# Update on the 22q11.2 deletion syndrome and its relevance to schizophrenia

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**Purpose of review**
Schizophrenia occurs in ~25% of individuals with 22q11.2 deletion syndrome (22q11.2DS), the strongest known molecular genetic risk factor for schizophrenia. This review highlights recent literature in 22q11.2DS as it pertains to psychosis and schizophrenia.

**Recent findings**
Advances in noninvasive prenatal testing allow for early detection of 22q11.2DS *in utero*, whereas premature birth has been shown to be a significant risk factor for development of psychotic illness in 22q11.2DS. Impairments in various domains of cognitive and social functioning, as well as neuroanatomical alterations, are comparable with those in other high-risk groups and may serve as early signs of psychosis in 22q11.2DS. Novel research on the pathogenesis of schizophrenia in 22q11.2DS using cellular and mouse models indicates changes in expression of genes within the 22q11.2 deletion region and elsewhere in the genome, implicating molecular pathways involved in schizophrenia and associated neurocognitive deficits. Increased risks of obesity and of Parkinson's disease in 22q11.2DS warrant consideration in antipsychotic management.

**Summary**
Progress in characterizing and predicting psychotic illness in 22q11.2DS supports this identifiable subpopulation as a molecular model with important implications for understanding the pathogenesis of schizophrenia in the general population and for development of potential novel therapies.

**Keywords**
DiGeorge syndrome, dopamine, genetic, microRNA, prodromal

## INTRODUCTION

The recurrent 22q11.2 deletion is the strongest known molecular genetic risk factor for schizophrenia [1]. One in four individuals born with this deletion develops schizophrenia, and ~0.5–1% of individuals with schizophrenia in the general population have the associated 22q11.2 deletion syndrome (22q11.2DS; OMIM 188400/192430, formerly called DiGeorge or velocardiofacial syndrome) [2]. This makes 22q11.2 deletions the most common of the clinically relevant copy number variations (CNVs) that combined account for ~3.5–5% of schizophrenia [3]. Recognition of 22q11.2DS is important for clinical management, including treatment and genetic counseling (there is a 50% risk of transmitting the deletion) [2], and for the opportunity such a molecular model presents for understanding schizophrenia, given the comparability of the schizophrenia phenotype including symptom profile and age at onset [4]. In this article, we provide an overview of research published within the last year in the area of 22q11.2DS, focusing on that most relevant to psychosis and schizophrenia (selecting from 60 articles identified on this topic).

## NEW PRENATAL SCREENING TECHNIQUES FOR 22q11.2 DELETIONS

The clinical importance of early diagnosis and relatively high prevalence of 22q11.2DS (estimated one in 3000–4000 live births [1]) has spurred the

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## KEY POINTS

- The 22q11.2 deletion, the strongest known molecular genetic risk factor for schizophrenia, has clinically based evidence that supports recommendations for clinical genome-wide testing, regardless of age, of individuals with developmental delay and/or intellectual disability and/or congenital anomalies.
- Advances in noninvasive prenatal testing allowing for detection of 22q11.2 deletions, whereas *in utero* have potential implications for anticipatory care of early features of 22q11.2DS that could ameliorate downstream risks of neuropsychiatric expression.
- Research using this genetically definable subpopulation has enhanced power to elucidate the pathogenesis of schizophrenia from prenatal factors to clinical and brain anatomical trajectories.
- Expression of psychosis in 22q11.2DS, including developmental trajectories, is largely comparable with that observed in general population samples (e.g., clinical ultra-high risk).
- Animal and human cellular models provide the means to investigate individual genetic risk factors, within the 22q11.2 deletion region and genome-wide.

extension of noninvasive prenatal testing (NIPT) used for aneuploidies (e.g., trisomy 21) to include screening for 22q11.2 deletions [5]. This work takes into account the fact that most 22q11.2 deletions occur as spontaneous (de novo) mutations during gametogenesis, that parental studies identify the deletion to be inherited in only 5–10% of cases, and that there is no association of the deletion with parental age [1]. Thus, the majority of fetuses and newborns with a 22q11.2 deletion arrive to young couples with no family history of schizophrenia, birth defects, or 22q11.2DS [6]. A recent report evaluated a single-nucleotide polymorphism-based NIPT method [7▪]. Follow-up confirmatory testing of 61 of 95 cases considered high risk for 22q11.2 deletion showed a positive predictive value (PPV) of 18.0% (range 11.6–47.4%) for this 22q11.2 deletion screening technique [7▪]. Amongst the true positive cases were those with no fetal ultrasound anomalies. Although further work is needed to optimize NIPT performance, this technology ushers in a new era of prenatal screening that could permit specialized management and/or anticipatory care of early features of 22q11.2DS, for example, neonatal hypocalcemia and seizures, that could have implications for brain development and downstream risk of related neuropsychiatric expression [6].

## CLINICAL DIAGNOSIS OF 22q11.2 DELETION SYNDROME AND EPIDEMIOLOGIC STUDIES

Clinical diagnostic testing for 22q11.2DS requires an index of suspicion; diagnostic delays are common. The variability of expression between patients and over development, including associated congenital anomalies, endocrine disorders such as hypocalcemia and hypothyroidism, and neuropsychiatric illness, however, presents challenges for clinical recognition. Consistent with this are findings for 747 individuals from clinical cytogenetic laboratories across France over an 18-year period that primarily involved targeted fluorescence in-situ hybridization (FISH) testing using a single probe from the 22q11.2 deletion region [8]. The average age at diagnosis was 9.8 years, and reasons for referral for testing most commonly involved typical congenital anomalies (e.g., congenital heart defect in 48.5%) and/or developmental delay/intellectual disability (40.7%) [8]. Neuropsychiatric disorders, for example, autism or schizophrenia, were less frequent (7.4%) at diagnosis [8].

A Danish population-wide record linkage study of individuals similarly clinically detected to have 22q11.2 deletions over a 20-year period reported increased risk for developing schizophrenia spectrum disorders over population expectations [9▪], consistent with previous research [2]. Lower than expected numbers overall and with schizophrenia spectrum disorders (four of 244 22q11.2DS cases identified) may have been related to low clinical recognition and referral for cytogenetic testing and/or the limited years of follow-up for psychiatric care in this study.

Modern genome-wide techniques, particularly clinical microarray, detect all pathogenic 22q11.2 deletions, including those missed by clinical testing using FISH [1]. Clinical guidelines recommend that regardless of age, all individuals with developmental delay, and/or intellectual disability, and/or congenital anomalies have genome-wide testing [2]. A research study using genome-wide microarrays confirmed the importance of the 22q11.2 deletion and other high-risk CNVs previously identified for intellectual disability in large samples of schizophrenia, indicating common molecular genetic causes for these neurodevelopmental conditions [10].

## PREDICTING SCHIZOPHRENIA IN 22q11.2 DELETION SYNDROME: PERINATAL RISK FACTORS

The relative genetic homogeneity of 22q11.2DS appears to magnify the impact of other factors,

providing further evidence of the strength of the 22q11.2 deletion model for studying the predictive factors and pathogenesis of schizophrenia [11▪,12▪,13▪▪]. The potential importance of perinatal factors in idiopathic forms of schizophrenia prompted two studies that have reported prematurity (<37 weeks gestational age) to be a significant additional risk factor for the expression of schizophrenia and related psychotic illnesses in individuals with 22q11.2 deletions [11▪,14]. Both studies also reported similarly elevated rates of prematurity in 22q11.2DS [11▪,14], compared with general population expectations. One of these studies, involving 123 adults with 22q11.2DS, reported that the PPV of being born premature or small for gestational age was 46% for schizophrenia, a figure approaching the highest known risks for schizophrenia in family history studies involving rare subgroups (identical twins of an individual with schizophrenia or the offspring of two affected parents) [11▪]. However, the small for gestational age finding was not replicated [14].

## PREDICTING SCHIZOPHRENIA IN 22q11.2 DELETION SYNDROME: EARLY CLINICAL SIGNS AND NEUROCOGNITIVE CHANGES

Studies of general population samples often use ultra-high-risk (UHR) criteria, including attenuated psychotic symptoms, to identify individuals at elevated risk for developing schizophrenia, in which the conversion rate to psychosis is approximately 25% at 4-year follow-up [15]. Showing comparable results with these clinical UHR studies in the general population, a study of 89 patients with 22q11.2DS (mean age 16.1 years) reported that at baseline, 22 (24.7%) met UHR criteria and that transition to psychosis occurred in 27.3% of the UHR group and in 4.5% of the non-UHR group (mean follow-up 32.5 months) [13▪▪].

An independent cross-sectional study compared 150 patients (aged 9–24 years) with 22q11.2DS and 150 age-matched and sex-matched individuals with no 22q11.2 deletion, selected to have comparable proportions with psychosis spectrum (including $n = 11$ with psychotic illness in the 22q11.2DS group) per ratings using the Structured Interview for Prodromal Syndromes. Findings were similar for both groups on mean age of onset for psychosis proneness and cognitive testing and overall symptom burden results for those with and without psychosis spectrum [12▪]. Cognitive measures did not correlate with psychosis spectrum designation; however, patients with estimated intelligence quotient less than 70 were excluded. As in previous studies [4], substance use was lower in 22q11.2DS [12▪]. There were however some subtle differences in specific psychotic-like symptoms between the groups, including a greater likelihood of avolition, stress intolerance, and low ideational richness in 22q11.2DS [12▪].

Using this cohort, together with an independent cohort, to compare individuals with 22q11.2DS with and without psychosis found that individuals with psychotic disorder had lower global neurocognitive performance and more significant deficits in executive functioning, episodic memory, and social cognition [16]. Other cross-sectional studies of youth with 22q11.2DS but without a clinical psychotic disorder have reported that those individuals with the worst social functioning and social skills had significantly elevated subclinical negative and positive symptoms of schizophrenia [17,18]. In another study, schizotypal traits, in particular excessive social anxiety and lack of close friends, were found to be more enriched in the 22q11.2DS population compared with individuals with no 22q11.2 deletion [19].

In a longitudinal study of youth with 22q11.2DS, individuals with 22q11.2DS who eventually progressed to psychosis were reported to have poorer premorbid functioning, especially in academic domains in childhood and early adolescence [20], and deficits in emotional recognition and cognitive flexibility (mean age 21.2 years at last follow-up) [21], when compared with those who did not develop a psychotic illness.

Collectively, as have other studies previously [22,23], these studies support the comparability of findings from prodromal studies in 22q11.2DS to those in idiopathic schizophrenia and thus suggest the potential for interventions such as social and/or cognitive skills training [24,25].

## PREDICTING SCHIZOPHRENIA IN 22q11.2 DELETION SYNDROME: NEUROIMAGING STUDIES

Previously, cross-sectional studies have characterized neuroanatomical alterations in 22q11.2DS, including small overall brain volume, midline defects, increased white matter hyperintensities, and decreased gray matter [26]. Growing numbers of longitudinal MRI studies of 22q11.2DS provide an opportunity to elucidate the anatomical and functional changes underlying the transition to psychosis and to explore predictive biomarkers. Multiple reports involving a cohort in which individuals with 22q11.2DS were assessed at up to four time points ($n = 73–76$) have proposed that changes in frontal cortical thickness, cerebral surface indentations in the orbitofrontal and inferior parietal lobule, and cortical-to-amygdala volumetric ratios could act as possible predictive biomarkers for positive symptoms of psychosis in 22q11.2DS in early adulthood

[27–29]. Study limitations include the relative youth of this cohort at last assessment (average age ~21 years) [27–29] and that only six (7.9%) individuals had a diagnosis of a psychotic disorder [28].

In cross-sectional MRI studies comparing ~20 individuals with 22q11.2DS and ~20 clinical UHR from the general population [30,31], both risk groups were reported to have positive symptom severity correlated to decreased cortical thickness of the rostral middle frontal gyrus [30]. Individuals with 22q11.2DS showed more severe prefrontal hypogyrification and cortical gray matter volume deficits than either UHR or healthy control groups [30]. Diffusion tensor imaging showed distinct patterns of white matter alterations for each risk group, with greatest between-group differences in the corpus callosum and anterior thalamic radiation white matter microstructure integrity [31].

## PROBING PATHOGENESIS: MOLECULAR MODELS USING HUMAN CELLS AND ANIMALS

A major advantage of identifying a molecular form of schizophrenia is the potential for cellular and animal models to help inform our general understanding of pathogenesis and assist with novel treatment development. In 22q11.2DS, there is reduced gene dosage of the 46 protein-coding and 44 other genes in the typical 22q11.2 deletion region and resultant potential effects on expression of these genes [1]. In addition, genome-wide factors may affect the likelihood of expression of schizophrenia through mechanisms that mediate neuronal development and function [32]. An in-vitro study using neurons derived from induced pluripotent stem cells (iPSC) from eight patients with 22q11.2DS schizophrenia and seven nonpsychotic controls with no 22q11.2 deletion reported an approximate two-fold reduction in 37 protein-coding genes in the 22q11.2 region [33▪]. This neuronal model also showed elevated expression of genes outside the 22q11.2 region involved in apoptosis, cell cycle, and MAPK signaling domains previously associated with deficits in learning and memory and with neurodevelopmental disorders including idiopathic schizophrenia [33▪]. Despite the promise of such iPSC models, limitations include the small sample size and relatively large amount of heterogeneity between samples [33▪].

Amongst the possible animal models for 22q11.2 deletions, multiple mouse models are available for study, including various lengths of deletion of the syntenic region on mouse chromosome 16 and mutations of individual genes from this region [34]. In *Df(16)A*$^{+/-}$ model mice, analogous to nested 1.5-Mb human 22q11.2 deletions, spatial working memory deficits, a phenotype posited to be related to schizophrenia, could be rescued through developmental antagonism of Gsk3, a protein previously implicated in this phenotype and hippocampal–prefrontal connectivity abnormalities, related to haploinsufficiency of the *Zdhhc8* 22q11.2 region gene [35▪]. The same group reported that age-dependent cellular alterations in hippocampal area CA2 caused deficits in social cognition in *Df(16)A*$^{+/-}$ model mice, revealing another possible theory of pathogenesis in 22q11.2DS [36]. Other studies using the same mouse model have provided data on the possible chain of events from the 22q11.2 deletion to brain changes and potential for novel therapies. A proteomic study of microRNA dysregulation in two brain regions suggested a possible epigenetic component and dysregulation of proteins, some of which were predicted targets of miR-185 [37▪▪], one of seven miRNAs from the 22q11.2 deletion region [34]. Identified pathway abnormalities included synaptic plasticity, transcription regulation, mitochondrial dysfunction, mammalian targets of rapamycin signaling in the prefrontal cortex, and glutamatergic signaling in the hippocampus [37▪▪]. Further implicating microRNA dysregulation that may be related to *DGCR8* haploinsufficiency in 22q11.2DS [1,34], is a study of a *Df(16)1/+* mouse model reporting age-related disruption in thalamocortical projections to the auditory cortex, a region correlated with auditory hallucinations [38▪▪]. Replenishing the microRNA miR-338-3p, a miRNA predicted to target the *Drd2* transcript, in these mice improved thalamocortical synaptic transmission [38▪▪]. The same group identified gene *Mrpl40* from the deletion region to be involved in dysfunction in short-term synaptic plasticity through mitochondria-mediated deregulation of presynaptic calcium levels, a cellular mechanism involved in learning and working memory thought to contribute to deficits commonly seen in schizophrenia [39].

## CLINICAL MANAGEMENT CONSIDERATIONS

Current guidelines for 22q11.2DS recommend, as for other associated conditions, standard management for schizophrenia, including treatment with antipsychotic medications [2]. Recent studies provide information that may affect treatment considerations. For example, independent of antipsychotic use, individuals with 22q11.2DS are reported to have a significantly elevated risk of developing obesity [40], suggesting enhanced consideration of metabolic side effects and preventive strategies for individuals with 22q11.2DS. Also, there is further evidence of the

22q11.2 deletion as a risk factor for Parkinson's disease, notably in the early onset form (onset <50 years) [41]. Given that Parkinson's disease diagnosis may be delayed up to 10 years in 22q11.2DS if symptoms are attributed to antipsychotic medication-induced parkinsonism [42], consideration of clozapine, a treatment used in both schizophrenia and Parkinson's disease, has been recommended using a start-low go-slow approach while addressing the elevated seizure risk through concomitant use of anticonvulsants [43].

A genetic counseling study indicated that early detection of 22q11.2DS allows for early disclosure and monitoring of neuropsychiatric risk and can help diffuse stigma and convey the treatability of psychiatric illness [44]. These recommendations contribute to a growing literature that a genetic diagnosis has potential clinical benefits for patients and families that include an understanding of the etiologic basis of a psychiatric disorder and attendant risks for such disorders [2].

## CONCLUSION

The current review highlights the recent findings related to detection of, and characterizing, predicting, and managing psychotic illness in, 22q11.2DS. The findings support the general comparability of 22q11.2DS with schizophrenia and clinical UHR groups in the general population. Advances in early diagnosis may lead to early interventions that may eventually alter the clinical trajectory and risk for psychosis in individuals with 22q11.2 deletions. On the horizon are genome-wide studies to identify additional genetic risk factors for expression of schizophrenia from an international consortium [23]. Multiple opportunities await further study of this genetically high-risk population, including related animal models, which promise to inform pathogenesis and management of schizophrenia in the general population.

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### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. McDonald-McGinn DM, Sullivan KE, Marino B, *et al.* 22q11.2 deletion syndrome. Nat Rev Dis Primers 2015; 1:1–46.
2. Fung WL, Butcher NJ, Costain G, *et al.* Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet Med 2015; 17:599–609.
3. Costain G, Lionel AC, Merico D, *et al.* Pathogenic rare copy number variants in community-based schizophrenia suggest a potential role for clinical microarrays. Hum Mol Genet 2013; 22:4485–4501.
4. Bassett AS, Chow EW, AbdelMalik P, *et al.* The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psychiatry 2003; 160:1580–1586.
5. Dugoff L, Mennuti MT, McDonald-McGinn DM. The benefits and limitations of cell-free DNA screening for 22q11.2 deletion syndrome. Prenat Diagn 2017; 37:53–60.
6. Bassett AS, Costain G, Marshall CR. Neuropsychiatric aspects of 22q11.2 deletion syndrome: considerations in the prenatal setting. Prenat Diagn 2017; 37:61–69.
7. ■ Gross SJ, Stosic M, McDonald-McGinn DM, *et al.* Clinical experience with single-nucleotide polymorphism-based noninvasive prenatal screening for 22q11.2 deletion syndrome. Ultrasound Obstet Gynecol 2016; 47:177–183.

First report of practical prenatal experience in screening for 22q11.2 deletions using single-nucleotide polymorphism-based noninvasive prenatal testing in a large sample.

8. Poirsier C, Besseau-Ayasse J, Schluth-Bolard C, *et al.* A French multicenter study of over 700 patients with 22q11 deletions diagnosed using FISH or aCGH. Eur J Hum Genet 2016; 24:844–851.
9. ■ Vangkilde A, Olsen L, Hoeffding LK, *et al.* Schizophrenia spectrum disorders in a Danish 22q11.2 deletion syndrome cohort compared to the total Danish Population – a nationwide register study. Schizophr Bull 2016; 42:824–831.

Large-scale population-based registry study confirming an increased risk of being diagnosed with a schizophrenia spectrum disorder in individuals clinically identified to have a 22q11.2 deletion.

10. Rees E, Kendall K, Pardinas AF, *et al.* Analysis of intellectual disability copy number variants for association with schizophrenia. JAMA Psychiatry 2016; 73:963–969.
11. ■ Van L, Butcher NJ, Costain G, *et al.* Fetal growth and gestational factors as predictors of schizophrenia in 22q11.2 deletion syndrome. Genet Med 2016; 18:350–355.

Largest study of adverse perinatal outcomes as potential predictors of schizophrenia in 22q11.2 deletion syndrome (22q11.2DS), reporting that small for gestational age and/or prematurity significantly increased risk.

12. ■ Tang SX, Moore TM, Calkins ME, *et al.* The psychosis spectrum in 22q11.2 deletion syndrome is comparable to that of nondeleted youths. Biol Psychiatry 2016. [Epub ahead of print]

Largest known comparison of clinical features, symptomatology, cognition, and comorbidity of psychotic disorder in 22q11.2DS. Psychotic symptoms exhibited by those with 22q11.2DS are comparable to those with idiopathic psychotic illnesses, demonstrating the power of the 22q11.2DS model.

13. ■■ Schneider M, Armando M, Pontillo M, *et al.* Ultra high risk status and transition to psychosis in 22q11.2 deletion syndrome. World Psychiatry 2016; 15:259–265.

The first study to examine the predictive value of ultra-high-risk criteria in 22q11.2DS reported the clinical trajectory leading to psychosis to be broadly comparable with that observed in other clinical high-risk samples.

14. Midbari Kufert Y, Nachmani A, Nativ E, *et al.* Association between prematurity and the evolution of psychotic disorders in 22q11.2 deletion syndrome. J Neural Transm (Vienna) 2016; 123:1491–1497.
15. Schultze-Lutter F, Michel C, Schmidt SJ, *et al.* EPA guidance on the early detection of clinical high risk states of psychoses. Eur Psychiatry 2015; 30:405–416.
16. Weinberger R, Yi J, Calkins M, *et al.* Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome. Eur Neuropsychopharmacol 2016; 26:1610–1618.
17. Mekori-Domachevsky E, Guri Y, Yi J, *et al.* Negative subthreshold psychotic symptoms distinguish 22q11.2 deletion syndrome from other neurodevelopmental disorders: a two-site study. Schizophr Res 2016. [Epub ahead of print]
18. Vangkilde A, Jepsen JR, Schmock H, *et al.* Associations between social cognition, skills, and function and subclinical negative and positive symptoms in 22q11.2 deletion syndrome. J Neurodev Disord 2016; 8:1–13.
19. Fonseca-Pedrero E, Debbane M, Schneider M, *et al.* Schizotypal traits in adolescents with 22q11.2 deletion syndrome: validity, reliability and risk for psychosis. Psychol Med 2016; 46:1005–1013.
20. Radoeva PD, Fremont W, Antshel KM, Kates WR. Longitudinal study of premorbid adjustment in 22q11.2 deletion (velocardiofacial) syndrome and association with psychosis. Dev Psychopathol 2017; 29:93–106.

  

21. Antshel KM, Fremont W, Ramanathan S, Kates WR. Predicting cognition and psychosis in young adults with 22q11.2 deletion syndrome. Schizophr Bull 2016. [Epub ahead of print]
22. Yuen T, Chow EW, Silversides CK, Bassett AS. Premorbid adjustment and schizophrenia in individuals with 22q11.2 deletion syndrome. Schizophr Res 2013; 151:221–225.
23. Vorstman JA, Breetvelt EJ, Duijff SN, *et al.* Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. JAMA Psychiatry 2015; 72:377–385.
24. Pena J, Ibarretxe-Bilbao N, Sanchez P, *et al.* Combining social cognitive treatment, cognitive remediation, and functional skills training in schizophrenia: a randomized controlled trial. NPJ Schizophr 2016; 2:1–7.
25. Mariano MA, Tang K, Kurtz M, Kates WR. Examining the durability of a hybrid, remote and computer-based cognitive remediation intervention for adolescents with 22q11.2 deletion syndrome. Early Interv Psychiatry 2016. [Epub ahead of print]
26. Boot E, van Amelsvoort TA. Neuroimaging correlates of 22q11.2 deletion syndrome: implications for schizophrenia research. Curr Top Med Chem 2012; 12:2303–2313.
27. Ramanathan S, Mattiaccio LM, Coman IL, *et al.* Longitudinal trajectories of cortical thickness as a biomarker for psychosis in individuals with 22q11.2 deletion syndrome. Schizophr Res 2016. [Epub ahead of print]
28. Radoeva PD, Bansal R, Antshel KM, *et al.* Longitudinal study of cerebral surface morphology in youth with 22q11.2 deletion syndrome, and association with positive symptoms of psychosis. J Child Psychol Psychiatry 2017; 58:305–314.
29. Berhanu D, Mattiaccio LM, Antshel KM, *et al.* Cortical-amygdala volumetric ratios predict onset of symptoms of psychosis in 22q11.2 deletion syndrome. Psychiatry Res 2017; 259:10–15.
30. Bakker G, Caan MW, Vingerhoets WA, *et al.* Cortical morphology differences in subjects at increased vulnerability for developing a psychotic disorder: a comparison between subjects with ultra-high risk and 22q11.2 deletion syndrome. PLoS One 2016; 11:1–16.
31. Bakker G, Caan MW, Schluter RS, *et al.* Distinct white-matter aberrations in 22q11.2 deletion syndrome and patients at ultra-high risk for psychosis. Psychol Med 2016; 46:2299–2311.
32. Merico D, Zarrei M, Costain G, *et al.* Whole-genome sequencing suggests schizophrenia risk mechanisms in humans with 22q11.2 deletion syndrome. G3 (Bethesda) 2015; 5:2453–2461.
33. ▪ Lin M, Pedrosa E, Hrabovsky A, *et al.* Integrative transcriptome network analysis of iPSC-derived neurons from schizophrenia and schizoaffective disorder patients with 22q11.2 deletion. BMC Syst Biol 2016; 10:1–20.

Study using induced pluripotent stem cell-derived neurons to explore possible molecular connections between 22q11.2 deletions and molecular pathways implicated in schizophrenia.

34. Guna A, Butcher NJ, Bassett AS. Comparative mapping of the 22q11.2 deletion region and the potential of simple model organisms. J Neurodev Disord 2015; 7:1–16.
35. ▪ Tamura M, Mukai J, Gordon JA, Gogos JA. Developmental inhibition of Gsk3 rescues behavioral and neurophysiological deficits in a mouse model of schizophrenia predisposition. Neuron 2016; 89:1100–1109.

Demonstrated that Gsk3 inhibition can reverse certain cognitive deficits in a mouse model of 22q11.2DS, implicating the dopaminergic system and/or aberrant axonal branching and suggesting molecular pathogenesis of certain phenotypes and potential targets for treatment.

36. Piskorowski RA, Nasrallah K, Diamantopoulou A, *et al.* Age-dependent specific changes in area CA2 of the hippocampus and social memory deficit in a mouse model of the 22q11.2 deletion syndrome. Neuron 2016; 89:163–176.
37. ▪▪ Wesseling H, Xu B, Want EJ, *et al.* System-based proteomic and metabolomic analysis of the Df(16)A+/− mouse identifies potential miR-185 targets and molecular pathway alterations. Mol Psychiatry 2016. [Epub ahead of print]

First study to analyze prefrontal cortex and hippocampal brain tissue for the combined effects of microRNA dysregulation and gene disruption related to the deletion in a mouse model. Profiling analyses suggested epigenetic components, hippocampal glutamatergic signaling changes, and network findings linked through O-GlcNAc transferase subunit p110 (OGT1), a predicted target of miR-185.

38. ▪▪ Chun S, Du F, Westmoreland JJ, *et al.* Thalamic miR-338-3p mediates auditory thalamocortical disruption and its late onset in models of 22q11.2 microdeletion. Nat Med 2016; 23:39–48.

Study using a mouse model of 22q11.2DS that suggests that haploinsufficiency of the 22q11.2 deletion region gene *DGCR8* leads to depletion of a thalamus-enriched microRNA (miR-338-3p), in turn leading to an increase in D2 dopamine receptor levels and thus to age-related disruption of thalamocortical synaptic transmission to the auditory cortex. Rescue of effects in the model suggests miR-338-3p as a potential therapeutic target for schizophrenia.

39. Devaraju P, Yu J, Eddins D, *et al.* Haploinsufficiency of the 22q11.2 microdeletion gene Mrpl40 disrupts short-term synaptic plasticity and working memory through dysregulation of mitochondrial calcium. Mol Psychiatry 2016. [Epub ahead of print]
40. Voll SL, Boot E, Butcher NJ, *et al.* Obesity in adults with 22q11.2 deletion syndrome. Genet Med 2017; 19:204–208.
41. Mok KY, Sheerin U, Simon-Sanchez J, *et al.* Deletions at 22q11.2 in idiopathic Parkinson's disease: a combined analysis of genome-wide association data. Lancet Neurol 2016; 15:585–596.
42. Butcher NJ, Kiehl TR, Hazrati LN, *et al.* Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. JAMA Neurol 2013; 70:1359–1366.
43. Butcher NJ, Fung WL, Fitzpatrick L, *et al.* Response to clozapine in a clinically identifiable subtype of schizophrenia. Br J Psychiatry 2015; 206:484–491.
44. Hart SJ, Schoch K, Shashi V, Callanan N. Communication of psychiatric risk in 22q11.2 deletion syndrome: a pilot project. J Genet Couns 2016; 25:6–17.