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Neuropsychiatric aspects of 22q11.2 deletion syndrome: considerations in the prenatal setting

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Abstract

Most major neuropsychiatric outcomes of concern to families are not detectable by prenatal ultrasound. The introduction of genome-wide chromosomal microarray analysis to prenatal clinical diagnostic testing has increased the detection of pathogenic 22q11.2 deletions, which cause the most common genomic disorder. The recent addition of this and other microdeletions to non-invasive prenatal screening methods using cell-free fetal DNA has further propelled interest in outcomes. Conditions associated with 22q11.2 deletions include intellect ranging from intellectual disability to average, schizophrenia and other treatable psychiatric conditions, epilepsy, and early-onset Parkinson's disease. However, there is currently no way to predict how severe the lifetime expression will be. Available evidence suggests no major role in these neuropsychiatric outcomes for the congenital cardiac or most other structural anomalies that may be detectable on ultrasound. This article provides an outline of the lifetime neuropsychiatric phenotype of 22q11.2 deletion syndrome that will be useful to clinicians involved in prenatal diagnosis and related genetic counselling. The focus is on information that will be most relevant to two common situations: detection of a 22q11.2 deletion in a fetus or newborn, and new diagnosis of 22q11.2 deletion syndrome in a parent without a previous molecular diagnosis.

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Background

In recent years, chromosomal microarray analysis ("microarray" testing) has become the standard for invasive prenatal diagnostic testing. Microarray allows for the genome-wide detection of copy number variations (CNVs), including those associated with established microdeletion and microduplication syndromes that have important clinical features not detectable by prenatal ultrasound. Microarray and other high resolution methods represent a clear increase in diagnostic yield over karyotype (a low resolution method that cannot detect most pathogenic CNV) and the targeted testing using fluorescence *in situ* hybridization (FISH), which requires an index of suspicion and misses pathogenic CNVs other than those targeted by the specific probe used.[1,2] Microarray has made routine the ability to detect the pathogenic 22q11.2 deletions associated with the most common microdeletion syndrome known: 22q11.2 deletion syndrome (22q11.2DS), previously known as DiGeorge or velocardiofacial syndrome.[1,2] In addition, several companies are now providing the means of non-invasive prenatal screening for 22q11.2 deletions.[3] The primary concern of parents is usually the neurodevelopmental outcome and risk of major psychiatric illness associated with a genetic finding.[4,5] Clinicians often have concerns about how best to provide information and appropriate counselling for families about these risks, particularly for long-term neuropsychiatric outcomes.[6,7] Fetal medicine specialists, medical geneticists, genetic counsellors, obstetricians, pediatric cardiologists, and other clinicians who are providing care and counselling at the time of genetic testing and molecular diagnosis thus need reliable, evidence-based, and current information about the neuropsychiatric implications of finding a 22q11.2 deletion.

We also aim to provide relevant information for those clinicians who are experienced in identifying and managing the physical congenital abnormalities that are discoverable on ultrasound, and that may be associated with a 22q11.2 deletion. Although this deletion is most often a new (*de novo*) genetic event in the family, in up to 1 in 10 cases a parent will be discovered to also have the 22q11.2 deletion. The counselling issues in this scenario therefore differ from those where only the fetus or newborn is receiving a molecular diagnosis. In this review, we provide an overview of the current state of knowledge about the variable neuropsychiatric expression in 22q11.2DS across the lifespan, together with the implications for management and counselling in the prenatal setting. [Although the reciprocal 22q11.2 duplication can be identified with the same tests, the associated psychiatric phenotype is less well delineated and is beyond the scope of this review.]

Epidemiology and Prevalence of 22q11.2 Deletions in Prenatal Settings

The 22q11.2 deletion is considered rare, but may affect up to 1 in 1000 pregnancies (Table 1).[1,2,8,9] The mutation occurs as a *de novo* event in about 90% of cases, unrelated to parental ages at birth or any other known factor.[10,11] Current universal prenatal and newborn molecular screening methods do not directly assess for a 22q11.2 deletion. There appear to be few major phenotypic differences between 22q11.2 deletions of various lengths, some of which cannot be detected by FISH using the standard clinical probe,[10-12] but would be detectable with recent prenatal diagnostic and screening methods.[1,2,3]{Helgeson, 2015 #PMID:26088833} Absence of the typical 22q11.2 deletion in very large control

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populations suggests complete penetrance For this reason, 22q11.2 deletion and 22q11.2DS are used interchangeably. However, there can be highly variable phenotypic expression, even within a family.[12] Awareness of the syndrome amongst the lay public (and also healthcare providers) is low.[13,14]

In a pregnancy, ultrasound can identify physical features that may be associated with 22q11.2DS. For example, the discovery of congenital heart disease (CHD) increases the risk for a 22q11.2 deletion substantially. Prevalence estimates for the 22q11.2 deletion include 5-10% of ventricular septal defect (VSD), ~15% of tetralogy of Fallot, ~33% of truncus arteriosus, and ~50% of interrupted aortic arch type B.[12,15,16] An anomaly of aortic arch laterality or branching may hint at an underlying 22q11.2 deletion, even in the absence of a major intracardiac defect.[15] Although conotruncal and select other anomalies are classically described, all types of CHD have been seen in association with 22q11.2 deletions.[12,16,17] If present (estimated 40-75% of patients with 22q11.2DS),[12,18] CHD severity can range from non-viable to subclinical (e.g., spontaneously closing VSD).[12]

22q11.2 deletions can result in many other fetal anomalies detectable on routine ultrasound screening. Some relatively rare features of 22q11.2DS like thymic hypoplasia, overt cleft palate, and renal anomalies may be detected antenatally.[19-24] The variable expression of the 22q11.2 deletion and a low threshold for clinical testing has resulted in its association in case reports or small case series with myriad other findings (e.g., fetal megalourethra, split-hand/foot malformation,[25] congenital diaphragmatic hernia, umbilical or inguinal hernia, tracheoesophageal fistula/esophageal atresia/laryngeal atresia, polydactyly, craniosynostosis,[12,26] and neurological abnormalities like neural tube defects and arhinencephaly).[12,25-28] Increased nuchal translucency, polyhydramnios, and intrauterine growth restriction may be consequences of the 22q11.2 deletion and/or of associated congenital anomalies.[12,23,29,30,31] One recent study reported dilation of the cavum septum pellucidum in 67.5% of second trimester fetuses with 22q11.2 deletions.[32] This non-specific radiological variant persists in some patients, with and without psychotic illness.[33]

When the fetus has a 22q11.2 deletion there is evidence that risks for maternal and fetal complications, such as prematurity and fetal growth abnormalities, are elevated.[19,31,34,35] This has been deemed to warrant consideration of high risk antepartum care in the context of affected fetuses.[31,35,36]

Previously, most prenatal detection of 22q11.2 deletions was prompted by abnormal ultrasound findings.[18,19] However, many children and adults with 22q11.2DS do not have CHD or other anomalies that would be readily detectable on routine fetal ultrasonography (and be significant enough to prompt chorionic villus sampling or amniocentesis).[12,18,26,37] Variable expression contributes to under-recognition. Even today, diagnosis of a 22q11.2 deletion is delayed in most cases, precluding opportunities for optimizing care and outcome.[12,36,38] Routine non-invasive prenatal testing for 22q11.2 deletions has the potential to reveal the full spectrum of early expression,[9] including spontaneously resolving developmental features.[32,36]

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Lifetime Neuropsychiatric Expression of 22q11.2 Deletions

Neuropsychiatric illnesses comprise the most common group of later onset conditions in 22q11.2DS.[12,26,36,39-43] These features are typically of great concern to families because of their seriousness, associated stigma, and effects on daily functioning.[4,5,44] Consensus ranges based on consistent findings exist for the prevalence of some major associated conditions (Figure 1),[36] but there has been no definitive cohort study with unbiased recruitment and long-term follow-up data. Such studies are needed to clarify for example the prevalence of developmental phenotypes that may evolve over time, and that can contribute to broader ranges of, and less consistent, prevalence figures (Figure 1). One smaller study that recruited patients from an adult congenital cardiac clinic to limit ascertainment bias reported that, at median age 30 years, 60% had at least one psychiatric disorder.[39] Most (40%) had treatable nonpsychotic disorders only, and others had schizophrenia; results were similar when restricted to those with no to mild intellectual disability.[39] In other studies, including the largest from the International Consortium on Brain and Behavior in 22q11.2DS (http://22q11-ibbc.org/about/), prevalence estimates of various psychiatric disorders (e.g., psychotic disorders in 41% of adults over age 25 years) are not corrected for ascertainment or for intellectual disability,[42] and thus are likely to be inflated.

Cognitive impairment and intellectual disability

After Down syndrome, 22q11.2 deletions are the most frequent chromosomal aberration responsible for intellectual disability.[12] A range of outcomes is possible. Most patients with 22q11.2DS have an IQ in the borderline range (70–84), and 30-40% have mild intellectual disability (IQ 55-69).[43] More severe intellectual disability is less common.[36,41,45-49] Structural brain anomalies reportable on clinical magnetic resonance imaging (MRI), such as polymicrogyria, are not present in the majority of individuals with 22q11.2 deletions, including those with severe deficits.[12,50,51-53] For individuals with 22q11.2DS who have intellect in the average range, learning difficulties are often present, e.g., in arithmetic skills, social judgment, and/or decision-making.[26,36,47,54] Relatively good verbal skills, despite speech deficits, may conceal deficits in receptive language and comprehension.[36] Cognitive impairments are often associated with impairment in several domains of functioning, including communication, living skills particularly in the work situation, and management of finances.[36,44,47]

Importantly, there is ample evidence to indicate that there is on average an intellectual decline over childhood and adolescence in 22q11.2DS.[55] While not present in all individuals, in part this may be related to a developmental trajectory in 22q11.2DS where discrepancy with age-related norms becomes evident with increasing cognitive demands in later childhood and adolescence.[43,55]

Schizophrenia

The most important associated treatable neurodevelopmental disorder is schizophrenia. Schizophrenia develops in about 1 in 4 patients with 22q11.2DS, a >20-fold increased risk over population expectations where the prevalence is about 1 in 100 individuals.[39,43,56] Age of onset and other clinical features of the illness, such as hallucinations, delusions, and

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disorganization of thinking, emotional states and/or behaviour (collectively known as psychotic features), are largely indistinguishable from those of schizophrenia in the general population.[45,56-59]. The main differences are that the average IQ is lower and the sex ratio more equal than in idiopathic schizophrenia.[57] While onset of this treatable illness is typically in late adolescence or early adulthood, as for general population forms, the schizophrenia in 22q11.2DS may arise rarely in childhood or in later adult years.[45,56-58] In adults, the presence of schizophrenia, but not other treated psychiatric illness, is associated with lower IQ and an impact on functioning.[44,47]

Other psychiatric disorders

In adults with 22q11.2DS, treatable non-psychotic psychiatric illnesses are collectively more common in 22q11.2DS than is schizophrenia.[26,39,42,56] Few illnesses however have evidence that they have higher prevalence than the high rates known for these conditions in the general population (Figure 1). Anxiety disorders do have elevated prevalence, even when correcting for ascertainment.[39] Conversely, bipolar disorder (manic depression) has a similar prevalence in 22q11.2DS to that in the general population, as do other more common disorders like major depression.[10,26,42,56] Substance use disorders may be less prevalent in 22q11.2DS than in the general population.[57] Treated mood disorders do not appear to materially change outcomes with respect to functioning (or cognitive profiles).[44]

In pediatric samples of 22q11.2DS, typical childhood onset conditions include autism spectrum disorders and attention deficit disorders, but conduct disorders and delinquency are rare.[42,43,60] The reported prevalence of autism spectrum disorder varies widely between centres, with diagnosis made challenging by the features of 22q11.2DS including developmental delays. There may be more social and communication and fewer stereotypic behaviour problems than in other forms of autism spectrum disorder.[43,61] Attention deficit disorder is common, perhaps even more so than in general population,[60] but as for autism, diagnosis is complicated by features of 22q11.2DS. The clinical presentation of attention deficit disorder in 22q11.2DS includes more inattentive subtype, equal prevalence in males and females, lower IQ, less hyperactivity, more anxiety, and fewer oppositional defiant or conduct disorder features.[60] It is as yet uncertain, if corrected for intellect and ascertainment, how much more prevalent these illnesses would be than in the general pediatric population. Also, although these conditions sometimes may persist into adulthood,[42,62] there is no apparent relationship to the later appearance of schizophrenia.[62]

Seizures and epilepsy

The lifetime prevalence of epilepsy in 22q11.2DS appears to be in the 5-7% range,[26,63] far greater than in the general population (0.5-1.0%).[53] In addition, all forms of seizures, both single and recurrent, are common across the lifespan in 22q11.2DS, although detailed data are limited.[26,53,63] Seizures may be unprovoked or related to identifiable factors, especially metabolic derangements like hypocalcemia, beginning in the neonatal period and at any age thereafter.[36,50,52,53] In a minority of cases seizures may be related to malformation of cortical development such as polymicrogyria, periventricular nodular heterotopia, and cortical dysplasia.[51-53] In some cases these malformations may be associated with a poorer

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cognitive prognosis,[53] perhaps especially where the 22q11.2 deletion has unmasked an additional mutation, e.g., involving the *SNAP29* gene.[64]

Early-onset Parkinson's disease

There is accumulating evidence that 22q11.2DS is associated with an increased risk for early-onset (age <50 years) Parkinson's disease.[65-67] In one study, 5.9% of n=68 patients aged 36 to 64 years were diagnosed with Parkinson's disease, with typical symptom pattern, disease course, treatment response, and where available, findings on neuropathology.[66] Other movement disorders may also be associated but more research is needed.[68] There are as yet few studies of other neurodegenerative disorders in 22q11.2DS. However in some individuals with severe intellectual disability and psychotic illness there may be a form of dementia.[41]

Prenatal Predictors of Neuropsychiatric Expression

At present, for fetuses with 22q11.2 deletions there is no way to routinely individualize predictions with respect to cognitive or neuropsychiatric outcomes using prenatal ultrasound or other clinical techniques for brain imaging such as MRI. Although structural brain findings may be visible in 22q11.2DS,[32] such findings cannot predict individual outcomes. The only exception would be unexpected catastrophic findings, as for any fetus. Notably, ultrasound detectable physical congenital anomalies, including congenital cardiac disease, do not appear to have significant associations with either the prevalence of psychiatric disorders or neurocognitive deficits.[69,70]

On the other hand, there is emerging evidence in 22q11.2DS that preterm birth (<37 weeks), usually late preterm, is associated with a clinically significant increase in risk for schizophrenia in adolescence or early adulthood.[31,70] A birth weight that is small for gestational age may also increase risk.[31] The directionality of these associations is unclear.

There is currently no additional clinical genetic testing available that can help to predict neuropsychiatric outcomes in 22q11.2DS. The 22q11.2 deletion is usually 2.5 Mb long, and expression is thought to involve reduced gene dosage of the overlapped genes and other factors, most as yet unidentified.[10,12,71] There are limited data available on any role for the deletion size or the parent-of-origin of the *de novo* deletion event in neuropsychiatric outcomes except that neither appears to play a major role for expression of schizophrenia.[10] As for other major phenotypes, neuropsychiatric outcomes such as schizophrenia have been reported for all 22q11.2 deletion extents, including so-called atypical or distal nested deletions.[10] These distal nested deletions at present account for ~5% of all 22q11.2 deletions and require broader coverage methods such as microarray to detect because they do not overlap the *TBX1* gene or the TUPLE1 probe used in clinical FISH testing.[3,10] Several studies have investigated the role of common variants on the intact 22q11.2 allele, e.g., in the *COMT* gene, but effect sizes are generally small and results are inconsistently replicated.[40,72,73] Emerging research now suggests that rare deleterious variants elsewhere in the genome, in addition to the 22q11.2 deletion, are likely to be involved in the variability of neuropsychiatric and other developmental expression.[10-12,71,74-76] This would be in keeping with data from the general population of individuals with neurodevelopmental disorders,

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where 2-5% have two rare contributing genetic mutations or diagnoses.[77-79] Family history is always an important consideration, including for phenotypic expression in 22q11.2DS.[80] For other recurrent CNVs, studies show the influence of family background on neuropsychiatric expression,[81-83] and comparable data for the 22q11.2 deletion indicate similar findings for intellect, particularly for verbal IQ.[76]

Genetic Counselling and Disclosing the Risk of Neuropsychiatric Problems

Chromosomal microarray analysis as a prenatal genetic test has the potential to identify mutations with cognitive and other later-onset neuropsychiatric implications,[8] with 22q11.2 deletions being the archetypal example. Once a 22q11.2 deletion is detected, parents cannot avoid learning about the risk for neuropsychiatric disorders. Even if purposefully not raised by the healthcare provider,[7] any routine Internet search will quickly bring these issues to light. Indeed, this is how many parents of children with 22q11.2DS have gathered information about lifetime neuropsychiatric expression,[4,84] instead of from discussion with an informed professional.

It is important to point out that the issue of what can be termed "ensuing findings", i.e., known later onset features of a genetic condition, is distinct from the oft-discussed "secondary findings" or "incidental findings" of genetic testing. The specific association of 22q11.2 deletions with neuropsychiatric disorders such as schizophrenia is often not disclosed in pretest or even at post-test counselling.[4,6,84] There is significant variability in practice with respect to the timing of discussing the elevated risks of neuropsychiatric conditions in 22q11.2DS, and the content of those discussions.[4,6,84] Stigma associated with psychiatric illness is an issue.[6] This situation is not new. The association between Down syndrome and Alzheimer disease is a common (but rarely discussed) example of the reticence about discussing late onset significant neuropsychiatric expression.

We note that a common question after discovery of CHD on fetal ultrasound is about neurodevelopmental outcomes. There is substantial evidence that outcomes are related to the presence of detectable genetic conditions such as 22q11.2DS.[85,86] In a recent survey study, fetal medicine experts and paediatric cardiologists involved in fetal cardiology endorsed a reluctance to discuss these issues.[7] Of interest is that this survey did not raise the issue of genetic findings like 22q11.2 deletions that are known to cause a significant proportion of all congenital cardiac disease, illustrating an apparent disconnect between contemporary molecular diagnosis/genetics and postnatal, and at times even fetal, specialists.

Genetic Counselling for a New Diagnosis of an Adult with 22q11.2DS

That a parent carries a 22q11.2 deletion may be known prior to conception, or may be a “secondary” finding following diagnosis of an affected fetus. Generally, parents will have less severe cognitive and neuropsychiatric expression of the 22q11.2 deletion than the offspring, likely because of reproductive fitness effects.[37,87,88] Reproductive fitness is greater in women than men with 22q11.2DS, thus there tend to be more affected mothers than fathers.[88] There are special considerations when counselling a parent who also has a 22q11.2 deletion.[89] Notably, someone who has experienced a life with 22q11.2DS (with or

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without a genetic diagnosis) may have a different perception of what the condition is, compared to an unaffected couple discovered to have an affected fetus or infant.[18] The phenotype of the parent with 22q11.2DS however does not predict that of their affected offspring. Also, although there are limited data, in theory the risk of peripartum depression and psychosis may be increased in mothers with a 22q11.2 deletion.[35] Published guidelines address genetic counselling and pregnancy considerations.[12,35,36,90]

Prevention and Treatment of Neuropsychiatric Disorders

Neuropsychiatric conditions may constitute a management challenge, but one can provide reassurance that these are usually treatable illnesses.[40,72,73] This represents one of the greatest concerns for parents of a patient with 22q11.2DS.[5] The anticipatory care and management of psychiatric illness in 22q11.2DS involves an individualized, multidisciplinary care plan that takes into account the other associated features of 22q11.2DS and other ameliorable factors (e.g., caffeine) that may complicate both symptoms and treatment.[36,38] Pro-active screening for, and management of, psychiatric illnesses is required for every individual with 22q11.2DS, starting early in life.[36,38] The available treatment strategies for paediatric and later onset neuropsychiatric disorders are effective and should be applied in accordance with the clinical practice guidelines appropriate for each condition.[36,38]

Cognitive impairment and intellectual disability

Early neuromotor deficits require remediation and cognitive potential may be facilitated with infant stimulation and early educational interventions.[36,38,43] At any age awareness of developmental deficits is crucial in order to avoid situations where the environmental expectations exceed abilities. Cognitive deficits may require accommodations in post-secondary education and workplace settings. Areas of relative strength and data that could help to inform vocational training and expectations are areas of active research interest.[44] One study reported an association between moderate-severe intellectual disability in 22q11.2DS and neonatal seizures, seemingly mediated by hypocalcemia, however this finding has yet to be replicated.[50]

Schizophrenia

The elevated risk for psychotic illness in 22q11.2DS prompts questions about prevention, early signs, diagnosis, and treatment. Informed discussion about schizophrenia as a lifelong but treatable and manageable condition is essential. Placing the disease in the context of other diseases like diabetes mellitus may be helpful.[90,91] Promptly seeking expert help in diagnosis and effective treatment may improve prognosis. Learning about early signs (changes) that may herald treatable psychiatric illness can facilitate this and may be empowering for families. There are no proven preventions for psychotic illness. However, avoiding substance use, particularly early marijuana use, and lifelong general health measures including good nutrition and activity levels are reasonable recommendations.[90] Research is ongoing with respect to identifying clinical and other genetic predictors of future psychotic illness in 22q11.2DS; these appear similar to factors identified for schizophrenia

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in the general population.[31,42,46,55,71,92-94] Meanwhile, concerns, misconceptions and a sense of stigma should be solicited and addressed.[5,6,95,96]

Other psychiatric disorders

Standard pharmacological and non-pharmacological treatments for attention deficit and anxiety and other mood disorders are effective in 22q11.2DS.[36,38,97,98] Emotional or temper outbursts, described in 22q11.2DS, may be a feature of untreated or undertreated anxiety or psychotic illness with various physical factors potentially contributing.[38,58]

Seizures and movement disorders

Although data are limited, standard treatments for seizures and for Parkinson's disease[65-67] appear to be effective, e.g., using typical anticonvulsant medications for epilepsy.[63,99-101] Hypocalcemic seizures will generally resolve with appropriate supplementation[38] and monitoring alone.[100,102-105] Anticonvulsant therapy may be indicated if seizures continue after ionized calcium levels have normalized.[101] Attention to increased risk of seizures and movement disorders is important when considering any medication for 22q11.2DS-related conditions.

Future Directions

Prenatal diagnosis of a 22q11.2 deletion invariably leads to questions about the future. Counselling is informed by our increasingly detailed understanding of the lifetime neuropsychiatric phenotype. Parental awareness can facilitate earlier recognition and prompt treatment. However, key knowledge gaps remain. There is a need to determine those who may be at greatest risk for adverse outcomes, and for a 22q11.2 deletion occurrence. New technologies like whole-genome sequencing will allow for testing proposed mechanisms of variable expression related to lifetime outcomes.[71,106] International consortia will aid in recruiting participants for large-scale studies and replicating results of smaller, individual research groups. Improved treatment or prevention are much wished for but future considerations. These would include determination of whether prenatal brain imaging could assist prediction of neuropsychiatric outcomes, or prenatal neuroprotective measures could improve such outcomes.[32] Yet there is reason to be optimistic about, e.g., potential advancements in the interval period of many years between a fetus diagnosed today with a 22q11.2 deletion and age at onset of schizophrenia.

22q11.2 deletions are the most common and best-studied examples of copy number variations with major late-onset neuropsychiatric expression.[95,107,108] However, prenatal chromosomal microarray analysis reveals other variants with risk for later onset neuropsychiatric problems.[8] Non-invasive prenatal testing may soon do likewise. Lessons learned from 22q11.2DS will thus be increasingly applicable to prenatal diagnosis more generally.

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REFERENCES

1. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. New England Journal of Medicine. 2012; 367:2175–84. [PubMed: 23215555]
2. Grati FR, Molina Gomes D, Ferreira JC, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. Prenat Diagn. 2015
3. Dugoff L, Mennuti MT, McDonald-McGinn DM. The benefits and limitations of cell-free DNA screening for 22q11.2 deletion syndrome. Prenat Diagn. 2016
4. Hercher L, Bruenner G. Living with a child at risk for psychotic illness: the experience of parents coping with 22q11 deletion syndrome: an exploratory study. Am J Med Genet A. 2008; 146A:2355–60. [PubMed: 18698620]
5. Karas DJ, Costain G, Chow EW, et al. Perceived burden and neuropsychiatric morbidities in adults with 22q11.2 deletion syndrome. J Intellect Disabil Res. 2014; 58:198–210. [PubMed: 23106770]
6. Martin N, Mikhaelian M, Cytrynbaum C, et al. 22q11.2 deletion syndrome: attitudes towards disclosing the risk of psychiatric illness. J Genet Couns. 2012; 21:825–34. [PubMed: 22833231]
7. Paladini D, Alfirevic Z, Carvalho J, et al. Prenatal counseling for neurodevelopmental delay in congenital heart disease: results of a worldwide survey of experts' attitudes advise caution. Ultrasound Obstet Gynecol. 2016; 47:667–71. [PubMed: 26749377]
8. Costain G, McDonald-McGinn DM, Bassett AS. Prenatal genetic testing with chromosomal microarray analysis identifies major risk variants for schizophrenia and other later-onset disorders. Am J Psychiat. 2013; 170:1498.
9. Gross S, Stosic M, McDonald-McGinn D, et al. Clinical experience with single-nucleotide polymorphism-based non-invasive prenatal screening for 22q11.2 deletion syndrome. Ultrasound Obstet Gynecol. 2016; 47:177–83. [PubMed: 26396068]
10. Bassett AS, Marshall CR, Lionel AC, et al. Copy number variations and risk for schizophrenia in 22q11.2 deletion syndrome. Hum Mol Genet. 2008; 17:4045–53. [PubMed: 18806272]
11. Delio M, Guo T, McDonald-McGinn DM, et al. Enhanced maternal origin of the 22q11.2 deletion in velocardiofacial and DiGeorge syndromes. Am J Hum Genet. 2013; 92:439–47. [PubMed: 23453669]
12. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. Nat Rev Dis Prim. 2015:15071. [PubMed: 27189754]
13. Costain G, Chow EW, Ray PN, et al. Caregiver and adult patient perspectives on the importance of a diagnosis of 22q11.2 deletion syndrome. J Intellect Disabil Res. 2012; 56:641–51. [PubMed: 22142442]
14. Kapadia RK, Bassett AS. Recognizing a common genetic syndrome: 22q11.2 deletion syndrome. Canadian Medical Association Journal. 2008; 178:391–3. [PubMed: 18268261]
15. Peyvandi S, Lupo PJ, Garbarini J, et al. 22q11.2 deletions in patients with conotruncal defects: data from 1,610 consecutive cases. Pediatr Cardiol. 2013; 34:1687–94. [PubMed: 23604262]
16. Costain G, Silversides C, Bassett A. The importance of copy number variation in congenital cardiac disease. Nature Genomic Medicine. 2016 in press.
17. Swaby JA, Silversides CK, Bekeschus SC, et al. Complex congenital heart disease in unaffected relatives of adults with 22q11.2 deletion syndrome. Am J Cardiol. 2011; 107:466–71. [PubMed: 21257016]
18. Bretelle F, Beyer L, Pellissier MC, et al. Prenatal and postnatal diagnosis of 22q11.2 deletion syndrome. Euro. J. Med. Genet. 2010; 53:367–70.
19. Besseau-Ayasse J, Violle-Poirsier C, Bazin A, et al. A French collaborative survey of 272 fetuses with 22q11.2 deletion: ultrasound findings, fetal autopsies and pregnancy outcomes. Prenatal Diagnosis. 2014; 34:424–30. [PubMed: 24395195]
20. Maarse W, Rozendaal A, Pajkrt E, et al. A systematic review of associated structural and chromosomal defects in oral clefts: when is prenatal genetic analysis indicated? J Med Genet. 2012; 49:490–8. [PubMed: 22889852]

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21. Bataeva R, Bellsham-Revell H, Zidere V, et al. Reliability of fetal thymus measurement in prediction of 22q11.2 deletion: a retrospective study using four-dimensional spatiotemporal image correlation volumes. Ultrasound Obstet Gynecol. 2013; 41:172–6. [PubMed: 22605637]
22. Chaoui R, Heling K, Lopez A, et al. The thymic-thoracic ratio in fetal heart defects: a simple way to identify fetuses at high risk for microdeletion 22q11. Ultrasound Obstet Gynecol. 2011; 37:397–403. [PubMed: 21308838]
23. Volpe P, Marasini M, Caruso G, et al. 22q11 deletions in fetuses with malformations of the outflow tracts or interruption of the aortic arch: Impact of additional ultrasound signs. Prenatal Diagnosis. 2003; 23(9):752–757. [PubMed: 12975788]
24. Barrea C, Yoo S-J, Chitayat D, et al. Assessment of the thymus at echocardiography in fetuses at risk for 22q11.2 deletion. Prenatal Diagnosis. 2003; 23:9–15. [PubMed: 12533805]
25. Lu J, Zhan C, Wu T, et al. Effectively suppressing dissolution of manganese from spinel lithium manganate via a nanoscale surface-doping approach. Nat Commun. 2014; 5:5693. [PubMed: 25514346]
26. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. Am J Med Genet A. 2005; 138:307–13. [PubMed: 16208694]
27. Canda MT, Demir N, Bal FU, et al. Prenatal diagnosis of a 22q11 deletion in a second-trimester fetus with conotruncal anomaly, absent thymus and meningomyelocele: Kousseff syndrome. Journal of Obstetrics & Gynaecology Research. 2012; 38:737–40. [PubMed: 22380655]
28. Noel AC, Pelluard F, Delezoide AL, et al. Fetal phenotype associated with the 22q11 deletion. Am J Med Genet A. 2014; 164A:2724–31. [PubMed: 25111715]
29. Grande M, Jansen F, Blumenfeld Y, et al. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015; 46:650–8. [PubMed: 25900824]
30. Vantrappen G, Devriendt K, Swillen A, et al. Presenting symptoms and clinical features in 130 patients with the velo-cardio-facial syndrome. The Leuven experience. Genetic Counseling. 1999; 10:3–9. [PubMed: 10191424]
31. Van L, Butcher N, Costain G, et al. Fetal growth and gestational factors as predictors of schizophrenia in 22q11.2 deletion syndrome. Genet Med. 2016; 18:350–5. [PubMed: 26087175]
32. Chaoui R, Heling K, Zhao Y, et al. Dilated cavum septi pellucidi in fetuses with microdeletion 22q11. Prenat Diagn. 2016
33. Schmitt J, Yi J, Roalf D, et al. Incidental radiologic findings in the 22q11.2 deletion syndrome. AJNR Am J Neuroradiol. 2014; 35:2186–91. [PubMed: 24948496]
34. Tarquinio DC, Jones MC, Jones KL, et al. Growth charts for 22q11 deletion syndrome. American Journal of Medical Genetics. 2012; 158A:2672–81. Part A. [PubMed: 22887711]
35. Chan C, Costain G, Ogura L, et al. Reproductive Health Issues for Adults with a Common Genomic Disorder: 22q11.2 Deletion Syndrome. J Genet Couns. 2015; 24:810–21. [PubMed: 25579115]
36. Fung WL, Butcher NJ, Costain G, et al. Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet Med. 2015; 17:599–609. [PubMed: 25569435]
37. McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! Genet Med. 2001; 3:23–9. [PubMed: 11339373]
38. Bassett AS, McDonald-McGinn DM, Devriendt K, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediat. 2011; 159:332–9. [PubMed: 21570089]
39. Fung WL, McEvilly R, Fong J, et al. Elevated prevalence of generalized anxiety disorder in adults with 22q11.2 deletion syndrome. American Journal of Psychiatry. 2010; 167:998. [PubMed: 20693476]
40. Philip N, Bassett AS. Cognitive, behavioural and psychiatric phenotype in 22q11.2 deletion syndrome. Behav Genet. 2011; 41:403–12. [PubMed: 21573985]
41. Evers LJ, van Amelsvoort TA, Candel MJ, et al. Psychopathology in adults with 22q11 deletion syndrome and moderate and severe intellectual disability. Journal of Intellectual Disability Research. 2014; 58:915–925. [PubMed: 24528781]

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42. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am J Psychiat. 2014; 171:627–39. [PubMed: 24577245]
43. Swillen A, McDonald-McGinn D. Developmental trajectories in 22q11.2 deletion syndrome. Am J Med Genet C Semin Med Genet. 2015; 169:172–81. [PubMed: 25989227]
44. Butcher N, Chow E, Costain G, et al. Functional outcomes of adults with 22q11.2 deletion syndrome. Genet Med. 2012; 14:836–43. [PubMed: 22744446]
45. Amelsvoort TV, Henry J, Morris R, et al. Cognitive deficits associated with schizophrenia in velo-cardio-facial syndrome. Schizophrenia Research. 2004; 70:223–232. [PubMed: 15329299]
46. Antshel KM, Shprintzen R, Fremont W, et al. Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: a 3-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2010; 49:333–44. [PubMed: 20410726]
47. Chow EW, Watson M, Young DA, et al. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophr Res. 2006; 87:270–8. [PubMed: 16753283]
48. Swillen A, Vandeputte L, Cracco J, et al. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability? Child Neuropsychology. 1999; 5:230–41. [PubMed: 10925707]
49. Swillen A, Vogels A, Devriendt K, et al. Chromosome 22q11 deletion syndrome: update and review of the clinical features, cognitive-behavioral spectrum, and psychiatric complications. American Journal Of Medical Genetics. 2000; 97:128–35. [PubMed: 11180220]
50. Cheung EN, George SR, Andrade DM, et al. Neonatal hypocalcemia, neonatal seizures, and intellectual disability in 22q11.2 deletion syndrome. Genet Med. 2014; 16:40–44. [PubMed: 23765047]
51. Kiehl TR, Chow EWC, Mikulis DJ, et al. Neuropathologic features in adults with 22q11.2 deletion syndrome. Cereb Cortex. 2009; 19:153–164. [PubMed: 18483005]
52. Andrade DM, Krings T, Chow EW, et al. Hippocampal malrotation is associated with chromosome 22q11.2 microdeletion. Canadian Journal of Neurological Sciences. 2013; 40:652–6. [PubMed: 23968937]
53. Kim E, Yum M, Lee B, et al. Epilepsy and Other Neuropsychiatric Manifestations in Children and Adolescents with 22q11.2 Deletion Syndrome. J Clin Neurol. 2016; 12:85–92. [PubMed: 26754781]
54. De Smedt B, Swillen A, Verschaffel L, et al. Mathematical learning disabilities in children with 22q11.2 deletion syndrome: a review. Dev Disabil Res Rev. 2009; 15:4–10. [PubMed: 19213009]
55. Vorstman JA, Breetvelt E, Duijff SN, et al. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. JAMA Psychiat. 2015; 72:377–85.
56. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry. 1999; 56:940–5. [PubMed: 10530637]
57. Bassett AS, Chow EW, AbdelMalik P, et al. The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psychiat. 2003; 160:1580–6. [PubMed: 12944331]
58. Bassett AS, Chow EW. Schizophrenia and 22q11.2 deletion syndrome. Curr Psychiatry Rep. 2008; 10:148–57. [PubMed: 18474208]
59. Stoddard J, Niendam T, Hendren R, et al. Attenuated positive symptoms of psychosis in adolescents with chromosome 22q11.2 deletion syndrome. Schizophrenia Research. 2010; 118:118–21. [PubMed: 20056393]
60. Niarchou M, Martin J, Thapar A, et al. The clinical presentation of attention deficit-hyperactivity disorder (ADHD) in children with 22q11.2 deletion syndrome. Am J Med Genet B Neuropsychiatr Genet. 2015; 168:730–8. [PubMed: 26400629]
61. Kates W, Antshel KM, Fremont W, et al. Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial syndrome (22q11DS) with and without autism. American Journal of Medical Genetics Part A. 2007; 143A:2642–2650. [PubMed: 17937445]
62. Vorstman JS, Breetvelt EJ, Thode KI, et al. Expression of autism spectrum and schizophrenia in patients with a 22q11.2 deletion. Schizophr Res. 2013; 143:55–9. [PubMed: 23153825]
63. Kao A, Mariani J, McDonald-McGinn DM, et al. Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. Am J Med Genet A. 2004; 129:29–34.

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64. McDonald-McGinn DM, Fahiminiya S, Revil T, et al. Hemizygous mutations in SNAP29 unmask autosomal recessive conditions and contribute to atypical findings in patients with 22q11.2DS. Journal of Medical Genetics. 2013; 50:80–90. [PubMed: 23231787]
65. Booij J, van Amelsvoort T, Boot E. Co-occurrence of early-onset Parkinson disease and 22q11.2 deletion syndrome: Potential role for dopamine transporter imaging. Am J Med Genet A. 2010; 152A:2937–8. [PubMed: 20949509]
66. Butcher N, Kiehl T, Hazrati L, 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 Neurology. 2013; 70:1359–1366. [PubMed: 24018986]
67. Mok K, 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; 15:585–96. [PubMed: 27017469]
68. Boot E, Butcher NJ, van Amelsvoort TA, et al. Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. Am J Med Genet A. 2015; 167A:639–45. [PubMed: 25684639]
69. Yi J, Tang S, McDonald-McGinn D, et al. Contribution of congenital heart disease to neuropsychiatric outcome in school-age children with 22q11.2 deletion syndrome. Am J Med Genet B Neuropsychiatr Genet. 2014; 165B:137–47. [PubMed: 24265253]
70. 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
71. 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
72. Ferrell RB, Wolinsky EJ, Kauffman CI, et al. Neuropsychiatric syndromes in adults with intellectual disability: issues in assessment and treatment. Curr Psychiatry Rep. 2004; 6:380–90. [PubMed: 15355761]
73. Tang SX, Yi JJ, Calkins ME, et al. Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. Psychological Medicine. 2014; 44:1267–77. [PubMed: 24016317]
74. Merico D, Costain G, Butcher NJ, et al. MicroRNA dysregulation, gene networks, and risk for schizophrenia in 22q11.2 deletion syndrome. Front Neurol. 2014; 5:238. [PubMed: 25484875]
75. 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. 2015
76. Klaassen P, Duijff S, Swanenburg de Veye H, et al. Explaining the variable penetrance of CNVs: Parental intelligence modulates expression of intellectual impairment caused by the 22q11.2 deletion. Am J Med Genet B Neuropsychiatr Genet. 2016; 171:790–6. [PubMed: 26953189]
77. Yang Y, Muzny D, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014; 312:1870–9. [PubMed: 25326635]
78. Wright C, Fitzgerald T, Jones W, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. 2015; 385:1305–14. [PubMed: 25529582]
79. Stavropoulos D, Merico D, Jobling R, et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. npj Genomic Medicine. 2016; 1:1–9.
80. Swaby J, Silversides C, Bekeschus S, et al. Complex congenital heart disease in unaffected relatives of adults with 22q11.2 deletion syndrome. Am J Cardiol. 2011; 107:466–71. [PubMed: 21257016]
81. Moreno-De-Luca A, Evans DW, Boomer KB, et al. The role of parental cognitive, behavioral, and motor profiles in clinical variability in individuals with chromosome 16p11.2 deletions. JAMA Psychiat. 2015; 72:119–26.
82. Duyzend MH, Nuttle X, Coe BP, et al. Maternal modifiers and parent-of-origin bias of the autism-associated 16p11.2 CNV. Am J Hum Genet. 2016; 98:45–57. [PubMed: 26749307]
83. Finucane B, Challman TD, Martin CL, et al. Shift happens: family background influences clinical variability in genetic neurodevelopmental disorders. Genet Med. 2015
84. van den Bree M, Miller G, Mansell E, et al. The internet is parents' main source of information about psychiatric manifestations of 22q11.2 deletion syndrome (22q11.2DS). Eur J Med Genet. 2013; 56:439–41. [PubMed: 23707654]

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85. Fuller S, Nord A, Gerdes M, et al. Predictors of impaired neurodevelopmental outcomes at one year of age after infant cardiac surgery. Eur J Cardiothorac Surg. 2009; 36:40–7. [PubMed: 19394849]

86. International Cardiac Collaborative on Neurodevelopment I. Impact of Operative and Postoperative Factors on Neurodevelopmental Outcomes After Cardiac Operations. Ann Thorac Surg. 2016; 102:843–9. [PubMed: 27496628]

87. Cirillo E, Giardino G, Gallo V, et al. Intergenerational and intrafamilial phenotypic variability in 22q11.2 deletion syndrome subjects. BMC Medical Genetics. 2014; 15:1. [PubMed: 24383682]

88. Costain G, Chow EW, Silversides CK, et al. Sex differences in reproductive fitness contribute to preferential maternal transmission of 22q11.2 deletions. Journal of Medical Genetics. 2011; 48:819–24. [PubMed: 22051516]

89. Finucane, B. Genetic Counselling Practice: Advanced Concepts and Skills. Wiley-Blackwell; Hoboken, NJ: 2010.

90. Bassett, AS., Chow, EWC., Hodgkinson, KA. Genetics of schizophrenia and psychotic disorders. In: Smoller, JW.Sheidley, BR., Tsuang, MT., editors. Psychiatric Genetics: Applications in clinical practice. American Psychiatric Publishing; Washington, DC: 2008. p. 99-130.

91. Hodgkinson KA, Murphy J, O'Neill S, et al. Genetic counselling for schizophrenia in the era of molecular genetics. Can J Psychiatry. 2001; 46:123–30. [PubMed: 11280080]

92. Gothelf D, Schaer M, Eliez S. Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. Develop Disabil Res Rev. 2008; 14:59–68.

93. Yuen T, Chow EW, Silversides CK, et al. Premorbid adjustment and schizophrenia in individuals with 22q11.2 deletion syndrome. Schizophr Res. 2013; 151:221–5. [PubMed: 24262682]

94. Radoeva P, Fremont W, Antshel K, et al. Longitudinal study of premorbid adjustment in 22q11.2 deletion (velocardiofacial) syndrome and association with psychosis. Dev Psychopathol. 2016:1–14.

95. Costain G, Esplen MJ, Toner B, et al. Evaluating Genetic Counseling for Family Members of Individuals With Schizophrenia in the Molecular Age. Schizophrenia Bulletin. 2012

96. Costain G, Esplen MJ, Toner B, et al. Evaluating Genetic Counseling for Individuals With Schizophrenia in the Molecular Age. Schizophr Bull. 2012

97. Dori N, Green T, Weizman A, et al. The effectiveness and safety of antipsychotic and antidepressant medications in individuals with 22q11.2 deletion syndrome. J Child Adolesc Psychopharmacol. 2015

98. Gothelf D, Gruber R, Presburger G, et al. Methylphenidate treatment for attention-deficit/hyperactivity disorder in children and adolescents with velocardiofacial syndrome: an open-label study. J Clin Psychiatry. 2003; 64:1163–9. [PubMed: 14658963]

99. Maalouf NM, Sakhaee K, Odvina CV. A case of chromosome 22q11 deletion syndrome diagnosed in a 32-year-old man with hypoparathyroidism. Journal of Clinical Endocrinology and Metabolism. 2004; 89:4817–20. [PubMed: 15472168]

100. Tsai P-L, Lian L-M, Chen W-H. Hypocalcemic seizure mistaken for idiopathic epilepsy in two cases of DiGeorge syndrome (chromosome 22q11 deletion syndrome). Acta Neurologica Taiwanica. 2009; 18:272–5. [PubMed: 20329596]

101. Gonzalez W, Bautista RE. Seizures and EEG findings in an adult patient with DiGeorge syndrome: a case report and review of the literature. Seizure. 2009; 18(9):648–651. [PubMed: 19665396]

102. Hirotani A, Morimoto S, Koh E, et al. Partial DiGeorge syndrome at the age of thirty-four. Internal Medicine. 1994; 33:418–21. [PubMed: 7949642]

103. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet. 1997; 34:798–804. [PubMed: 9350810]

104. Tonelli AR, Kosuri K, Wei S, et al. Seizures as the first manifestation of chromosome 22q11.2 deletion syndrome in a 40-year old man: a case report. J Med Case Rep. 2007; 1:167. [PubMed: 18053182]

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105. Kinoshita H, Kokudo T, Ide T, et al. A patient with DiGeorge syndrome with spina bifida and sacral myelomeningocele, who developed both hypocalcemia-induced seizure and epilepsy. Seizure. 2010; 19:303–5. [PubMed: 20430655]

106. Brzustowicz LM, Bassett AS. miRNA-mediated risk for schizophrenia in 22q11.2 deletion syndrome. Front Genet. 2012; 3:291. [PubMed: 23248646]

107. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014; 129:2183–242. [PubMed: 24763516]

108. Tansey KE, Rees E, Linden DE, et al. Common alleles contribute to schizophrenia in CNV carriers. Mol Psychiatry. 2015 in press.

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What's already known about this topic?

- 22q11.2 deletions are common findings in prenatal testing with important implications for neurodevelopment and later onset conditions

What does this study add?

- A summary of the lifetime neuropsychiatric phenotype of 22q11.2 deletion syndrome for clinicians involved in prenatal diagnosis and related genetic counselling
- Information relevant to common situations: parents of a fetus/newborn with a 22q11.2 deletion, and new diagnosis of 22q11.2 deletion syndrome in an adult (e.g., parent)

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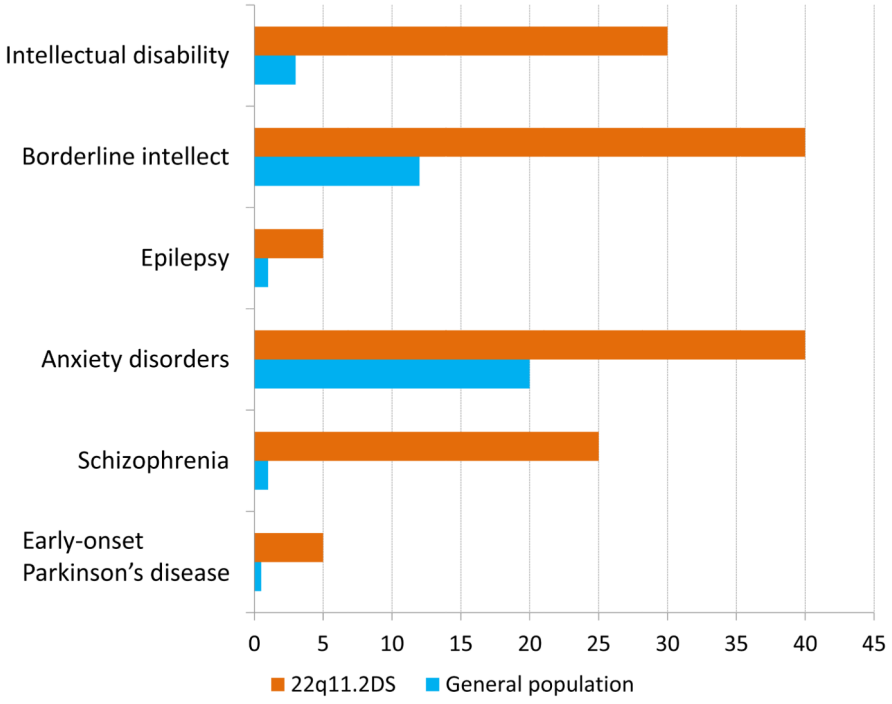

Figure 1.

shows approximate values for risk estimates available for the neuropsychiatric features of 22q11.2DS (orange bars) known to differ significantly from general population estimates (blue bars). Prevalence estimates for 22q11.2DS are from Fung et al. 2015[36] and from standard sources for population estimates.[39,66] Where ranges were provided, the lower value was used for 22q11.2DS. Neuropsychiatric disorders are ordered by expected age at detection. Intellectual disability ranges from mild (most common) to severe. Other associated neuropsychiatric conditions for which consistent prevalence estimates for 22q11.2DS are not yet available and/or may overlap with population prevalence are not shown; these would include developmental delay, hypotonia, autism spectrum disorder, and attention deficit hyperactivity disorder.

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Table 1

22q11.2 microdeletions account for a notable proportion of all pathogenic unbalanced rearrangements identified on prenatal chromosomal microarray in n=3822 fetuses with a normal karyotype (reported by Wapner et al., 2012)[1]

Indication for prenatal diagnostic testing	Pathogenic rearrangements						
	Total (all) genome-wide microdeletions and duplications		22q11.2 deletions				
			Typical (A to D)* *de novo*			Atypical nested†	Any (typical and atypical)
	n	(%)	n	(%)	Prevalence	n	Prevalence
Any (n=3822)	35	(0.9)	11	(31.4)	1 in 348	5	1 in 239
Anomaly on ultrasonography (n=755)	21	(2.8)	8	(38.1)	1 in 95	2	1 in 76
No anomaly on ultrasonography‡ (n=3067)	14	(0.5)	3	(21.4)	1 in 1023	3	1 in 512

*Segmental duplications thought to confer susceptibility to recurrent rearrangements within the 22q11.2 region are identified using sequential letters from the most proximal to the most distal regions: A and D indicate flanking positions for typical 22q11.2 deletions of ~ 2.5 Mb.

†Includes B to D (n=3), C to D (n=1), and C to ~E (n=1) atypical nested 22q11.2 deletions; 4 of these 5 were *de novo* rearrangements; published and unpublished evidence supports the pathogenicity of these deletions, with similar phenotype and variable expressivity to the typical A to D 22q11.2 deletion.[106]

‡Advanced maternal age (n=1966); positive on Down syndrome screening (n=729), other reason for testing (n=372). Note: details not provided re reason for invasive prenatal tesing for individual rearrangements, including 22q11.2 deletions. This table was adapted from data in Table 3 and Supplementary Appendix to: Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med 2012;367:2175-84.[1]