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16p12.2 Recurrent Deletion

Synonym: 16p12.1 Microdeletion

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Summary

Clinical characteristics

16p12.2 recurrent deletion is characterized by variable clinical findings that do not constitute a recognizable syndrome. Of note, the significant bias in ascertainment of individuals undergoing clinical chromosomal microarray analysis (i.e., children with intellectual disability and developmental delay; individuals with schizophrenia) makes it difficult to accurately associate specific phenotypes with the 16p12.2 recurrent deletion. Findings commonly observed in children (probands) with this deletion include: developmental delay, cognitive impairment (ranging from mild to profound), growth impairment (including short stature), cardiac malformations, epilepsy, and psychiatric and/or behavioral issues. Other findings can include: hearing loss, dental abnormalities, renal and genital anomalies (the latter in males), and cleft palate ± cleft lip.

Diagnosis/testing

The diagnosis of 16p12.2 recurrent deletion is established by identification of a 520-kb heterozygous deletion on chromosome 16p12.2 on chromosomal microarray analysis or other genomic analyses.

Management

Treatment of manifestations: Treatment is directed to specific problems identified and may include developmental therapies; routine treatment of cardiac malformations, epilepsy, psychiatric and behavioral issues, hearing loss, and other malformations (e.g., orofacial clefting; renal, genitourinary, and dental anomalies).

Surveillance: Periodic: developmental evaluations; monitoring of cardiac, renal, urologic, and/or dental abnormalities, as needed; reevaluation by a clinical geneticist.

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Evaluation of relatives at risk: Older and younger sibs of a proband should be tested for a 16p12.2 recurrent deletion to allow for close assessment/monitoring of developmental milestones and monitoring for neuropsychiatric manifestations in children with the deletion.

Genetic counseling

The 16p12.2 recurrent deletion is inherited in an autosomal dominant manner. The majority (~95%) of individuals with this recurrent deletion inherited the deletion from a parent (who may or may not have clinical features related to the recurrent deletion). If a parent is heterozygous for the 16p12.2 recurrent deletion, the risk that the sibs of a proband would inherit the deletion is 50%; however, the risk that sibs would be affected is less than 50% because of reduced penetrance for the deletion. Children with a family history of neurodevelopmental and psychiatric disease are more likely to present with severe clinical features of the deletion. If a 16p12.2 recurrent deletion has been identified in a family member, prenatal testing for pregnancies at increased risk is possible; however, it is not possible to reliably predict phenotype based on the laboratory finding of a 16p12.2 recurrent deletion.

Diagnosis

No formal diagnostic criteria have been established for 16p12.2 recurrent deletion.

Because of the variable clinical presentation of 16p12.2 recurrent deletion, the diagnosis is made by detection of 16p12.2 recurrent deletion on chromosomal microarray analysis (CMA) or other genomic analyses.

Suggestive Findings

The 16p12.2 recurrent deletion **should be considered** in individuals with the following clinical findings:

- Developmental delays
- Mild-to-moderate intellectual disability
- Speech delays
- Psychiatric and behavioral abnormalities including autism, bipolar disorder, depression, and schizophrenia
- Mild dysmorphic facial features without a consistent pattern
- Congenital cardiac defects
- Sleep disturbance
- Epilepsy
- A positive family history of learning disorders or psychiatric issues

Of note, most individuals with the 16p12.2 recurrent deletion are identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, and/or autism spectrum disorder.

Establishing the Diagnosis

The diagnosis of the 16p12.2 recurrent deletion is established by detection of the 520-kb heterozygous deletion at chromosome 16p12.2 (see Table 1 and Molecular Genetics).

For this *GeneReview*, the 16p12.2 recurrent deletion is defined as the presence of a recurrent 520-kb deletion at the approximate position of 21948445-22430805 in the reference genome (NCBI Build GRCh37/hg19).

ISCN nomenclature for this deletion is: seq[GRCh37] del(16)(p12.2) chr16:g.21,948,445-22,430,805del. Note: Since this deletion is recurrent and mediated by segmental duplications, the unique genetic sequence that is deleted is the same in all individuals with the syndrome; however, the reported size of the deletion may: (1) be

larger if adjacent segmental duplications are included in the size and (2) vary based on the design of the microarray used to detect it (see Molecular Pathogenesis).

Note: The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 16p12.2 recurrent deletion (see Genetically Related Disorders).

Although seven genes of interest (*UQCRC2*, *PDZD9*, *MOSMO*, *VWA3A*, *EEF2K*, *POLR3E*, and *CDR2*) are within the 520-kb recurrent deletion, no single gene for which pathogenic variants are causative has been identified (see Molecular Genetics for genes of interest in the deleted region).

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray (CMA)** or **targeted deletion analysis**. Note: The 16p12.2 recurrent deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

CMA using oligonucleotide or SNP arrays can detect the recurrent deletion in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 16p12.2 region.

Note: (1) Most individuals with a 16p12.2 recurrent deletion are identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, or autism spectrum disorder. (2) Prior to 2010 several CMA platforms did not include coverage for this region and thus may not have detected this deletion. (3) The deletion would not have been detected using BAC arrays.

Targeted deletion analysis. FISH analysis, quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), or other targeted quantitative methods may be used to test relatives of a proband who is known to have the 16p12.2 recurrent deletion.

Note: (1) Targeted deletion testing is not appropriate for an individual in whom the 16p12.2 recurrent deletion was not detected by CMA designed to target this region. (2) It is not possible to size the deletion routinely by use of targeted methods.

Table 1. Genomic Testing Used in 16p12.2 Recurrent Deletion

Deletion [1]	Method	Sensitivity	
		Proband	At-risk family members
520-kb heterozygous deletion at 16p12.2 ISCN: seq[GRCh37] del(16)(p12.2) chr16:g.21,948,445-22,430,805del [2] ClinGen ID: ISCA-37409	CMA [3]	100%	100%
	Targeted deletion analysis [4]	NA [5]	100% [6]

1. See Molecular Genetics for details of the deletion and genes of interest included in the region.
2. Standardized ISCN annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays (ISCA) Consortium). Genomic coordinates represent the minimum deletion size associated with the 16p12.2 recurrent deletion as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the deletion as calculated from these genomic positions may differ from the expected deletion size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the 16p12.2 recurrent deletion (see Genetically Related Disorders).
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 16p12.2 region. Note: The 16p12.2 recurrent deletion may not have been detectable by older oligonucleotide or BAC platforms.
4. Targeted deletion analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.
5. Targeted deletion analysis is not appropriate for an individual in whom the 16p12.2 recurrent deletion was not detected by CMA designed to target this region.
6. Targeted deletion analysis may be used to test at-risk relatives of a proband who is known to have the 16p12.2 recurrent deletion.

Evaluating at-risk relatives. FISH, qPCR, or other quantitative methods of targeted deletion analysis can be used to identify the 16p12.2 recurrent deletion in at-risk relatives of the proband. Testing of parental samples is important in determining recurrence risk (see Genetic Counseling).

Clinical Characteristics

Clinical Description

Due to the variable expressivity of deletion 16p12.2, this variant was not known prior to the use of chromosomal microarray testing in genetic diagnosis. The significant bias in ascertainment of children with intellectual disability and developmental delay [Girirajan et al 2010, Cooper et al 2011] and of individuals with schizophrenia [Rees et al 2014] undergoing clinical chromosomal microarray analysis makes it difficult to accurately associate specific phenotypes with the 16p12.2 recurrent deletion (Table 2).

Table 2. Clinical Features in Probands with 16p12.2 Recurrent Deletion

Finding	Frequency	%
Developmental delay	76/113	67%
Speech delay	68/92	74%
Intellectual disability	46/59	78%
Craniofacial features	50/85	59%
Musculoskeletal features	30/57	53%
Growth restriction	26/74	35%
Microcephaly	25/81	31%
Congenital cardiac defect	13/34	38%
Epilepsy	27/71	38%
Psychiatric/behavioral disorders	9/16	56%
Autism	31/67	46%
Hearing loss	12/59	20%
Hypotonia	24/71	34%
Genital problems	12/47	25%
Sacral dimple or tethered cord	4/24	17%

de Jong et al [2010], Girirajan et al [2010], D'Alessandro et al [2014], Rai & Sharif [2015], Pizzo et al [2019]
Some probands had additional genetic abnormalities identified that likely contributed to their phenotypes; frequencies therefore likely represent an ascertainment bias.

A study including 23 unrelated probands with 16p12.2 recurrent deletion from a (postnatal) clinical genetic testing cohort yielded the following phenotypic findings [Girirajan et al 2010]. A more recent study [Pizzo et al 2019] analyzed 141 children with 16p12.2 deletion (median age 7 years) referred for clinical genetic testing, further extending the clinical spectrum observed in the initial reports. Because of the nature of these clinical populations, some of the phenotypes may reflect an ascertainment bias.

Developmental delay. In the report of Girirajan et al [2010], developmental delay ranging from mild to profound was present in all individuals with a 16p12.2 recurrent deletion. All individuals older than age 12 months showed speech delay; some remained nonverbal into childhood and adolescence. Motor milestones could also be affected, and many individuals were noted to have global delays. Among the individuals assessed

for developmental milestones by Pizzo et al [2019], 67% showed developmental delay or psychomotor retardation while 74% exhibited speech delay.

In contrast, individuals with the recurrent deletion who were specifically ascertained for heart defects did not show delayed development [D'Alessandro et al 2014]. Similarly, normal early language development was described in the report of a child age one year with the recurrent deletion [Rai & Sharif 2015].

Cognitive development. Girirajan et al [2010] described a spectrum of cognitive abilities in individuals with a 16p12.2 recurrent deletion, ranging from normal in heterozygous parents to mild impairments to profoundly affected, nonverbal individuals. However, parents with the recurrent deletion were more likely to manifest learning disabilities than parents who did not have the recurrent deletion. Analysis of cognitive and psychiatric phenotypes by Pizzo et al [2019] identified learning difficulties in school in 53% of parents with the 16p12.2 deletion. Individuals from the general population with the 16p12.2 deletion were found to have decreased cognitive function (verbal IQ scores and logical memory) compared to controls who did not have the deletion [Stefansson et al 2014].

Dysmorphic features. While dysmorphic features are reported in a majority of individuals with a 16p12.2 recurrent deletion, no consistent pattern was evident [Girirajan et al 2010].

Growth. Approximately two fifths of pediatric probands had growth restriction; three were specifically noted to have short stature [Girirajan et al 2010]. These features were also observed by Pizzo et al [2019], with 35% of individuals exhibiting intrauterine growth delay, short stature, and/or delayed growth.

Microcephaly was present in seven of 22 pediatric probands [Girirajan et al 2010], including two who had otherwise normal growth parameters [de Jong et al 2010, Girirajan et al 2010, Rai & Sharif 2015]. Twenty-five of the 81 children with 16p12.2 deletion analyzed by Pizzo et al [2019] exhibited microcephaly, and six showed increased head circumference z scores, corresponding to a macrocephaly phenotype.

Cardiac malformations. Recurrent deletions of 16p12.2 may be a risk factor for cardiac malformations. While not all individuals with these deletions have had echocardiography, 14 children had cardiac defects, including hypoplastic left heart (found in 4 individuals, 2 of whom also had heterotaxy), ventricular septal defect, patent foramen ovale, absence of posterior pericardium, bicuspid aortic valve, aortic valve stenosis, patent ductus arteriosus, and tetralogy of Fallot [Girirajan et al 2010, D'Alessandro et al 2014, Pizzo et al 2019]. However, 16p12.2 recurrent deletions are unlikely to be a major cause of left-sided cardiac lesions [D'Alessandro et al 2014].

Epilepsy. Approximately 40% of probands with a 16p12.2 deletion experienced seizures and/or had abnormal findings on EEG. Seizure types included West syndrome, Lennox-Gastaut syndrome, staring spells, epilepsy with myoclonus, and febrile seizures [Girirajan et al 2010, Pizzo et al 2019].

Psychiatric and behavior issues. Psychiatric and/or behavioral issues were identified in more than half (9/16) of individuals with a 16p12.2 recurrent deletion who were assessed for these features. Autistic features or stereotypies were specifically noted in three individuals, poor attention was noted in three, and aggression was noted in two [Girirajan et al 2010]. Further analysis in a larger population identified a diagnosis of autism in 31/67 children (67%) with the deletion [Pizzo et al 2019].

Recurrent deletions of 16p12.2 have also been reported to be significantly enriched among individuals with schizophrenia, with an associated odds ratio of 2.72 (95% confidence interval, 1.48-5.02) relative to a control population [Rees et al 2014]. Additionally, one control identified to have a 16p12.2 recurrent deletion was retrospectively diagnosed with major depressive disorder, and parents with a 16p12.2 recurrent deletion were also significantly more likely to have mild learning disability or psychiatric issues (e.g. depression, bipolar disorder) than parents without the deletion [Girirajan et al 2010]. Pizzo et al [2019] showed that among parents with the 16p12.2 deletion, 53% (17/32) had exhibited learning difficulties in school, 52% (11/21) exhibited

depressive behaviors, 13% (2/15) alcohol or drug addiction, 19% (3/16) schizophrenic-like behaviors, 28% epilepsy, and 13% (2/16) bipolar disorder.

Other neurologic features. Hearing loss including unilateral, bilateral, sensorineural, and unspecified has been described in eight individuals [Girirajan et al 2010, Pizzo et al 2019].

Hypotonia was reported in 34%-45% of individuals assessed for this feature [Girirajan et al 2010, Rai & Sharif 2015].

Either a sacral dimple or tethered cord was present in four of 24 individuals assessed [de Jong et al 2010, Girirajan et al 2010, D'Alessandro et al 2014, Rai & Sharif 2015].

Abnormal brain imaging was reported in 56%-63% of individuals, with features including cerebellar and cerebral atrophy, decreased white matter, unspecified periventricular changes, and agenesis of the corpus callosum [Girirajan et al 2010, Pizzo et al 2019].

One individual with a 16p12.2 recurrent deletion had postnatal onset of hydrocephalus due to cervicomedullary spinal stenosis [Rai & Sharif 2015], and an additional individual reportedly had congenital hydrocephalus without additional clinical details available [Girirajan et al 2010].

Other congenital anomalies. Aside from heart defects, other congenital anomalies have only occasionally been reported, and some of these may be attributable to other unknown genetic factors. Out of 26 reported probands with 16p12.2 recurrent deletions [de Jong et al 2010, Girirajan et al 2010, D'Alessandro et al 2014, Rai & Sharif 2015]:

- Four children had absence of canine teeth with duplication of incisors bilaterally, pegged incisors, crowded teeth, and/or dental caries.
- Three children had renal abnormalities (small kidneys, horseshoe kidney, or hydronephrosis).
- Three males had genital anomalies including chordee, hypospadias, and cryptorchidism [de Jong et al 2010, Girirajan et al 2010].
- Two had cleft palate, one with cleft lip.
- Two had clubfoot or bowed legs.
- Single individuals have been reported with craniosynostosis, inguinal hernia, and tracheal agenesis, although the last was in an individual who had an additional rare copy number variant [de Jong et al 2010, Girirajan et al 2010].

Genotype-Phenotype Correlations

Probands with 16p12.2 recurrent deletion manifesting abnormal phenotypes are significantly more likely than controls to have a second rare, unrelated, large (>500 kb) copy number variant (CNV) [Girirajan et al 2010, Girirajan et al 2012]. Such individuals had distinct or more severe phenotypes – compared to the classic phenotypes associated with the known second pathogenic CNV – suggesting that the 16p12.2 recurrent deletion is an independent risk factor for neurodevelopmental phenotypes in association with other large, pathogenic CNVs [Girirajan et al 2010]. Furthermore, exome sequencing analysis of 26 families with the deletion showed that probands present an enrichment of rare (<0.1%) likely pathogenic variants affecting functionally intolerant genes ("other hits") compared to their parent with 16p12.2 recurrent deletion, likely contributing to the more severe clinical manifestation with early-onset features [Pizzo et al 2019].

Penetrance

Penetrance for 16p12.2 recurrent deletions is incomplete.

The 16p12.2 recurrent deletion was documented to be enriched in a population undergoing clinical chromosomal microarray analysis [Girirajan et al 2010, Cooper et al 2011] and among individuals with schizophrenia [Rees et al 2014]. Further studies also identified the deletion in apparently healthy parents of probands and controls. On further follow up, parents with the deletion were found to be more likely to have clinical findings such as seizures, mild intellectual disability, and/or psychiatric issues, suggesting that the 16p12.2 recurrent deletion is a risk factor for abnormal neurodevelopmental phenotypes with reduced penetrance and variable expressivity.

Based on data from children undergoing clinical chromosome microarray analysis and adult controls, estimates for intellectual disability / developmental delay and/or congenital malformations in those with a 16p12.2 recurrent deletion were 12.3% (95% confidence interval, 7.91%-18.8%) [Rosenfeld et al 2013] and 13% (95% confidence interval, 5.7%-30%) [Kirov et al 2014].

Kirov et al [2014] estimated the penetrance of schizophrenia among individuals with a 16p12.2 recurrent deletion at 3.1% (95% confidence interval, 1.2%-8.3%).

In addition, individuals with a 16p12.2 recurrent deletion are more likely to have a family history of neuropsychiatric phenotypes, suggesting segregation of neuropsychiatric risk factors other than 16p12.2 recurrent deletion. Of note, ten (~25%) of 42 probands with 16p12.2 recurrent deletion also had another large (>500-kb) CNV elsewhere in the genome. The "second hit" was frequently *de novo* or transmitted from the parent who did not have the 16p12.2 recurrent deletion. These observations suggest that the deletion confers risk for neuropsychiatric features and that the penetrance and expressivity of the deletion-associated phenotype depends on the presence of a second large CNV or, potentially, other genetic modifiers elsewhere in the genome. Probands with a strong family history of psychiatric and neurodevelopmental disease present a more heterogeneous and severe manifestation of the deletion and a higher burden of additional likely pathogenic variants. Family history of psychiatric and neurodevelopmental disease should be interrogated to assess prognosis in the children with 16p12.2 deletions [Pizzo et al 2019].

The proportion of males is higher among all individuals with a CNV associated with reduced penetrance and variable expressivity (like a 16p12.2 recurrent deletion) as compared to those with syndromic CNVs (like Smith-Magenis syndrome, where the proportion of males is ~50%), suggesting that penetrance may be higher in males than females [Girirajan et al 2012, Jacquemont et al 2014]. Among 140 individuals analyzed by Pizzo et al, 68% were males and 32% were females [Pizzo et al 2019].

Anticipation

While almost all reports describe identification of the 16p12.2 recurrent deletion in individuals who are more severely affected than a parent with the deletion, this is more likely to reflect an ascertainment bias than genetic anticipation. Changes in the size of a 16p12.2 recurrent deletion on transmission from one generation to the next have not been described [Girirajan et al 2010].

Nomenclature

The chromosomal location of the recurrent deletion originally described at 16p12.1 (from coordinates ~21850000-~22370000, genome build hg18/NCB136) has changed to 16p12.2 (from coordinates ~21948445-~22430805, genome build hg19/GRCh37). Clinical reports and descriptions now use the 16p12.2 location/nomenclature.

Prevalence

The estimated frequency of 16p12.2 recurrent deletion – on the order of 0.19% of individuals undergoing clinical microarray-based testing [Rosenfeld et al 2013] – is similar to that of Smith-Magenis syndrome, suggesting that

Smith-Magenis syndrome and 16p12.2 recurrent deletion associated with an abnormal phenotype may have a similar incidence of approximately 1:15,000 live births [Girirajan et al 2010].

However, this estimate does not account for healthy or mildly affected individuals who are heterozygous for the deletion.

- Control studies show the frequency of the 16p12.2 recurrent deletion to be 0.050%-0.072%, or approximately one in 1,400-2,000 individuals [Girirajan et al 2010, Rosenfeld et al 2013, Kirov et al 2014, Rees et al 2014].
- One study estimated the prevalence of the 16p12.2 recurrent deletion in the general population (including healthy and affected individuals) at 0.057% (95% confidence interval, 0.032%-0.10%) [Kirov et al 2014].

Genetically Related (Allelic) Disorders

16p12.2 recurrent duplication. The reciprocal recurrent duplication has not been shown to be enriched in a patient population [Cooper et al 2011] and is therefore likely a benign variant.

16p11.2-p12.2 recurrent deletion. A deletion syndrome encompassing a larger portion the 16p region has been described. Common features include characteristic dysmorphic features, congenital anomalies, feeding difficulties, frequent ear infections, and cognitive and developmental delays. The commonly deleted region is ~7.1 Mb, from coordinates ~21,500,000 to ~28,600,000 (genome build UCSC hg19), including the recurrently deleted 16p12.2 region [Ballif et al 2007, Battaglia et al 2009, Hempel et al 2009, Okamoto et al 2014].

No phenotypes other than those discussed in this *GeneReview* are known to be associated with copy number variants (CNVs) in the genes located within the 16p12.2 520-kb critical region.

Differential Diagnosis

The differential diagnosis of the 16p12.2 recurrent deletion is broad due to the variable spectrum and presence of relatively common abnormal phenotypes that occur in affected individuals including developmental delay, learning problems, and neuropsychiatric disorders. All manifestations of the 16p12.2 recurrent deletion can also be seen in individuals with other genomic disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with the 16p12.2 recurrent deletion, the following evaluations are recommended if they have not already been completed:

- Consultation with a clinical geneticist and/or genetic counselor
- Measurement of height and weight
- Broad review of all organ systems
- Developmental assessment with cognitive and behavioral testing

To consider:

- Consultation with a neurologist and EEG testing if history suggests the possibility of seizures
- Evaluation and echocardiogram by a cardiologist

Treatment of Manifestations

Because manifestations of 16p12.2 recurrent deletion are variable, treatment should be targeted to the specific problems identified. Early diagnosis and treatment facilitate the best outcome. Referral to other appropriate medical specialists is recommended based on specific signs and symptoms. Specialists may include a developmental/behavioral pediatrician, pediatric neurologist, and/or clinical geneticist.

Developmental and cognitive delays. Initiate developmental therapies promptly when indicated. Cognitive testing in older children may help identify any specific learning or cognitive disabilities that could be addressed by therapies or specialized education plans.

Cardiac malformations. Individuals with 16p12.2 recurrent deletion and cardiac malformations should have standard treatment for the malformation, including surgical correction and prophylactic antibiotic treatments as indicated.

Epilepsy. A history suggestive of possible seizure activity should prompt referral to a neurologist for additional testing, including brain imaging and EEG, and consideration of medical intervention.

Psychiatric and/or behavior issues. In individuals of any age, signs of psychiatric or behavioral issues should prompt referral to specialists including developmental/behavioral pediatricians, psychologists, or psychiatrists so that formal assessments may be performed and appropriate interventions (medical, social, behavioral, and/or educational) may be made.

Hearing loss. Standard treatment should be provided for hearing loss. See Hereditary Hearing Loss and Deafness.

Other malformations. Standard treatment should be provided for any other malformations, including orofacial clefting and renal, genitourinary, or dental anomalies.

Surveillance

Periodic:

- Developmental evaluations because of the increased incidence of developmental delay, intellectual disability, autism spectrum disorders, and other behavioral features
- Monitoring of cardiac, renal, urologic, and/or dental abnormalities, as needed
- Reevaluation by a clinical geneticist who can apprise the family of new recommendations for monitoring for medical or mental health concerns.

Evaluation of Relatives at Risk

Older and younger sibs of a proband should be tested for a 16p12.2 recurrent deletion to encourage close assessment/monitoring of developmental milestones and monitoring for neuropsychiatric and congenital manifestations in children with the deletion.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The 16p12.2 recurrent deletion is inherited in an autosomal dominant manner, with an estimated 95% of deletions inherited from a parent and 5% occurring *de novo*.

A single, apparently *de novo* 16p12.2 recurrent deletion was reported by Rosenfeld et al [2013]. However, additional testing to confirm parentage was not performed. Seven more *de novo* 16p12.2 recurrent deletions were identified by Pizzo et al [2019], corresponding to a *de novo* rate of 7.6% (7/92) in this study.

Risk to Family Members

Parents of a proband

- Evaluation of the parents by genomic testing that will detect the 16p12.2 recurrent deletion present in the proband is recommended.
- Note: Germline mosaicism, somatic mosaicism, and balanced chromosomal rearrangements involving the 16p12.2 region have not been reported with 16p12.2 recurrent deletions.
- The family history of some individuals diagnosed with a 16p12.2 recurrent deletion may appear to be negative because of reduced penetrance and variable expressivity. Therefore, an apparently negative family history cannot be confirmed unless appropriate genomic testing followed by detailed clinical evaluation has been performed on the parents of the proband. Even in individuals with a *de novo* deletion, eliciting family history is important as neuropsychiatric disease can be caused by pathogenic variants other than a 16p12.2 recurrent deletion.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- If the 16p12.2 recurrent deletion identified in the proband is not identified in a parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism for the deletion.
- If one of the parents has the 16p12.2 recurrent deletion, the risk to each sib of inheriting the deletion is 50%. However, it is not possible to reliably predict the expressivity of 16p12.2 recurrent deletion in sibs of a proband.

  The presence of neuropsychiatric phenotypes in a parent with the deletion may indicate higher penetrance within a family (see Penetrance).

Offspring of a proband

- Offspring of an individual with a 16p12.2 recurrent deletion have a 50% chance of inheriting the deletion.
- The risk to offspring of being affected is less than 50% because of reduced penetrance (see Penetrance).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 16p12.2 recurrent deletion, the parent's family members may also have the deletion.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with the 16p12.2 recurrent deletion.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 16p12.2 recurrent deletion. Once the 16p12.2 recurrent deletion has been identified in an affected family member, prenatal and preimplantation genetic testing for 16p12.2 recurrent deletion are possible. Note: It is not possible to reliably predict the expressivity of 16p12.2 recurrent deletion based on the results of prenatal testing. However, a family history of neuropsychiatric and neurodevelopmental features is reported to correlate with increased severity in the manifestation of the deletion.

Prenatal testing using targeted deletion analysis that will detect the 16p12.2 recurrent deletion found in the proband may be offered when:

- A parent has the recurrent deletion; or
- The parents do not have the recurrent deletion but have had a child with the 16p12.2 recurrent deletion. In this instance, the recurrence risk associated with the possibility of parental germline mosaicism or other predisposing genetic mechanisms is probably slightly greater than that of the general population (though still <1%).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Pregnancies not known to be at increased risk for the 16p12.2 recurrent deletion. CMA performed in a pregnancy not known to be at increased risk may detect the recurrent deletion.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for 16p12.2 recurrent deletion, prenatal test results cannot reliably predict the phenotype.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  16p12.2 microdeletion

- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table B. OMIM Entries for 16p12.2 Recurrent Deletion (View All in OMIM)

136570	CHROMOSOME 16p12.1 DELETION SYNDROME, 520-KB

Molecular Pathogenesis

The 520-kb deletion at chromosome 16p12.2 (coordinates ~21948445-~22430805, genome build UCSC hg19/GRCh37) results in the deletion of seven genes: *UQCRC2*, *PDZD9*, *MOSMO*, *VWA3A*, *EEF2K*, *POLR3E*, and *CDR2* (RefSeq genes, UCSC hg19/GRCh37). While the pericentromeric region of chromosome 16 has many segmental duplications that can mediate recurrent deletions, this 16p12.2 recurrent deletion specifically refers to a deletion with these specific coordinates.

The 16p12.2 recurrent deletion is mediated by recombination between flanking 68-kb low-copy segmental duplications with 99.5% sequence identity [Antonacci et al 2010, Girirajan et al 2010] that contains six additional genes. Based on the number and orientation of segmental duplications, two common haplotypes have been identified in the general population [Antonacci et al 2010]. Haplotype S2 has the 68-kb segmental duplications in direct orientation flanking the 16p12.2 deletion region, suggesting that it would predispose to the recurrent 16p12.2 deletion. Consistent with this hypothesis, the S2 haplotype is enriched among individuals with a 16p12.2 recurrent deletion. The population frequency of the S2 haplotype varies by ancestry:

- African (97.5%)
- European (83.1%)
- Asian (71.6%)

Therefore, African and European populations likely have a higher risk for 16p12.2 recurrent deletions than Asian populations [Antonacci et al 2010].

Genes of interest in this region. The underlying mechanism for how the heterozygosity of one or more of the seven genes in 16p12.2 results in disease is unknown; however, these genes have been studied to a variable extent:

- *UQCRC2* is a fundamental protein for the assembly of the mitochondrial respiratory chain complex.
- *CDR2* is an onco-neural antigen and has been associated with cerebellar ataxia.
- *POLR3E* is a component of the RNA polymerase that synthesizes small RNAs.
- *EEF2K* is a kinase involved in the regulation of protein synthesis elongation and has been recently associated with learning and memory, synaptic plasticity, and the short-term antidepressant action of ketamine. *eef2k*-knockout mice have been described to have defects in the reproductive system, and those carrying a homozygous-inactivating pathogenic variant leading to 0.5% residual activity showed learning memory deficits and altered brain activity.
- *MOSMO* is a negative regulator of hedgehog signaling.

Functional information on *PDZD9* and *VWA3A* is limited.

Chapter Notes

Author Notes

Santhosh Girirajan's Laboratory

I am interested in understanding the causes and consequences of genome structure and function as related to human neurodevelopmental disorders such as intellectual disability and developmental delay, autism, schizophrenia, and epilepsy. My graduate work on Smith-Magenis syndrome (SMS) trained me in understanding how all individuals carrying a deletion encompassing the retinoic acid induced 1 gene (*RAI1*) have invariable phenotypes [Girirajan et al 2005, Girirajan et al 2006]. Further, analysis of mouse models altering *Rai1* gene dosage confirmed the role of *RAI1* in SMS [Girirajan et al 2008, Girirajan & Elsea 2009a, Girirajan & Elsea 2009b]. As a postdoctoral fellow in Evan Eichler's lab, I was involved in identifying and studying another class of CNVs where the causal gene is not known and individuals carrying the same deletion or duplication manifest a wide variety of phenotypes. I was able to demonstrate that a second variant in addition to the primary genomic lesion can explain the observed phenotypic variability. Originally described for 16p12.1 deletion [Girirajan et al 2010], the "two-hit" model was successfully replicated to explain the phenotypic heterogeneity in other recently identified CNVs such as 16p11.2 deletion, 15q13.3 deletion,17q12 deletion, 15q11.2 deletion, and 1q21.1 deletion [Girirajan et al 2012].

Revision History

- 13 September 2018 (sw) Comprehensive update posted live
- 26 February 2015 (me) Review posted live
- 9 September 2014 (sg) Original submission

References

Literature Cited

Antonacci F, Kidd JM, Marques-Bonet T, Teague B, Ventura M, Girirajan S, Alkan C, Campbell CD, Vives L, Malig M, Rosenfeld JA, Ballif BC, Shaffer LG, Graves TA, Wilson RK, Schwartz DC, Eichler EE. A large and complex structural polymorphism at 16p12.1 underlies microdeletion disease risk. Nat Genet. 2010;42:745-50. PubMed PMID: 20729854.

Ballif BC, Hornor SA, Jenkins E, Madan-Khetarpal S, Surti U, Jackson KE, Asamoah A, Brock PL, Gowans GC, Conway RL, Graham JM Jr, Medne L, Zackai EH, Shaikh TH, Geoghegan J, Selzer RR, Eis PS, Bejjani BA, Shaffer LG. Discovery of a previously unrecognized microdeletion syndrome of 16p11.2-p12.2. Nat Genet. 2007;39:1071-3. PubMed PMID: 17704777.

Battaglia A, Novelli A, Bernardini L, Igliozzi R, Parrini B. Further characterization of the new microdeletion syndrome of 16p11.2-p12.2. Am J Med Genet A. 2009;149A:1200-4. PubMed PMID: 19449418.

Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, Vu TH, Baker C, Williams C, Stalker H, Hamid R, Hannig V, Abdel-Hamid H, Bader P, McCracken E, Niyazov D, Leppig K, Thiese H, Hummel M, Alexander N, Gorski J, Kussmann J, Shashi V, Johnson K, Rehder C, Ballif BC, Shaffer LG, Eichler EE. A copy number variation morbidity map of developmental delay. Nat Genet. 2011;43:838-46. PubMed PMID: 21841781.

D'Alessandro LC, Werner P, Xie HM, Hakonarson H, White PS, Goldmuntz E. The prevalence of 16p12.1 microdeletion in patients with left-sided cardiac lesions. Congenit Heart Dis. 2014;9:83-6. PubMed PMID: 23682798.

de Jong EM, Douben H, Eussen BH, Felix JF, Wessels MW, Poddighe PJ, Nikkels PG, de Krijger RR, Tibboel D, de Klein A. 5q11.2 deletion in a patient with tracheal agenesis. Eur J Hum Genet. 2010;18:1265-8. PubMed PMID: 20551993.

Girirajan S, Elsas LJ 2nd, Devriendt K, Elsea SH. RAI1 variations in Smith-Magenis syndrome patients without 17p11.2 deletions. J Med Genet. 2005;42:820-8. PubMed PMID: 15788730.

Girirajan S, Elsea SH. Abnormal maternal behavior, altered sociability, and impaired serotonin metabolism in Rai1-transgenic mice. Mamm Genome. 2009a;20:247-55. PubMed PMID: 19319603.

Girirajan S, Elsea SH. Distorted Mendelian transmission as a function of genetic background in Rai1-haploinsufficient mice. Eur J Med Genet. 2009b;52:224-8. PubMed PMID: 19116176.

Girirajan S, Patel N, Slager RE, Tokarz ME, Bucan M, Wiley JL, Elsea SH. How much is too much? Phenotypic consequences of Rai1 overexpression in mice. Eur J Hum Genet. 2008;16:941-54. PubMed PMID: 18285828.

Girirajan S, Rosenfeld JA, Coe BP, Parikh S, Friedman N, Goldstein A, Filipink RA, McConnell JS, Angle B, Meschino WS, Nezarati MM, Asamoah A, Jackson KE, Gowans GC, Martin JA, Carmany EP, Stockton DW, Schnur RE, Penney LS, Martin DM, Raskin S, Leppig K, Thiese H, Smith R, Aberg E, Niyazov DM, Escobar LF, El-Khechen D, Johnson KD, Lebel RR, Siefkas K, Ball S, Shur N, McGuire M, Brasington CK, Spence JE, Martin LS, Clericuzio C, Ballif BC, Shaffer LG, Eichler EE. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. N Engl J Med. 2012;367:1321-31. PubMed PMID: 22970919.

Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC, Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gecz J, Delisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. Nat Genet. 2010;42:203-9. PubMed PMID: 20154674.

Girirajan S, Vlangos CN, Szomju BB, Edelman E, Trevors CD, Dupuis L, Nezarati M, Bunyan DJ, Elsea SH. Genotype-phenotype correlation in Smith-Magenis syndrome: evidence that multiple genes in 17p11.2 contribute to the clinical spectrum. Genet Med. 2006;8:417-27. PubMed PMID: 16845274.

Hempel M, Rivera Brugues N, Wagenstaller J, Lederer G, Weitensteiner A, Seidel H, Meitinger T, Strom TM. Microdeletion syndrome 16p11.2-p12.2: clinical and molecular characterization. Am J Med Genet A. 2009;149A:2106-12. PubMed PMID: 19676056.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, Beckmann JS, Rosenfeld JA, Eichler EE. A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet. 2014;94:415-25. PubMed PMID: 24581740.

Kirov G, Rees E, Walters JT, Escott-Price V, Georgieva L, Richards AL, Chambert KD, Davies G, Legge SE, Moran JL, McCarroll SA, O'Donovan MC, Owen MJ. The penetrance of copy number variations for schizophrenia and developmental delay. Biol Psychiatry. 2014;75:378-85. PubMed PMID: 23992924.

Okamoto N, Fujii T, Tanaka J, Saito K, Matsui T, Harada N. A clinical study of patients with pericentromeric deletion and duplication within 16p12.2-p11.2. Am J Med Genet A. 2014;164A:213-9. PubMed PMID: 24259393.

Pizzo L, Jensen M, Polyak A, Rosenfeld JA, Mannik K, Krishnan A, McCready E, Pichon O, Le Caignec C, Van Dijck A, Pope K, Voorhoeve E, Yoon J, Stankiewicz P, Cheung SW, Pazuchanics D, Huber E, Kumar V, Kember RL, Mari F, Curró A, Castiglia L, Galesi O, Avola E, Mattina T, Fichera M, Mandarà L, Vincent M, Nizon M, Mercier S, Bénéteau C, Blesson S, Martin-Coignard D, Mosca-Boidron AL, Caberg JH, Bucan M,

Zeesman S, Nowaczyk MJM, Lefebvre M, Faivre L, Callier P, Skinner C, Keren B, Perrine C, Prontera P, Marle N, Renieri A, Reymond A, Kooy F, Isidor B, Schwartz C, Romano C, Sistermans E, Amor DJ, Andrieux J, Girirajan S. Rare variants in the genetic background modulate cognitive and developmental phenotypes in individuals carrying disease-associated variants. Genet Med. 2019;21;816-25. PubMed PMID: 30190612.

Rai B, Sharif F. Cervicomedullary spinal stenosis and ventriculomegaly in a child with developmental delay due to chromosome 16p12.1 microdeletion syndrome. J Child Neurol. 2015;30:394-6. PubMed PMID: 24813870.

Rees E, Walters JT, Chambert KD, O'Dushlaine C, Szatkiewicz J, Richards AL, Georgieva L, Mahoney-Davies G, Legge SE, Moran JL, Genovese G, Levinson D, Morris DW, Cormican P, Kendler KS, O'Neill FA, Riley B, Gill M, Corvin A, Sklar P, Hultman C, Pato C, Pato M, Sullivan PF, Gejman PV, McCarroll SA, O'Donovan MC, Owen MJ, Kirov G. CNV analysis in a large schizophrenia sample implicates deletions at 16p12.1 and SLC1A1 and duplications at 1p36.33 and CGNL1. Hum Mol Genet. 2014;23:1669-76. PubMed PMID: 24163246.

Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013;15:478-81. PubMed PMID: 23258348.

Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, Bjornsdottir G, Walters GB, Jonsdottir GA, Doyle OM, Tost H, Grimm O, Kristjansdottir S, Snorrason H, Davidsdottir SR, Gudmundsson LJ, Jonsson GF, Stefansdottir B, Helgadottir I, Haraldsson M, Jonsdottir B, Thygesen JH, Schwarz AJ, Didriksen M, Stensbøl TB, Brammer M, Kapur S, Halldorsson JG, Hreidarsson S, Saemundsen E, Sigurdsson E, Stefansson K. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. 2014;505:361-6 PubMed PMID: 24352232.

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