^{2+} ATPase in synaptosomal preparations from the hippocampus and increased long-term potentiation (79). Additionally, several microRNAs were reduced in these mice, and restoration of some of these could normalize sarco(endo) plasmic reticulum Ca^{2+} ATPase expression and restore long-term potentiation in *Dgcr8*$^{+/-}$ mice.

DISCUSSION

Animal models have been generated for five CNVs associated with highly increased risk of schizophrenia (Figure 1 and Table 2). These models have the potential to provide a platform for advancing the mechanistic understanding of alterations that can lead to schizophrenia. However, when interpreting and evaluating this contribution it is important to consider 1) construct and face validity, 2) comparison of CNV models, 3) single-gene contribution, and 4) identification of treatment targets.

Animal models of CNVs have very strong genetic links to schizophrenia, and currently they arguably represent the best available construct validity for schizophrenia. However, they have limitations relating to penetrance and specificity, as discussed below.

The CNVs do not always lead to schizophrenia—human carriers have a lifetime schizophrenia risk of around 5% to 30% depending on the CNV, and some carriers are apparently unaffected by the CNV. Therefore, it may not be surprising that the phenotypes of the animal models are relatively mild. It has been shown that both common low-risk SNP variants and additional rare CNVs contribute to schizophrenia risk in carriers of recurrent CNVs (80,81). Thus, the phenotypic consequence of schizophrenia-associated CNVs depend on the genetic makeup and environmental risk factors. Moving forward, schizophrenia construct and face validity may be enhanced by testing different genetic background strains, combining CNVs or exposing CNV animals to environmental insults. It has been shown that stress during development results in schizophrenia-related phenotypes, suggesting that environmental risk factors can modify schizophrenia-relevant behavior (1,82). Hence, combining CNVs with stress during development might result in models with a more pronounced phenotype than seen in the CNVs on their own (83).

Specificity is another issue when evaluating construct and face validity. All schizophrenia-associated CNVs additionally predispose to other disorders such as epilepsy, autism, and developmental delay. This complicates interpretation, since some phenotypes in the CNV models may be irrelevant to schizophrenia, but related to other associated disorders. This pleiotropy issue is not limited to the CNVs, as other genetic variants, SNPs and single nucleotide variants, linked to schizophrenia also predispose to other conditions than schizophrenia (20).

The CNV animal models recapitulate some of the behavioral, anatomical, and physiological features of schizophrenia demonstrating some degree of face validity (Figure 1C and Table 2). However, they are arguably not schizophrenia models as such, but rather models of the clinically heterogeneous CNV syndromes, and thereby models of schizophrenia liability. Consequently, other phenotypes that characterize the CNV syndromes are also relevant for evaluation of face validity as illustrated in Figure 1C. Examples include translational similarities between models and human carriers of weight in 15q13.3 and height in 1q21.2 (27,41).

Further clinical data are needed for an improved understanding of the association between CNVs and schizophrenia. Schizophrenia is a very heterogenous clinical construct, and the link between the CNVs and schizophrenia comes from large genome-wide association studies, which lack detailed clinical description of individuals. Data on neurophysiology, neuroanatomy, positive, cognitive, and negative symptoms as well as the response to antipsychotic treatment for the schizophrenia-associated CNVs would greatly facilitate the interpretation of the findings from the respective animal models. These data are emerging for 22q11.1 deletion carriers, and such data will be important for guiding and interpreting future studies of psychiatric CNV animal models (84–88).

While findings from individual CNV models cannot be extrapolated to a broader schizophrenia population, common phenotypes, i.e., convergence in several models, may suggest broader relevance to schizophrenia (Figure 1C). An example is decreased PPI, which has been observed in *Nrxn-1*$\alpha^{-/-}$, 15q13$^{-/-}$, and 22q11$^{+/-}$ mice, and also seen in response to psychostimulants in the 1q21$^{+/-}$ mice (Table 2) (27,33,42,68). Decreased PPI has been reported in schizophrenia, though it is not unique to this disorder (38). Importantly, 22q11 deletion carriers without a schizophrenia diagnosis also display decreased PPI (74). More interestingly, convergence on molecular pathways may provide truly new insight into pathways that can lead to schizophrenia. For common phenotypes, it is important to consider whether they are specifically related to the genetic variant or if many or most genetic manipulations may result in such phenotypes. Data reviewed here, however, speak against this as a major concern. First, most single-gene knockouts do not recapitulate the phenotype of the respective CNVs. Second, although relevant to schizophrenia, the phenotypes observed in the 1q21, 15q13, and 22q11 mouse lines are different and reflect different aspects of schizophrenia.

Most of the animal modeling of schizophrenia-associated CNVs has been done in mice. But because the individual models have been generated and characterized by different groups, a direct comparison of the results is difficult, as different background strains, breeding conditions, and assays have been used (Table 2). An exception, however, is the parallel generation of the 1q21, 15q13, and 22q11 deletion mice by a group at Lundbeck (27,41,68). These three models were characterized in many of the same behavioral and physiological assays by Lundbeck and collaborators in the NEWMEDS (Novel Methods leading to New MEdications in Depression and Schizophrenia) consortium, allowing direct phenotypical comparison (27,41,68,89).

Dissecting the contribution of individual genes of the CNV regions is a key step toward mechanistic understanding of the CNV models. For the four CNVs with animal models that span

several genes, single-gene contributions can be assessed by comparing the CNV models with mice in which only a single gene is targeted. For the 15q13.3 CNV, *Chrna7* and *Otud7a* knockout mice have been assessed in relevant assays. Overall, *Otud7a*$^{-/-}$ display more phenotypes relevant for the 15q13 microdeletion syndrome than *Chrna7*$^{-/-}$ (41,42,53,90,91). Several, but far from all, of the many genes in the 22q11.2 CNV have been tested in knockout mice, and while some relevant phenotypes have been demonstrated, the relative contributions of the different genes to the phenotypic domains are still unclear (62). For the 16p11.2 duplication, it has been shown that the *KTCD13* gene can drive the microcephaly phenotype associated with the duplication (59). It is unknown, however, if other genes contribute to the microcephaly phenotype and which genes are important for other phenotypes, such as the social phenotype observed in the mouse model of the 16q11.2 duplication. Four of the eight genes in the 1q21.1 CNV region have been knocked out in mice (92–95), but they have not been tested for amphetamine sensitivity, and it is therefore not yet known which gene(s) in the region drive the schizophrenia-related phenotypes (27). Consequently, more work is needed to clarify which gene or combination of genes drives the schizophrenia predisposition associated with these CNVs.

Data from human neurons derived from induced pluripotent stems cells is emerging for the *NRXN1* deletion, the 7q11.23 duplication, the 15q13.3 deletion, the 16p11.2 duplication and the 22q11 deletion, but so far only few clones have been developed and even fewer phenotypes have been demonstrated (58,96–103). Induced pluripotent stems cells could address the concerns of cross-species translatability that are associated with animal models, although it comes at the cost of in vitro to in vivo translational risk. Furthermore, other challenges including batch-to-batch variability relating to both generation and differentiation of induced pluripotent stems cells complicate interpretation of data and lead to the requirement of many biological as well as technical replicates (104).

In general, cellular systems, either human cells or primary neuronal cultures from rodent CNV models, may serve as tools to identify molecular pathways involved in disease. If robust phenotypes are identified in such cells, it could enable phenotypic screening with compounds or single gene manipulation with CRISPR (clustered regularly interspaced short palindromic repeats), small interfering RNA, or other gene-editing tools. This could be used both to identify target candidates and to explore biological pathways.

A few studies have exemplified how new drug targets may be identified by studies of CNV models. A recent example is a study by Tamura *et al.* (105) showing that a Gsk3 inhibitor rescued memory impairment in 22q11$^{+/-}$ mice. The study was propelled by findings of memory impairments in mice with hemizygous deletion of one of the 22q11.2 genes, *Zdhhc8*, which indirectly inhibits GSK3β (106). Consequently, it was hypothesized that GSK3 inhibition during development would reverse cognitive impairment in 22q11$^{+/-}$ mice (105). A second example is a study in 15q13$^{+/-}$ mice, in which a positive allosteric modulator of the nicotinic acetylcholine alpha 7 receptor normalized elevated functional connectivity among prefrontal and frontal, hippocampal, striatal, thalamic, and auditory regions (107). A third example is a study in which altered dendritic arborization in cultured cortical pyramidal neurons from 16p11.2 duplication mice was normalized by targeting the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway identified by a CNV-based network analysis (56). Such comparison of molecular changes in different CNV models arguably holds the largest potential for identification of new drug targets (Figure 1C). Further investigation of molecular changes in individual CNV models by phenotypic screening, genetic manipulation of individual CNV genes, transcriptomics, electrophysiology, intracellular signaling tests, etc., is needed to provide the basis for identification of molecular convergence and drug targets.

In conclusion, several animal models of CNVs associated with schizophrenia present with overlapping as well as individual schizophrenia-like phenotypes and provide a promising avenue for a better understanding of the molecular mechanisms that can lead to schizophrenia. This could ultimately lead to identification of new and better drug targets addressing the underlying biology.

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