Published in final edited form as:

Curr Opin Psychiatry. 2019 March ; 32(2): 67–72. doi:10.1097/YCO.0000000000000466.

Recent developments in understanding the relationship between 22q11.2 Deletion Syndrome and psychosis

Linda O'Rourke¹ and Kieran C Murphy¹

¹Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Beaumont, Dublin 9, Ireland

Abstract

Purpose of Review: Individuals with 22q11.2 Deletion Syndrome (22q11.2DS) have high rates of comorbid mental illness, particularly psychosis and schizophrenia. The purpose of this review is to summarise recent research in the area of 22q11.2DS and psychosis.

Recent Findings: Research over the past year has identified negative symptoms, functional impairment, dysphoric mood and a childhood diagnosis of attention deficit hyperactivity disorder as important clinical predictors of psychosis risk in 22q11.2DS. As previously reported in non-deleted schizophrenia, recent studies have implicated neuroinflammation as a possible neurobiological mechanism for psychosis in 22q11.2DS. Recent neuroimaging findings suggest the cortex is significantly thinner in those with 22q11.2DS and psychosis compared to those without psychosis, replicating similar findings in non-deleted schizophrenia. Further data from the International 22q11.2DS Brain and Behavior Consortium has suggested that chromosomal microdeletions are significantly more likely to involve protein-coding genes and several rare copy number variants are associated with the presence of psychosis in deleted individuals.

Summary: There have been several significant recent advances to further characterise the high rates of psychosis in 22q11.2DS, to identify additional clinical predictors of psychosis and to increase our understanding of the neural substrate and genetic aetiology of psychosis in 22q11.2DS.

Keywords

22q11.2 Deletion Syndrome; psychosis; schizophrenia; neuroimaging; genetics

Introduction:

22q11.2 Deletion Syndrome (22q11.2DS) is the most common chromosomal microdeletion in humans, ranging in prevalence from 1/1,000 on foetal testing to 1/6,000 at the population

Corresponding author: Linda O'Rourke, Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Beaumont, Dublin 9, Ireland. lindaorourke@rcsi.ie. Tel:+35318093470.

Conflicts of Interest:

KCM is a member of the International 22q11.2 Deletion Syndrome Brain Behavior Consortium and the Enigma Consortium. LOR has no conflicts of interest.

level [1]. A recent study by Palmer et al [2] showed the median time to molecular diagnosis ranges from zero to 20.7 years and physical anomalies of the heart and/or palate rather than developmental delay or intellectual disability were associated with an earlier diagnosis. Despite the widespread availability of molecular testing, only a minority of cases were diagnosed in infancy.

Psychiatric comorbidities are highly prevalent in 22q11.2DS, affecting three-quarters of all diagnosed individuals. In particular, a diagnosis of 22q11.2DS constitutes a 30-fold increased risk of developing psychosis compared to the general population [3]. Although a recent register-based population study reported only a six-fold relative risk of schizophrenia or related psychotic disorder in 22q11.2DS [4], this may be explained by methodological issues including ascertainment strategies utilised [5]. In a study using data from the International 22q11.2 Deletion Syndrome Brain and Behavior Consortium, Weisman et al [3] examined 760 subjects aged 6 to 55 years with 22q11.2DS. They found that nearly one-third of participants (32.8%) met criteria for positive subthreshold psychotic symptoms with adolescents and young adults (13–25 years) showing the highest rates. In addition, higher rates of anxiety disorders and attention deficit hyperactivity disorder (ADHD) were found in those with subthreshold symptoms compared to those without. Furthermore, they reported age-related changes in subthreshold psychotic symptoms and evidence that cognitive deficits are associated with subthreshold psychosis in this population.

There is now a wealth of evidence suggesting that deletion of 22q11.2 represents the strongest known molecular genetic risk factor for the development of psychosis. Consequently, the study of 22q11.2DS represents a promising model for studying both the aetiology of schizophrenia and early signs of psychosis proneness [3]. In this article, we review research published over the past year focusing on papers relating to 22q11.2DS and psychosis selected from over seventy papers identified in this area.

Clinical predictors of psychosis in 22q11.2DS

Identification of co-morbid psychiatric disorders in people with 22q11.2DS may have important implications for predicting the subsequent development of psychosis in affected individuals. Niarchou et al [6] examined 72 individuals with 22q11.2DS and subthreshold psychosis and reported a greater prevalence of ADHD inattentive symptoms in those with 22q11.2DS compared to typically developing individuals with prodromal psychotic symptoms.

In a further study, using longitudinal data from the International 22q11.2 Deletion Syndrome Brain Behavior Consortium, Niarchou et al [7*] tested the hypothesis that the presence of ADHD inattentive symptoms predicts the development of psychotic symptoms in a group of 250 individuals with 22q11.2DS. The mean age of their cohort at first assessment was 11.2 years and mean age at follow-up was 14.3 years. ADHD was diagnosed using DSM-IV-TR and onset of psychotic symptoms was recorded using self-report questionnaires. They demonstrated a strong association between a childhood diagnosis of ADHD and later onset of psychotic symptoms and development of a psychotic disorder. While a direct link between childhood ADHD and later-onset psychotic disorder could possibly explain these findings, other potential explanations include a shared genetic variance, that inattentive

symptoms or an ADHD diagnosis in 22q11.2DS are prodromal or premorbid forms of schizophrenia or that the 22q11.2 deletion increases the risk of inattentive symptoms and ADHD which in turn increases the risk for psychotic outcomes. As the mean age at follow-up was only 14.3 years, study participants had not yet passed the peak age of onset for a psychotic disorder and it is likely that the reported associations are an underestimate. Larger studies are required to replicate these findings.

Building on previous work showing subthreshold symptoms, global functioning and ultra high-risk status are clinical predictors of psychosis, Tang et al [8*] examined the demographic, clinical and cognitive predictors of psychosis in a sample of 75 individuals with 22q11.2DS aged 8–35 years. They found that negative symptoms and functional impairment were predictive of positive psychosis-spectrum symptoms while dysphoric mood and anxiety were predictive of emergent and persistent-positive psychosis-spectrum symptoms.

Previous reports that a childhood diagnosis of autism spectrum disorder (ASD), with associated social-communication skill deficits and repetitive ritualised behaviours, may predict later onset psychosis were re-examined by Fiksinski et al [9]. They used a prospective longitudinal study design to follow 52 children with both 22q11.2DS and ASD. Participant mean age at first assessment was 14.3 years and second assessment was 19 years. Similar to a previous retrospective study of adults with schizophrenia [10], no association was found between a childhood diagnosis of ASD and subsequent development of a psychotic disorder.

Tang et al [11] conducted a pilot study of 32 individuals to examine olfactory functioning as a possible biomarker for psychosis in 22q11.2DS. They showed that both odour identification and discrimination are significantly impaired in individuals with 22q11.2DS compared to healthy controls. In addition, they found that odour discrimination in particular correlated with overall psychosis spectrum symptoms, independent of cognitive function.

Neuroinflammation and psychosis in 22q11.2DS

Previous evidence suggests that neuroinflammation, with high circulatory levels of proinflammatory and anti-inflammatory cytokines, is associated with schizophrenia in the general population [12,13]. Mekori-Domachevsky et al [14] reported similar findings in 13 individuals with 22q11.2DS and psychosis, showing significantly higher serum levels of Interleukin-6 and higher ratio of Interleukin-6 to Interleukin-10, an indicator of proinflammatory activation, compared to 36 nonpsychotic 22q11.2DS individuals and 30 matched controls. Similarly, Vergaelen et al [15] reported significantly higher percentages of inflammatory T-helper (Th) cells; Th1, Th17 and Th memory cells in 34 adults with 22q11.2DS compared to non-deleted controls. A notably higher percentage of Th17 was reported in those with comorbid psychosis and the percentage of Th17 cells was related to higher scores on the PANSS positive symptom scale. These recent preliminary studies suggest that neuroinflammation may be associated with the development of psychosis in 22q11.2DS and are consistent with accumulating evidence for the role of neuroinflammation in non-deleted schizophrenia.

Identifying the neural substrate of psychosis in 22q11.2DS

Determining the neural substrates of psychosis in 22q11.2DS continues to be major focus in 22q11.2 neuroimaging studies. Previous studies suggested widespread cortical changes including lower frontal and superior temporal gyrus gray matter volumes are associated with schizophrenia in 22q11.2DS subjects [16,17,18]. While previous studies supported an overlap between neuroanatomical abnormalities in 22q11.2 deleted and non-deleted schizophrenia, they were underpowered and their relatively small sample sizes limited the conclusions that could be made. To address this, the 22q11.2 Working Group as part of Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) was formed. This consortium, by harmonising data collected across multiple sites, represents the largest-ever analysis of brain structural alterations in 22q11.2DS. The consortium compared imaging data from 474 participants with 22q11.2DS to typically developing controls [19*]. They demonstrated a generalised reduction in surface area, most noticeably in the medial occipital cortex and anterior cingulate cortex. In addition, participants with larger 22q11.2 deletions were seen to demonstrate more significant reductions in cortical surface area, particularly in the anterior medial cortical and lateral cortical regions, providing the first evidence that deletion size impacts on brain structure. However, there were no significant differences in surface area identified between deleted subjects with or without psychosis. Compared to controls, those with 22q11.2DS showed thicker cortical gray matter in both right and left hemispheres but thinner cortex in the temporal, cingulate and parahippocampal regions. When 22q11.2DS subjects with and without psychosis were compared, the psychosis group showed significantly thinner cortex in the left superior temporal gyrus and lateral occipital cortex, and right medial superior frontal, cingulate, pre-and post-central and supramarginal gyri. Overall, the cortex was significantly thinner in the psychosis group, with similar, moderate effect sizes in the right and left hemispheres. Similar neuroanatomical abnormalities have been reported in non-deleted schizophrenia, providing further support for 22q11.2DS as a biological model of schizophrenia.

To examine changes in cortical thickness over time, Ramanathan et al [20] carried out a series of MRI scans of 75 adolescents with 22q11.2DS, 18 of whom had at least one positive symptom, across a nine year period. Six individuals developed psychosis during the study period. They showed baseline cortical thickness in the left parietal region to be significantly smaller in subjects compared to controls and rates of thinning was slower. The authors noted a shift in the linear trajectory of cortical thinning and later peak and decline in the 22q11.2DS group.

Given the high prevalence of negative symptoms in individuals with 22q11.2DS, Mihailov et al [21] examined cortical volume, thickness and gyrification of 71 individuals with 22q11.2DS without an overt psychotic disorder to determine which structural brain changes, if any, were associated with the presence of negative symptoms. Although no differences were noted in cortical volume or thickness, they found an association between reduced gyrification in the medial occipital and temporal regions and high negative scores on the SIPS and PANSS.

Increasingly, schizophrenia is seen as a disorder of functional network dysconnectivity rather than regionally specific pathophysiology. Schreiner et al [22] investigated intrinsic-

connectivity-networks in two independent comparison groups of 22q11.2DS individuals and typically developing controls. They reported significant hypoconnectivity in those with 22q11DS. In addition they found that, within the 22q11.2DS group, connectivity alterations within the anterior cingulate/precuneus, default mode, left executive and salience networks predicted psychosis risk.

Using a functional connectivity analysis, Mattiaccio et al [23] reported on 15 individuals with 22q11.2DS and prodromal or overt positive psychotic symptoms. They showed the presence of such psychotic symptoms to be positively associated with increased functional connectivity between the left precuneus and right superior frontal gyrus and reduced functional connectivity between the bilateral precalcarine. They also showed prodromal or overt positive symptoms to be negatively associated with increased functional connectivity between the right pericalcarine and the right postcentral gyrus.

Padula et al [24] used structural connectivity to compare 22q11.2DS subjects with and without attenuated positive psychotic symptoms using both univariate and multivariate approaches. While the univariate comparison yielded no differences between groups, the multivariate prediction showed altered connections involving the limbic system, particularly the anterior cingulate cortex, which discriminated between the groups. The authors suggest that these alterations may represent a potential biomarker for psychosis in 22q11.2DS.

The anterior cingulate cortex was further implicated by the same group when investigating dynamic brain function in 22q11.2DS by assessing the variability of blood oxygenation level dependent (BOLD) signals in 22q11.2DS subjects with and without psychotic symptoms [25]. They reported a missing positive age-relationship in the dorsal anterior cingulate cortex (dACC) in individuals with higher positive psychotic symptoms, leading to globally lower variability in dACC. In addition to providing further evidence to implicate the anterior cingulate gyrus in the development of psychosis in 22q11.2DS, the authors suggested that aberrant BOLD signal variability development may be an additional potential biomarker for psychosis.

Genetic studies in 22q11.2DS and psychosis

Previously, the gene claudin-5 was shown to be weakly associated with schizophrenia in non-deleted populations [26]. Claudin-5 is a tight junction protein, a major component of the blood-brain barrier (BBB) and also maps to chromosome 22q11.2. Greene et al [27] reported a variant of the claudin-5 gene to be weakly associated with the presence of schizophrenia in individuals with 22q11.2DS. In addition, they found that persistent and targeted suppression of claudin-5 at the BBB induced a correlative phenotype of psychosis-like behaviours in mouse models. They suggested that regulation of BBB integrity and dynamism may be an additional therapeutic strategy for the treatment of schizophrenia in both deleted and non-deleted populations.

The incomplete penetrance of psychotic disorders in 22q11.2DS suggests that additional genetic risk factors are required for the development of psychosis. To test this hypothesis, Guipponi et al [28] sequenced the entire 22q11.2 non-deleted region in eighty-eight 22q11.2DS subjects, 40 of whom had a comorbid psychotic disorder and 48 of whom did

not. The distribution of single nucleotide variants, small insertions/deletions and copy number variants were compared between groups and although sufficiently powered to detect risk variants, no genetic variants of large effect size were detected. Consequently, this study did not support the hypothesis that specific genetic variants of major effect in the non-deleted 22q11.2 allele are associated with the development of psychotic illness in individuals with 22q11.2DS.

Using a similar rationale, Bassett et al [29*] reported initial findings from the International 22q11.2DS Brain and Behavior Consortium. They hypothesised a role for “second hits” and investigated whether additional copy number variants outside the 22q11.2 deleted region may increase the risk for psychosis in those with 22q11.2DS. Although they found no difference in the overall burden of copy number variants between 22q11.2 deletions in subjects with and without psychosis, they reported that chromosomal microdeletions were significantly more likely to involve protein-coding genes in the psychotic compared to the non-psychotic group. They also found that additional rare copy number variants, including 1q21.1 and 16p12.2 which have both been associated with schizophrenia in non-deleted populations, were associated with the presence of psychosis in those with 22q11.2DS. Their findings give further support for a multigenic hypothesis for schizophrenia in this population [29*,30].

Identification of protective loss-of-function (LoF) mutations offers potential for novel therapeutic interventions for genetic disorders such as 22q11.2DS. Using a mouse model carrying a hemizygous 1.3-Mb deletion on chromosome 16 [Df(16)A], which is syntenic to the human 22q11.2 deletion, Diamantopoulou et al [31**] reported that combination of the Df(16)A deletion with a LoF Mirta22 allele results in rescue of key schizophrenia-related deficits. These included prepulse inhibition decrease, working memory impairment, social memory deficits and both synaptic and structural plasticity abnormalities in the prefrontal cortex offering potential for new therapeutic strategies for psychosis in individuals with 22q11.2DS.

Conclusion:

The current review identifies several significant recent advances to further characterise the high rates of psychosis in 22q11.2DS, to identify additional clinical predictors of psychosis and to increase our understanding of the neural substrate and genetic aetiology of psychosis in 22q11.2DS. These converging lines of evidence provide further support for 22q11.2DS as a biological model of schizophrenia in the general non-deleted population.

Acknowledgements:

None

Financial support and sponsorship:

Supported by NIMH grant 5U01MH101723-02 and Health Research Board of Ireland grant HRA-POR-2015-1077

References:

*Of special interest

**Of outstanding interest

1. McDonald-McGinn D, Sullivan K, Marino B et al. 22q11.2 deletion syndrome. *Nature Reviews Disease Primers* 2015; 1:1–19.
2. Palmer L, Butcher N, Boot E et al. Elucidating the diagnostic odyssey of 22q11.2 deletion syndrome. *Am J Med Genet Part A* 2018;176(4):936–944. [PubMed: 29575622]
3. Weisman O, Guri Y, Gur R et al. Subthreshold psychosis in 22q11.2 deletion syndrome: Multisite naturalistic study. *Schizophr Bull* 2017; 43(5):1079–1089. [PubMed: 28204757]
4. Hoeffding L, Trabjerg B, Olsen L et al. Risk of psychiatric disorders among individuals with the 22q11.2 deletion or duplication: A Danish nationwide, register-based study. *JAMA Psychiatry* 2017;74(3):282–290. [PubMed: 28114601]
5. Harris J Understanding psychiatric disorders in people with 22q11.2 deletion and duplication. *JAMA Psychiatry* 2017;74(3):290–292. [PubMed: 28114510]
6. Niarchou M, Calkins M, Moore T et al. Attention deficit hyperactivity disorder symptoms and psychosis in 22q11.2 deletion syndrome. *Schizophr Bull* 2017;44(4):824–833.
- 7*. Niarchou M, Chawner S, Fiksinski A et al. Attention deficit hyperactivity disorder symptoms as antecedents of later psychotic outcomes in 22q11.2 deletion syndrome. *Schizophr Res* 2018; 10.1016/j.schres.2018.07.044.*This paper reports that inattentive symptoms and a diagnosis of ADHD are associated with subsequent psychotic outcomes in 22q11.2DS, this may have important clinical implications for treatment.
- 8*. Tang S, Moore T, Calkins M et al. Emergent, remitted and persistent psychosis-spectrum symptoms in 22q11.2 deletion syndrome. *Translational Psychiatry* 2017;7(7):1–8.*This paper reports that negative symptoms and functional impairment were predictive of positive psychosis-spectrum symptoms while dysphoric mood and anxiety were predictive of emergent and persistent-positive psychosis-spectrum symptoms.
9. Fiksinski A, Breetvelt E, Duijff S et al. Autism spectrum and psychosis risk in the 22q11.2 deletion syndrome. Findings from a prospective longitudinal study. *Schizophr Res* 2017;188:59–62. [PubMed: 28119035]
10. Vorstman J, Breetvelt E, Thode K et al. Expression of autism spectrum and schizophrenia in patients with a 22q11.2 deletion. *Schizophr Res* 2013;143(1):55–59. [PubMed: 23153825]
11. Tang S, Moberg P, James J et al. Olfactory deficits and psychosis-spectrum symptoms in 22q11.2 deletion syndrome. *Schizophr Res* 2018; 10.1016/j.schres.2018.07.012.
12. Gao L, Li Z, Chang S et al. Association of interleukin-10 polymorphisms with schizophrenia: A meta-analysis. *PLoS One* 2014;9(3):e90407. [PubMed: 24603720]
13. Hope S, Hoseth E, Dieset I et al. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. *Schizophr Res* 2015;165:188–194. [PubMed: 25956633]
14. Mekori-Domachevsky E, Taler M, Shoenfeld Y et al. Elevated proinflammatory markers in 22q11.2 deletion syndrome are associated with psychosis and cognitive deficits. *J Clin Psychiatry* 2017;78(9):e1219–1225. [PubMed: 29141125]
15. Vergaelen E, Schiweck C, Van Steeland K et al. A pilot study on immuno-psychiatry in the 22q11.2 deletion syndrome: A role for Th17 cells in psychosis? *Brain Behav Immu* 2018;70:88–95.
16. Van Amelsvoort T, Daly E, Henry J et al. Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia: Preliminary results of a structural magnetic resonance imaging study. *Arch Gen Psychiatry* 2004;61(11):1085–1096. [PubMed: 15520356]
17. Chow E, Ho A, Wei C et al. Association of schizophrenia in 22q11.2 deletion syndrome and gray matter volumetric deficits in the superior temporal gyrus. *Am J Psychiatry* 2011;168(5):522–529. [PubMed: 21362743]

18. Bakker G, Caan M, Vingerhoets W 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(11):e0159928. [PubMed: 27828960]
- 19*. Sun D, Ching C, Lin A et al. Large-scale mapping of cortical alterations in 22q11.2 deletion syndrome: Convergence with idiopathic psychosis and effects of deletion size. *Mol Psychiatry* 2018; 10.1038/s41380-018-0078-5. *This paper reports that the cortex is significantly thinner in people with 22q11.2DS and psychosis compared to those without psychosis, replicating similar findings in non-deleted schizophrenia and providing further support for 22q11.2DS as a biological model of schizophrenia. In addition, this study provides the first evidence that deletion size impacts on brain structure. the first evidence that deletion size impacts upon brain structure.
20. Ramanathan S, Mattiaccio L, Coman I et al. Longitudinal trajectories of cortical thickness as a biomarker for psychosis in individuals with 22q11.2 deletion syndrome. *Schizophr Res* 2017;188:35–41. [PubMed: 27988073]
21. Mihailov A, Padula M, Scariati E et al. Morphological brain changes associated with negative symptoms in patients with 22q11.2 deletion syndrome. *Schizophr Res* 2017;188:52–58. [PubMed: 28139357]
22. Schreiner M, Forsyth J, Karlsgodt K et al. Intrinsic connectivity network-based classification and detection of psychotic symptoms in youth with 22q11.2 deletions. *Cereb Cortex* 2017;27(6):3294–3306. [PubMed: 28383675]
23. Mattiaccio L, Coman I, Thompson C et al. Frontal dysconnectivity in 22q11.2 deletion syndrome: An atlas-based functional connectivity analysis. *Behav Brain Funct* 2018;14(1):2. [PubMed: 29352808]
24. Padula M, Scariati E, Schaer M et al. Altered structural network architecture is predictive of the presence of psychotic symptoms in patients with 22q11.2 deletion syndrome. *NeuroImage: Clinical* 2017;16:142–150. [PubMed: 28794975]
25. Zöllner D, Padula M, Sandini C et al. Psychotic symptoms influence the development of anterior cingulate BOLD variability in 22q11.2 deletion syndrome. *Schizophr Res* 2018;193:319–328. [PubMed: 28803847]
26. Falcone T, Carlton E, Lee C et al. Does systemic inflammation play a role in pediatric psychosis? *Clinical Schizophrenia & Related Psychoses* 2015;9(2):65–78B. [PubMed: 23491967]
27. Greene C, Kealy J, Humphries M et al. Dose-dependent expression of claudin-5 is a modifying factor in schizophrenia. *Mol Psychiatry* 2017;00:1–11.
28. Guipponi M, Santoni F, Schneider M et al. No evidence for the presence of genetic variants predisposing to psychotic disorders on the non-deleted 22q11.2 allele of VCFS patients. *Translational Psychiatry* 2017;7:e1039. [PubMed: 28221368]
- 29*. Bassett A, Lowther C, Merico D et al. Rare genome-wide copy number variation and expression of schizophrenia in 22q11.2 deletion syndrome. *Am J Psych* 2017;174(11):1054–1063. *This paper reports that chromosomal microdeletions in 22q11.2DS were significantly more likely to involve protein-coding genes in the psychotic compared to the non-psychotic group. The authors also found that additional rare copy number variants, including 1q21.1 and 16p12.2 which have both been associated with schizophrenia in non-deleted populations, were associated with the presence of psychosis in those with 22q11.2DS. Their findings give further support for a multigenic hypothesis for schizophrenia in this population.
30. Goes F, Sawa A. Psychosis beyond the 22q11.2 deletion: Do additional genetic factors play a role? *Am J Psych* 2017;174(11):1027–1029.
- 31**. Diamantopoulou A, Sun Z, Mukai J et al. Loss-of-function mutation in Mirta22/Emc10 rescues specific schizophrenia-related phenotypes in a mouse model of the 22q11.2 deletion. *Proc Natl Acad Sci* 2017;114(30):E6127–6136. [PubMed: 28696314] **This paper reports that combination of the Df(16)A deletion with a LoF Mirta22 allele results in rescue of key schizophrenia-related deficits. These included prepulse inhibition decrease, working memory impairment, social memory deficits and both synaptic and structural plasticity abnormalities in the prefrontal cortex offering potential for new therapeutic strategies for psychosis in individuals with 22q11.2DS.

Key Points:

Individuals with 22q11.2 Deletion Syndrome (22q11.2DS) have high rates of comorbid mental illness, particularly psychosis and schizophrenia.

Research over the past year has identified negative symptoms, functional impairment, dysphoric mood, inattention symptoms and a childhood diagnosis of attention deficit hyperactivity disorder as important clinical predictors of psychosis risk in 22q11.2DS.

Recent neuroimaging findings suggest that the cortex is significantly thinner in people with 22q11.2DS and psychosis compared to those without psychosis, replicating similar findings in non-deleted schizophrenia and providing further support for 22q11.2DS as a biological model of schizophrenia.

Chromosomal microdeletions are significantly more likely to involve protein-coding genes and several rare copy number variants that have been associated with non-deleted schizophrenia in the general population are associated with the presence of psychosis in people with 22q11.2DS.