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2q37 Microdeletion Syndrome – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Albright Hereditary Osteodystrophy-Like Syndrome, Brachydactyly-Mental Retardation Syndrome

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Summary

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Clinical characteristics

2q37 microdeletion syndrome is characterized by mild-moderate developmental delay/intellectual disability, brachymetaphalangy of digits 3-5 (often digit 4 alone) (>50%), short stature, obesity, hypotonia, characteristic facial appearance, autism or autism spectrum disorder (30%), joint hypermobility/dislocation, and scoliosis. Other findings include seizures (20%-35%), congenital heart disease, CNS abnormalities (hydrocephalus, dilated ventricles), umbilical/inguinal hernia, tracheomalacia, situs abnormalities, gastrointestinal abnormalities, and renal malformations. Wilms tumor has been reported in two individuals.

Diagnosis/testing

Chromosome analysis confirms the diagnosis of 2q37 deletion syndrome in 80%-85% of affected individuals. In about 15%-20% of cases the small size of the deleted region can only be detected using deletion analysis (which relies on a variety of methods). In some individuals, 2q37 microdeletion syndrome results from chromosome rearrangements involving 2q37 (e.g., chromosome 2 inversion, ring chromosome 2, or translocation between chromosome 2 and another chromosome). Mutation of *HDAC4* has been proposed as causative for most of the features of the 2q37 microdeletion syndrome. Several affected individuals without microdeletions had inactivating mutation of *HDAC4*, a gene in the 2q37 deleted region, leading to the proposal that mutation of this gene may be causative for most of the features of the 2q37 microdeletion syndrome.

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Management

Treatment of manifestations: Multidisciplinary care by specialists in the following fields is often required: clinical genetics, speech pathology, occupational and physical therapy, child development, neurology, cardiology, gastroenterology, nutrition/feeding, ophthalmology, and audiology. Infants benefit from enrollment in an early-intervention program; most school-age children benefit from an individualized educational program (IEP).

Surveillance: Ongoing routine primary care; periodic reevaluation by a clinical geneticist to provide new recommendations and information about the syndrome; periodic neurodevelopmental and/or developmental/behavioral pediatric evaluation to assist in the management of cognitive and behavioral problems. Screening for renal cysts at age four years and again at puberty is suggested. For young children with a deletion that includes 2q37.1, screening for Wilms tumor can be considered.

Evaluation of relatives at risk: It is reasonable to perform genetic testing of any young child at risk, so that Wilms tumor surveillance can be considered in those with a deletion that includes 2q37.1.

Genetic counseling

Most individuals with the 2q37 microdeletion syndrome have a *de novo* chromosome deletion and their parents have normal karyotypes. In approximately 5% of published cases, probands have inherited the deletion from a parent who is a balanced translocation carrier. The risk to sibs of a proband depends on the chromosome findings in the parents: the recurrence risk for future pregnancies is negligible when parental karyotypes are normal; if a parent has a balanced structural chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement. Regarding risks to offspring: no individual with a cytogenetically visible 2q37 deletion is known to have reproduced; however, it is reasonable to expect normal fertility in mildly affected individuals with the 2q37 microdeletion syndrome. Prenatal diagnosis for pregnancies at increased risk is possible. Deletion or mutation of *HDAC4* may be inherited in an autosomal dominant manner but is more commonly *de novo*.

Diagnosis

Clinical Diagnosis

2q37 microdeletion syndrome is suspected in individuals with the following characteristics:

- Developmental delay/intellectual disability
- Brachymetaphalangy of digits 3-5 (often digit 4 alone), referred to as type E brachydactyly
- Short stature
- Obesity
- Hypotonia
- Characteristic facial appearance:
  - Round face (variable)
  - Frontal bossing
  - Arched eyebrows
  - Deep-set eyes
  - Upslanted palpebral fissures
  - Epicanthal folds
  - Hypoplastic alae nasi
  - Prominent columella
  - Thin upper lip
  - Minor ear anomalies

- Autism or autism spectrum disorder
- Joint hypermobility/dislocation, scoliosis

Note: When present together, the first four features (developmental delay/intellectual disability, brachymetaphalangy of digits 3-5, short stature, obesity) are often referred to as the Albright hereditary osteodystrophy (AHO)-like phenotype.

Other structural anomalies

- Seizures
- Congenital heart disease (atrial/ventricular septal defects, PDA)
- CNS abnormalities (hydrocephalus, dilated ventricles)
- Umbilical/inguinal hernia
- Tracheomalacia
- Situs abnormalities
- Gastrointestinal abnormalities
- Renal malformations

Other clinical findings

- Eczema
- Osteopenia
- Behavioral problems (hyperactivity, attention deficits)

Neoplasms. Wilms tumor

Testing

Cytogenetic testing. Chromosome analysis confirms the diagnosis of 2q37 microdeletion syndrome in 80%-85% of affected individuals.

In about 15%-20% of cases, the conventional karyotype is normal because of the small size of the deleted region [Shrimpton et al 2004, Aldred 2006, Lacbawan et al 2006]. 2q37 microdeletions (deletions that are not visible with routine cytogenetics) have been reported in persons with the AHO-like phenotype [Bijlsma et al 1999, Chassaing et al 2004]. Small terminal deletions of 2q may be missed on routine cytogenetic studies, and microdeletions may be undetectable unless more detailed deletion/duplication analysis is employed (Table 1: footnotes 2-4).

Some individuals with the 2q37 microdeletion syndrome have chromosome rearrangements involving 2q37, including chromosome 2 inversion, ring chromosome 2, or translocation between chromosome 2 and another chromosome that results in deletion of 2q37.

Molecular Genetic Testing

Genes. The largest reported telomeric deletion in the 2q37 chromosome region is about 10 Mb while the smallest is frequently around 3 to 4 Mb [Aldred 2006, Lacbawan et al 2006]. The smallest terminal deletion reported to date was 2.7 Mb [Williams et al 2010], although an individual with developmental delay with dysmorphic features had a paternally inherited 1.6-Mb terminal deletion [Balikova et al 2007]. Most likely, deletion of the genes in this chromosome region is the genetic defect known to be associated with microdeletion 2q37 syndrome. Several individuals with features of the 2q37 microdeletion syndrome have been found to have either isolated intragenic pathogenic variants of *HDAC4* or decreased *HDAC4* expression without a contiguous gene deletion, leading to the proposal that pathogenic variants in *HDAC4* are causative of most of the syndromic features of the 2q37 microdeletion syndrome [Williams et al 2010, Morris et al 2012]. See Molecular Genetics for further discussion of candidate genes in the region.

Table 1. Molecular Genetic Testing Used in 2q37 Deletion Syndrome

Genetic Defect in 2q37 Region	Method	Variant Detection Frequency by Method [1]
Deletion or chromosome rearrangement involving 2q37	Cytogenetic analysis	80%-85%
	Deletion/duplication analysis [2]	>99% [3, 4, 5]
HDAC4 pathogenic variant in absence of 2q37 deletion/rearrangement	Sequence analysis [6] of *HDAC4*	Unknown, but rare

1. The ability of the test method used to detect a genetic defect that is present in the indicated gene
2. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
3. Subtelomeric 2q probes are commercially available. A subtelomeric FISH probe should confirm the vast majority of chromosome 2q37 deletions. Theoretically, an interstitial 2q37 deletion could be missed if the subtelomeric sequence is present [Aldred et al 2004, Chaabouni et al 2006].
4. Chromosomal microarray (CMA) using BAC clones confirmed a cryptic unbalanced translocation involving 2q37.2 in a spontaneously aborted fetus after cultured embryonic tissue failed to grow [Bruyere et al 2003]. Most 2q37 microdeletions are detectable with commercially available CMA, although more precise mapping of the deleted region is typically performed only on a research basis [Aldred et al 2004; Shrimpton et al 2004; Lacbawan et al, unpublished].
5. Although submicroscopic deletions are demonstrated using FISH or CMA, concurrent duplication/deletion may be missed by FISH study [Lacbawan et al 2006].
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm/establish the diagnosis of 2q37 microdeletion in a proband, the following testing should be performed:

First alternative

- Deletion/duplication analysis could be performed first, as it will detect large deletions, microdeletions, and microduplications of the 2q37 region. In addition, it would screen for other microdeletion/microduplication syndromes (e.g., Smith-Magenis syndrome) that have overlapping clinical features with the 2q37 microdeletion syndrome.

  Note: Deletion/duplication analyses (e.g., CMA) typically do not directly evaluate chromosome structure; thus, when results suggest an unbalanced translocation or a ring chromosome, conventional cytogenetic studies are needed to confirm these structural chromosome anomalies.

Second alternative

- For familial cases where other chromosome rearrangements may be present, karyotype (i.e., routine cytogenetic study) should be done.
- If the chromosome study is normal but the index of suspicion is high, targeted deletion analysis of the 2q37 region may be performed.

If the proband has clinical features of the 2q37 microdeletion syndrome but no microdeletion or chromosome anomaly involving 2q37 is found on the above testing, sequence analysis of *HDAC4* could be considered.

Prenatal diagnosis and preimplantation genetic testing for at-risk pregnancies require prior identification of the deletion or pathogenic variant in the proband and/or of balanced carrier status in a parent.

Clinical Characteristics

Clinical Description

The 2q37 microdeletion syndrome may present with a broad spectrum of clinical findings as described below [Smith et al 2001, Casas et al 2004, Chassaing et al 2004, Lacbawan et al 2005, Aldred 2006, Chaabouni et al 2006, Lacbawan et al 2006, Kitsiou-Tzeli et al 2007].

In individuals with isolated microdeletion 2q37 (i.e., those without an unbalanced translocation), functional outcome was affected by the presence of autism, developmental delay, and/or major congenital anomalies.

The phenotype observed in individuals with 2q37 microdeletion syndrome seems variable in earlier reports because the molecular breakpoints were not defined.

The published female-to-male ratio is greater than one.

Developmental delay. Most affected individuals have mild-moderate developmental delay. However, one individual with delayed developmental milestones was reported to work as a librarian's assistant and a second individual was a college student with autism and average-range cognitive function.

Autism or autism spectrum disorder. 2q37 microdeletions are common in individuals with syndromic autism [Jacquemont et al 2006]. Approximately one third of those reported with 2q37 microdeletion syndrome have autism or autistic features, which show significant variation among individuals. Nonetheless, no behavioral phenotype appears to be specific to the 2q37 microdeletion syndrome.

Brachymetaphalangy. Short metacarpals/metatarsals of digits 3-5, often of digit 4 alone, are present in more than half of reported cases. No functional implications are associated with the shortened digit(s). Brachymetaphalangy may not be clinically apparent in young children, though this feature has been described in several children under age one year.

Growth. The incidence of short stature is increased in individuals with 2q37 microdeletion syndrome. Failure to thrive is sometimes reported in affected infants.

Obesity. Obesity may be noted in childhood. The prevalence of obesity appears to increase with age.

Hypotonia. A significant number of individuals with 2q37 microdeletion syndrome have hypotonia and feeding difficulties. Genu valgum/recurvatum and pes planus are also common.

Characteristic facial appearance and other dysmorphic features. The typical facial characteristics include thin, arched eyebrows with deeply set eyes, hypoplastic nares, prominent columella, thin vermilion border, and minor ear dysmorphism with or without round face. The facial phenotype can be subtle, and may not be easily recognized by less experienced clinicians. Use of stereophotogrammetry has been shown to be able to distinguish the facial phenotype.

Low-set, hypoplastic nipples are often seen. Joint hyperextensibility and skin hyperlaxity may be observed.

Seizures of some type, including grand mal, partial, and myoclonic, have been noted in approximately 20%-35% of reported cases; very little clinical information is provided in most reports.

Eczema. Moderate-to-severe eczema has been reported in a few individuals.

Osteopenia. Though osteopenia is not well known to be associated with 2q37 deletion, a number of affected individuals have had osteopenia on further radiologic studies. Clinical implications have not been described.

Gastroesophageal reflux (GER). Moderate-to-severe GER can occur, and can be severe enough to necessitate surgical intervention.

Wilms tumor. Three individuals with isolated 2q37 microdeletion syndrome and Wilms tumor have been reported [Conrad et al 1995, Olson et al 1995, Viot-Szoboszlai et al 1998]. All three children presented before age two years. Olson et al [1995] reported another individual with an unbalanced translocation der(2)t(2;15)(q37;q22) and Wilms tumor. An individual with a 46,XY,add(2)(q35) karyotype and Wilms tumor was reported by Jones et al [2011]. Both individuals presented between age two and age three years. However, screening of a large cohort of individuals with 2q terminal deletions did not find other individuals with Wilms tumor. Jones and colleagues estimate a 1% risk of Wilms tumor in individuals with 2q deletions.

Other structural anomalies [Reddy et al 1999, Lehman et al 2001, Aldred 2006, Masumoto et al 2006]:

- Cleft palate
- Congenital hearing loss
- Congenital heart disease (typically atrial/ventricular septal defects)
- Situs abnormalities
- Renal malformations including horseshoe kidney
- CNS abnormalities including separate cases reported with holoprosencephaly, agenesis of the corpus callosum, and hydrocephalus
- Gastrointestinal abnormalities, including hiatal hernia, pyloric stenosis, malrotation, anal atresia, and esophageal atresia
- Joint hypermobility/dislocation and scoliosis
- Umbilical/inguinal hernia

Life span. The presence of congenital malformations appears to be the single greatest factor in determining life expectancy. Few older adults have been reported with 2q37 microdeletion syndrome; however, the authors anticipate that this will change as more individuals are ascertained with the use of subtelomeric FISH and CMA studies and longitudinal data are collected on those with the disorder. The literature continues to demonstrate that the vast majority of individuals with this syndrome do not have a shortened life span.

Genotype-Phenotype Correlations

Penetrance is complete in the 2q37 microdeletion syndrome; however, phenotypic variability is observed. Using both cytogenetic and molecular analyses, deletion size does not appear to correlate well with phenotype. Brachymetaphalangy is observed in approximately half of individuals with deletions of the Albright hereditary osteodystrophy (AHO)-like critical region containing *HDAC4* [Aldred et al 2004].

Further genotype-phenotype correlations have not been established.

A parent-of-origin effect has not been convincingly demonstrated.

Penetrance

Clinical characteristics of 2q37 microdeletion syndrome are apparent and no case of mosaicism has been documented to date.

Nomenclature

The 2q37 microdeletion syndrome has also been referred to as Albright hereditary osteodystrophy 3.

Prevalence

The prevalence of the 2q37 microdeletion syndrome is unknown. It is likely that this syndrome is underdiagnosed because of difficulty in recognizing the small terminal deletion on routine cytogenetic studies, and failure to recognize the clinical syndrome on physical examination. It is expected that more individuals will be diagnosed as the clinical use of subtelomeric FISH and CMA studies increases.

Genetically Related (Allelic) Disorders

The 2q37 microdeletion syndrome may present with a broad spectrum of clinical findings. Prior to the clinical introduction of chromosomal microarray, subtelomeric FISH identified 2q37 deletions in a number of individuals referred for developmental delay/intellectual disability with or without other dysmorphic features [Anderlid et al 2002, Sogaard et al 2005, Ravnan et al 2006]. The 2q37 microdeletion syndrome phenotype was not clearly described in any of these individuals.

A pilot study of children with autism reported one nondysmorphic child with a normal examination and a subtelomeric deletion of 2q [Wolff et al 2002]. Similarly, in a large cohort of more than 400 autistic individuals, Reddy [2005] reported a child with autism and macrocephaly who had a 2q37 deletion identified by FISH. Further molecular characterization of these individuals would be helpful.

Differential Diagnosis

Albright hereditary osteodystrophy (AHO) is characterized by obesity, short stature, brachydactyly, subcutaneous ossifications, and intellectual disability. Most individuals with AHO have an inactivating pathogenic variant in *GNAS*, the gene encoding the alpha subunit of a G-protein.

- Maternally inherited pathogenic variants are associated with resistance to parathyroid hormone (PTH) (known as pseudohypoparathyroidism type 1A), thyroid stimulating hormone (TSH), and gonadotropins.
- Paternally inherited pathogenic variants are associated only with AHO (also known as pseudopseudohypoparathyroidism).

The clinical overlap between AHO/pseudopseudohypoparathyroidism and the 2q37 microdeletion syndrome may be substantial [Aldred et al 2004, Aldred 2006]. The authors are not aware of any individuals with the 2q37 microdeletion syndrome who had subcutaneous calcifications or hormone resistance, both of which can be seen in AHO. See Disorders of *GNAS* Inactivation.

Smith-Magenis syndrome. Phenotypic overlap with Smith-Magenis syndrome was clearly demonstrated by Williams et al [2010].

Kabuki syndrome. Two individuals with phenotypic features suspicious for Kabuki syndrome had chromosome rearrangements that included 2q37 deletion [Cuscó et al 2008].

CHARGE syndrome. Two children in a family with an unbalanced translocation between 2q and 21q resulting in a 2q37 microdeletion presented with choanal atresia and were initially misdiagnosed as having CHARGE syndrome [Fernández-Rebollo et al 2009].

Type E brachydactyly (metacarpal 3-5 shortening) has been described in Turner syndrome. *HOXD13* pathogenic variants have been reported in a skeletal malformation syndrome with overlap between brachydactyly types D and E [Johnson et al 2003].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with the 2q37 microdeletion syndrome, the following evaluations are recommended:

- Complete medical history to include evidence of any congenital malformations, seizure disorder, or behavioral problems
- Complete physical and dysmorphology examination
- Determination of head circumference, height, weight, and other anthropometric measurements
- Specialty evaluation of obesity or failure to thrive
- Multidisciplinary developmental and neurologic evaluation to assess motor and cognitive skills as well as autism, autism spectrum behaviors, and other behavioral issues
- Echocardiogram to evaluate for congenital cardiac anomaly
- Renal ultrasound examination to evaluate for possible Wilms tumor, renal malformation, or other renal problems
- Ophthalmology evaluation for strabismus and/or refractive errors
- Audiologic assessment for possible hearing loss
- Brain imaging studies (MRI, CT scan) in individuals with abnormal neurologic findings
- EEG for evaluation of seizures and treatment monitoring
- X-ray to evaluate for the presence of scoliosis and skeletal anomalies examination. While the clinical implications of osteopenia have not been studied in the 2q37 microdeletion syndrome, clinicians should be aware that this is a common finding. X-rays should be performed at diagnosis and should be repeated as warranted by clinical examination. The youngest individual with osteopenia in the authors' series is age three years.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Depending on the age and presenting concerns of the individual with the 2q37 microdeletion syndrome, care from specialists in the following areas is often necessary: clinical genetics, speech pathology, occupational and physical therapy, child development, neurology, cardiology, gastroenterology, nutrition/feeding in cases of failure to thrive, ophthalmology, and audiology.

Medical care may be coordinated by a clinical geneticist or other health care professional skilled at managing patients with complex needs.

Infants benefit from enrollment in an early-intervention program. Most school-age children benefit from an individualized educational program (IEP) with input from a multispecialty group of physical, occupational, and speech therapists with pediatric assessment.

Prevention of Secondary Complications

At this time, it is not known why many individuals with the 2q37 microdeletion syndrome are obese. To the extent that it is feasible, the authors recommend an active lifestyle and good dietary habits to help avoid development of obesity.

Surveillance

Jones et al [2011] suggested that individuals with 2q deletions sparing 2q37.1 likely have a less than 5% risk of developing Wilms tumor; therefore, they do not recommend surveillance for the development of Wilms tumor

in these individuals. Wilms tumor screening can be considered for individuals with deletions including 2q37.1, although screening intervals are not delineated. Wilms tumor screening protocols in individuals with WAGR syndrome and Beckwith-Wiedemann syndrome include abdominal ultrasounds every three months until mid-childhood [Beckwith 1998]. The practitioner caring for an infant or young child with a 2q37 deletion is encouraged to monitor the literature for updates.

When the 2q37 microdeletion is identified in early childhood, screening for the development of renal cysts at age four years and again at puberty is suggested [Falk & Casas 2007].

The following are also appropriate:

- Ongoing routine pediatric care
- Periodic reevaluation by a clinical geneticist to provide new recommendations and information about the syndrome
- Periodic neurodevelopmental and/or developmental/behavioral pediatric evaluation to assist in the management of cognitive and behavioral problems

Evaluation of Relatives at Risk

It is reasonable to perform genetic testing of any young child at risk, so that Wilms tumor surveillance can be considered in those with a deletion that includes 2q37.1.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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

2q37 microdeletion syndrome can be the result of a *de novo* chromosome abnormality or may be inherited from a parent who is a balanced translocation or inversion carrier.

Instances of deletion or mutation of *HDAC4* may be inherited in an autosomal dominant manner but are more commonly *de novo*.

Risk to Family Members

Parents of a proband

- Most probands have a *de novo* chromosome deletion and their parents have normal karyotypes. Familial chromosome rearrangements have been identified in approximately 5% of published cases. Some of these rearrangements are cytogenetically cryptic [Bijlsma et al 1999].
- Most cases of deletion or mutation of *HDAC4* are *de novo*, but familial cases have been reported [Villavicencio-Lorini et al 2013].

- Parents of a proband with a structurally unbalanced chromosome constitution (e.g., deletion or translocation) are at risk of having a balanced chromosome rearrangement and should be offered chromosome analysis.

Sibs of a proband

- The risk to sibs of a proband with 2q37 deletion syndrome depends on the genetic status of the parents.
- As with other *de novo* chromosome rearrangements, the recurrence risk for future pregnancies is negligible when parental karyotypes are normal.
- If a parent has a balanced structural chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement and the possibility of other variables.
- The occurrence of germline mosaicism has not been reported in individuals with 2q37 deletion syndrome, although the possibility cannot be excluded.
- If a parent has an *HDAC4* pathogenic variant, the risk to each sib is 50%.

Offspring of a proband

- To date, no individual with a cytogenetically visible 2q37 deletion has been reported to reproduce.
- An affected female with some features of the 2q37 microdeletion syndrome was born to a "normal" father with a cryptic subtelomeric deletion [van Karnebeek et al 2002]. Menarche was reported in an adolescent girl who subsequently experienced secondary amenorrhea [Wilson et al 1995], and the authors have personally examined a second female with normal menses. It is reasonable to expect normal fertility in mildly affected individuals with the 2q37 microdeletion syndrome. In this case, the risk of transmitting the chromosome deletion would be 50% for each pregnancy.

Other family members

- The risk to other family members depends on the genetic status of the proband's parents.
- If a parent has a balanced chromosome rearrangement, his or her family members may be at risk and should be offered chromosome analysis and FISH.

Carrier Detection

If a parent of the proband has a balanced chromosome rearrangement, at-risk family members can be tested by chromosome analysis and/or FISH.

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, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Prenatal diagnosis for pregnancies at increased risk is possible by chromosome analysis of fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks' gestation or by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. It is difficult to visualize terminal chromosome deletions in fetal cells; therefore, confirmation of the result with FISH should be performed.

Prenatal diagnosis for pregnancies at increased risk for an *HDAC4* pathogenic variant/deletion is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS). The pathogenic variant in an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic testing may be an option for some families at increased risk for a pregnancy with 2q37 deletion syndrome or with an *HDAC4* pathogenic variant/deletion.

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.

No specific resources for 2q37 Microdeletion Syndrome have been identified by *GeneReviews* staff.

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 A. 2q37 Microdeletion Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HDAC4	2q37.3	Histone deacetylase 4	HDAC4 @ LOVD	HDAC4	HDAC4
Not applicable	2q37	Not applicable			

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for 2q37 Microdeletion Syndrome (View All in OMIM)

600430	CHROMOSOME 2q37 DELETION SYNDROME
605314	HISTONE DEACETYLASE 4; HDAC4

Molecular Pathogenesis

Proposed candidate genes responsible for the Albright hereditary osteodystrophy (AHO)-like phenotype in individuals with 2q37 microdeletion syndrome include the following:

- Chaabouni et al [2006] initially narrowed the critical region for the AHO-like phenotype to an approximately 2-Mb interstitial region at 2q37.3 containing *HDAC4*, *GPC1*, and *STK25*.
  - ***HDAC4.*** In 2010, Williams et al published two AHO-like cases with apparently isolated intragenic inactivating pathogenic variants of *HDAC4*. They proposed *HDAC4* as the gene in which a pathogenic variant caused the syndromic features of the 2q37 microdeletion syndrome (see OMIM

605314 for a summary of the allelic variants identified in these two cases). Recently, an individual with a cryptic balanced translocation between chromosomes 2q37 and 10q26 was found to have mild features of the 2q37 microdeletion syndrome. *HDAC4* expression was 67% compared to expression in control individuals. This individual's son, who had an unbalanced translocation resulting in a 9.84-Mb deletion of 2q37.1, was found to have a more severe phenotype and 23% expression of *HDAC4* compared to control individuals [Morris et al 2012]. *HDAC4* has 27 exons (NM_006037.3) and encodes a protein of 1084 amino acids (NP_006028.2).

- Three individuals with Wilms tumor and constitutional 2q37 or 2q37.1 deletion (without other chromosome anomalies) have been reported [Conrad et al 1995, Olson et al 1995, Viot-Szoboszlai et al 1998]. Since 2q37.1 is centromeric to *HDAC4*, it is hypothesized that there is a tumor-suppressor gene at 2q37.1, and that individuals with "larger" chromosome deletions involving 2q37.1 may be at increased risk of developing Wilms tumor. Drake et al [2009] studied a series of sporadic Wilms tumors and found evidence of a tumor suppressor role for a 360-kb critical region containing *DIS3L2* and adjacent noncoding microRNA *miR-562*. Astuti et al [2012] subsequently identified *DIS3L2* pathogenic variants in individuals with Perlman syndrome, a Wilms tumor predisposition syndrome.
- Genome-wide linkage studies have shown an autism susceptibility region on 2q37 [International Molecular Genetic Study of Autism Consortium 2001, Morrow et al 2008].

Proposed candidate genes responsible for the autistic features in individuals with 2q37 microdeletion syndrome include the following:

- *KIF1A*, previously known as *ATSV*, is an axonal transporter of syntaptic vesicles [Smith et al 2001, Devillard et al 2010].
- *FARP2*, *HDLBP*, and *PASK* were identified as candidate genes because of their structural and functional relation to pathways in neuronal and skeletal pathways. All three were downregulated in an individual with a 3.5-Mb deletion and autism, compared to family members and healthy controls [Felder et al 2009]. FARP2 is a GTPase involved in neurite growth and axonal guidance. Vigilin (high density lipoprotein-binding protein, HDLBP) is a multi-KH domain-containing protein in cholesterol metabolism and structurally similar to FMR1 (Fragile X); PASK (Pas-domain serine/threonine kinase) is a kinase important in normal axonal ensheathment.
- Lukusa et al [2004] considered *CENTG2* (now known as *AGAP1*) a candidate gene for autism. Wassink et al [2005] confirmed deletion of this gene in an autistic female with a cytogenetically visible 2q37 deletion, AHO-like features, and normal intelligence. *AGAP1* is expressed in the fetal and adult brain and is involved in endocytic trafficking [Nie et al 2002].

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Chapter Notes

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Revision History

- 18 January 2018 (ma) Chapter retired: non-recurrent deletions or duplications; refers to deletions/duplications of varying size – in contrast to a recurrent deletion/duplication, defined as a deletion/duplication of a specific size (usually mediated by nonallelic homologous recombination) occurring multiple times in the general population
- 31 January 2013 (cd) Revision: additional information on the role of *HDAC4*
- 9 August 2012 (me) Comprehensive update posted live
- 3 May 2007 (me) Review posted live
- 21 March 2007 (esd) Original submission

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