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1p36 Deletion Syndrome – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Monosomy 1p36 Syndrome

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

1p36 deletion syndrome is characterized by typical craniofacial features consisting of straight eyebrows, deeply set eyes, midface retrusion, wide and depressed nasal bridge, long philtrum, pointed chin, large, late-closing anterior fontanel (77%), microbrachycephaly (65%), epicanthal folds (50%), and posteriorly rotated, low-set, abnormal ears. Other characteristic findings include brachy/camptodactyly and short feet. Developmental delay/intellectual disability of variable degree are present in all, and hypotonia in 95%. Seizures occur in 44%-58% of affected individuals. Other findings include structural brain abnormalities (88%), congenital heart defects (71%), eye/vision problems (52%), hearing loss (47%), skeletal anomalies (41%), abnormalities of the external genitalia (25%), and renal abnormalities (22%).

Diagnosis/testing

The diagnosis of 1p36 deletion syndrome is suggested by clinical findings and confirmed by detection of a deletion of the most distal band of the short arm of chromosome 1 (1p36). Conventional G-banded cytogenetic analysis, FISH, or chromosomal microarray (CMA) can all be used to detect deletions; however, the complexity of some deletions may be detected only by CMA.

Management

Treatment of manifestations: Rehabilitation/educational program with attention to speech/communication, use of sign language, motor development, cognition, and social skills; ACTH for infantile spasms; routine antiepileptic drugs (AEDs) for other seizure types; special feeding techniques and/or devices including

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gastrostomy tube for feeding difficulties; standard pharmacotherapy for non-compaction cardiomyopathy; standard care for eye/vision problems, skeletal anomalies, hearing loss, hypothyroidism, and renal abnormalities.

Surveillance: Systematic follow up for adjustment of rehabilitation/education and medical treatment as needs change over time.

Genetic counseling

1p36 deletion syndrome is caused by deletion of the 1p36 chromosome region by one of several genetic mechanisms. Approximately 52% of individuals with 1p36 deletion syndrome have a *de novo* terminal 1p36 deletion, approximately 29% have an interstitial deletion, approximately 12% have more complex chromosome rearrangements that may include more than one 1p36 deletion or a 1p36 deletion with a 1p36 duplication, and approximately 7% have a derivative chromosome 1 (in which the 1p telomeric region is replaced by another chromosome end). Risks to family members depend on the mechanism of origin of the deletion. Prenatal testing is possible for families who have had a child with 1p36 deletion syndrome or a family in which one parent is a known carrier of a chromosome rearrangement involving 1p36.

Diagnosis

Clinical Diagnosis

The diagnosis of 1p36 deletion syndrome is suggested by the characteristic facial appearance, hypotonia, psychomotor retardation, and poor or absent speech and is confirmed by detection of a deletion of the most distal band of the short arm of chromosome 1 (1p36).

Typical facial features. The facial appearance of individuals with 1p36 deletion syndrome remains easily recognizable over time [Battaglia et al 2008], representing a hallmark of the condition [Battaglia 2005] (see Figure 1). Facial features include straight eyebrows, deeply set eyes, midface retrusion, wide and depressed nasal bridge, long philtrum, and pointed chin. Other craniofacial features are microcephaly, brachycephaly, epicanthal folds, large (>3 cm at birth) and late-closing anterior fontanel, and posteriorly rotated, low-set, abnormally formed ears [Shapira et al 1997, Heilstedt et al 2003b, Battaglia et al 2008].

Developmental delay/intellectual disability of variable degree is present in all. Generalized hypotonia is observed in 95% of individuals [Battaglia et al 2008].

Testing

Cytogenetic analysis. The four classes of rearrangements identified in individuals with monosomy 1p36 are shown in Table 1 [Heilstedt et al 2003b, Gajecka et al 2007]:

- An apparently "pure" terminal deletion
- Interstitial deletion
- More complex rearrangements including more than one deletion or deletions with duplications, triplications, insertions, and/or inversions
- Derivative chromosome 1 resulting from an unbalanced translocation

Note: (1) No common breakpoint or deletion size is present in individuals with monosomy 1p36. (2) Determining whether a cytogenetically visible deletion is a true terminal deletion or a more complex rearrangement may be accomplished using specialized molecular cytogenetic techniques (see Molecular Genetic Testing).

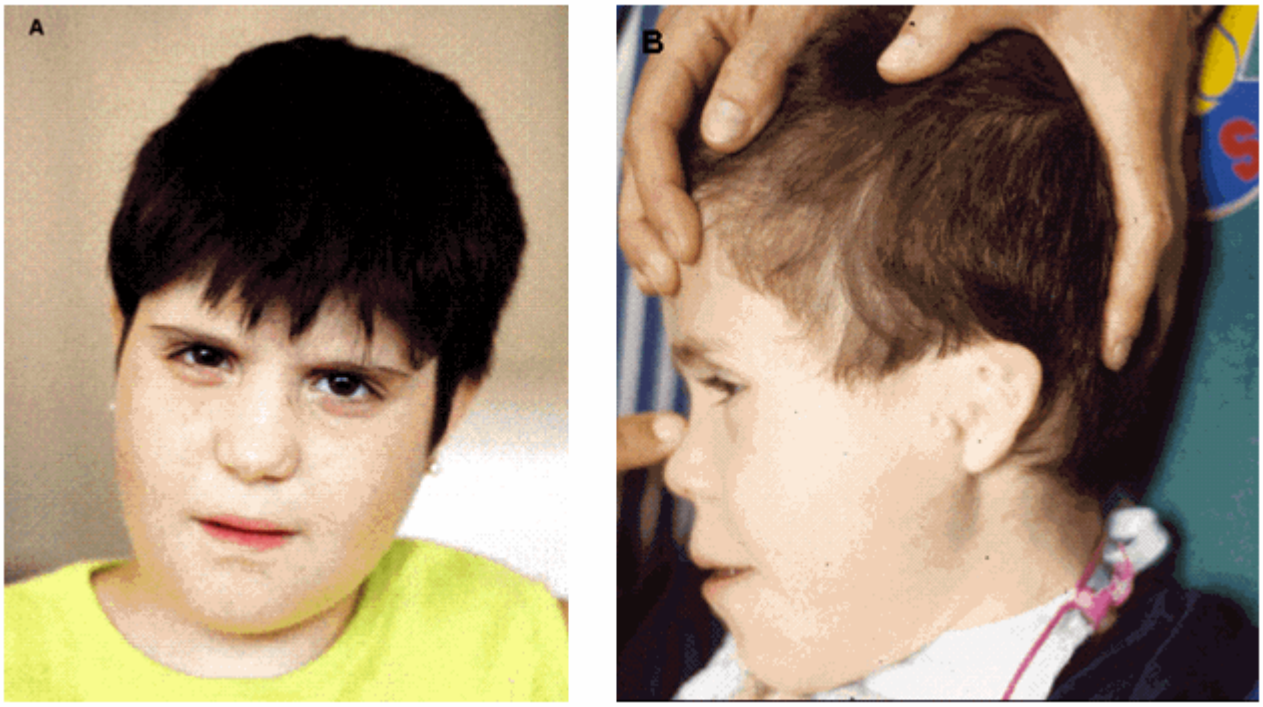
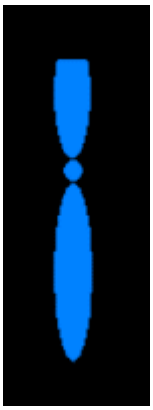
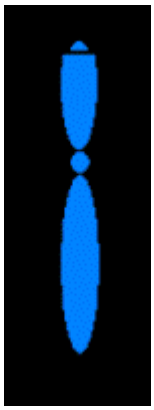
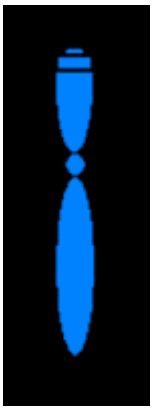


Figure 1. Two unrelated children showing microbrachycephaly, straight eyebrows, deeply set eyes, wide and depressed nasal bridge, midface retrusion, elongated philtrum, pointed chin, and hypotonic face

A. Girl age 9.5 years

B. Boy age 6.5 years; also showing grade II left microtia with atresia of the external auditory canal and preauricular tag

Table 1. Chromosome Abnormalities Seen in 1p36 Deletion Syndrome

	Chromosome Abnormality			
	Terminal deletion	Interstitial deletion	Complex rearrangement [1]	Derivative chromosome [2]
Chromosome diagram				
Proportion of 1p36 deletion syndrome	52%	29%	12%	7%

Heilstedt et al [2003b], Gajecka et al [2007]

1. Including more than one deletion or deletions with duplications, triplications, insertions, and/or inversions affecting chromosome 1p36

2. The 1p telomeric region is replaced by another chromosome end.

Molecular Genetic Testing

Genes. Deletion of genes in the 1p36 critical region is the only known cause of 1p36 deletion syndrome.

Table 2. Cytogenetic and Molecular Genetic Testing Used in 1p36 Deletion Syndrome

Method [1]	Variants Detected	Variant Detection Frequency by Method [2]
Cytogenetic analysis [3]	>5-Mb deletion of 1p36 [4]	~25%
FISH [5]	>100-kb deletion of 1p36 [4]	>95%
Deletion/duplication analysis by CMA [6, 7]		>95%

Mb = 10^6 DNA base pairs; kb = 10^3 DNA base pairs
1. MLPA is not a recommended method of detection of deletions of these sizes.
2. The ability of the test method used to detect a variant that is present in the indicated gene
3. Conventional G-banded cytogenetic studies (routine and high-resolution)
4. Deletions greater than 5 Mb occur at approximately the same frequency as deletions smaller than 5 Mb.
5. FISH using at least two subtelomeric region-specific probes (Vysis 1p subtel probe, Vysis p58 probe; D1Z2 Oncor probe or CEB108/T7) can identify parental rearrangements and may detect terminal and interstitial deletions and derivative chromosomes.
6. 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.
7. Terminal deletions, interstitial deletions, complex rearrangements, and derivative chromosomes can potentially be detected by CMA.

Testing Strategy

To confirm/establish the diagnosis in a proband. It is appropriate to test any individual suspected of having 1p36 deletion syndrome as follows:

- **Conventional cytogenetic studies** to detect large deletions (i.e., >5 Mb) and more complex cytogenetic rearrangements (unbalanced chromosome translocations)
- **FISH** with at least two subtelomeric region-specific probes (Vysis 1p subtel probe, Vysis p58 probe; D1Z2 Oncor probe or CEB108/T7) to detect unbalanced translocations and to identify parental chromosome rearrangements
- **Deletion/duplication analysis by CMA** to detect smaller deletions (i.e., <5 Mb) or interstitial deletions or complex rearrangements

Notes: (1) Subtelomere FISH detects the presence/absence of the two probes used; thus, FISH (a) cannot detect an interstitial deletion proximal to the probes; (b) cannot distinguish between a "true" terminal deletion and a more complex rearrangement; or (c) cannot define the extent of the deletion. However, CMA has the potential to do all three. (2) MLPA, a type of deletion/duplication analysis, is not a recommended method for detection of deletions of these sizes.

Clinical Characteristics

Clinical Description

The frequencies of the major clinical findings associated with 1p36 deletion syndrome are summarized in Table 3.

Table 3. Frequency of Major Clinical Findings in 1p36 Deletion Syndrome

Findings	Frequency
• Distinctive facial features (see Clinical Diagnosis) • Intellectual disability • Poor/absent speech • Hypotonia • Brachycamptodactyly • Short feet • Brain abnormalities	>75%
• Congenital heart defects • Eye/vision problems including visual inattention • Seizures	50%-75%
• Skeletal anomalies • Sensorineural deafness • Gastrointestinal anomalies • Abnormalities of the external genitalia • Behavior disorders	25%-50%
• Non-compaction cardiomyopathy • Renal anomalies • Anal anomalies • Hypothyroidism	<25%

Bahi-Buisson et al [2008], Battaglia et al [2008]

Intellectual disability. Developmental delay and intellectual disability are hallmarks of the syndrome. Battaglia et al [2008] found that 25% of affected individuals can walk alone, with a broad-based gait, by age two to seven years. Approximately 90% have severe to profound intellectual disability, whereas 10% have mild to moderate cognitive impairment. Expressive language is absent in 75% and limited to a few isolated words or at the level of first word associations in the remainder. Comprehension seems to be limited to a specific context. Intention to communicate, limited in early years, tends to improve over time, with extension of the gesture repertoire.

Behavior disorders, present in 50%, include poor social interaction, temper tantrums, self-biting of hands and wrists, a number of stereotypies, and, less frequently, hyperphagia.

Central nervous system defects, present in 88% of affected individuals, mainly include dilatation of the lateral ventricles and subarachnoid spaces; cortical atrophy; diffuse brain atrophy; and hypoplasia, thinning, and total or partial absence of the corpus callosum. Other reported anomalies are delay in myelination, multifocal hyperintensity areas in the white matter [Battaglia et al 2008], periventricular nodular heterotopia [Neal et al 2006, Descartes et al 2011], and polymicrogyria [Dobyns et al 2008].

Seizures occur in 44% to 58% of individuals with 1p36 deletion syndrome [Heilstedt et al 2001, Heilstedt et al 2003b, Bahi-Buisson et al 2008, Battaglia et al 2008]. Age at onset ranges from four days to two years, eight months. First seizures are either generalized (tonic, tonic-clonic, clonic, myoclonic) or partial (simple or complex). Almost 20% of all persons with the disorder have infantile spasms associated with hypsarrhythmia on EEG. Infantile spasms may either be the presenting seizure type or may follow other seizure types. Most seizure types are well controlled by standard pharmacotherapy. However, in one series [Bahi-Buisson et al 2008] nearly one third of persons developed drug-resistant epilepsy.

Of note, epileptic apneas can also occur in some children [Kanabar et al 2012]; and early infantile epileptic encephalopathy with suppression bursts (Ohtahara syndrome) has also been reported in an individual [Paciorkowski et al 2011].

A variety of EEG abnormalities are present in nearly all affected individuals [Heilstedt et al 2001, Bahi-Buisson et al 2008, Battaglia et al 2008].

Feeding difficulties may be caused by hypotonia and/or oral facial clefts with related difficulty in sucking, poorly coordinated swallow with consequent aspiration, and/or gastroesophageal reflux and vomiting. Mild to severe oropharyngeal dysphagia has been observed on swallow studies in 72% of individuals [Heilstedt et al 2003b].

Congenital heart defects are noted in 43% to 71% of individuals. Structural heart defects reported are (in order of frequency) atrial and ventricular septal defects, valvular anomalies, patent ductus arteriousus, tetralogy of Fallot, coarctation of the aorta, infundibular stenosis of the right ventricle, and Ebstein anomaly [Heilstedt et al 2003b, Battaglia et al 2008]. Twenty-seven percent had a history of cardiomyopathy in infancy and childhood. Cardiomyopathy was of the non-compaction type in 23% and tended to improve over time [Battaglia et al 2008].

Ophthalmologic abnormalities. Strabismus, nystagmus, refractive errors, and visual inattention are the most common ophthalmic manifestations of 1p36 deletion syndrome [Heilstedt et al 2003b, Battaglia et al 2008]. Cataract, retinal albinism, and optic nerve coloboma have occasionally been observed [Battaglia et al 2008].

Skeletal anomalies found in 40% of individuals with 1p36 deletion syndrome [Battaglia et al 2008] include delayed bone age, scoliosis, rib anomalies, and lower-limb asymmetry.

Hearing loss, mostly of the sensorineural type, can be detected in 47% to 82% of individuals with 1p36 deletion syndrome [Heilstedt et al 2003b, Battaglia et al 2008].

Genitourinary malformations can be seen in 22% of affected individuals and include unilateral renal pelvis with hydronephrosis of the upper pole, kidney ectopia with right kidney cyst, and unilateral pelvic ectasia [Battaglia et al 2008].

Cryptorchidism, hypospadias, scrotal hypoplasia, and micropenis are seen in a minority of males [Battaglia et al 2008].

Small labia minora and small clitoris, labia majora hypertrophy, and uterine hypoplasia have been reported in females [Battaglia et al 2008].

Hypothyroidism has been reported in 15% to 20% of persons of varied ages with deletion 1p36 syndrome in whom TSH and T4 levels were studied [Heilstedt et al 2003b, Battaglia et al 2008].

Other. Other abnormalities reported in a few individuals with 1p36 deletion syndrome include the following:

- Telangiectatic skin lesions and hyperpigmented macules [Keppler-Noreuil et al 1995]
- Polydactyly [Keppler-Noreuil et al 1995]
- Congenital spinal stenosis [Reish et al 1995]
- Congenital fiber type disproportion myopathy [Okamoto et al 2002]
- Redundant skin on the nape of the neck [Wang & Chen 2004]
- Intestinal malrotation, anular pancreas, and anomalous arrangement of the pancreaticobiliary duct [Minami et al 2005, Kawashima et al 2011]
- Liver steatosis [Haimi et al 2011]
- Hypertrophic pyloric stenosis
- Anteriorly placed or imperforate anus, hooked or bilobed gallbladder, and small spleen [Battaglia et al 2008]
- Neuroblastoma (in 3 individuals) [Laureys et al 1990, Biegel et al 1993, Anderson et al 2001]
- Pemphigus vulgaris (in 1 individual) [Halpern et al 2006]

Genotype-Phenotype Correlations

To explain the phenotypic variability of 1p36 deletion syndrome, investigators have searched for correlations between size of the 1p deletion and severity of clinical manifestations.

Wu et al [1999] and Heilstedt et al [2003b] suggested a complete genotype-phenotype correlation, identifying the critical regions for certain features and considering 1p36 deletion syndrome as a contiguous gene deletion syndrome. However, Gajecka et al [2007] found no correlation between deletion size and number of observed clinical features in a large cohort; even individuals with small (<3 Mb) deletions of 1p36 presented with most of the features commonly associated with the syndrome.

Redon et al [2005] hypothesized that the features associated with 1p36 deletion syndrome may result from a position effect rather than a contiguous gene deletion.

Prevalence

The prevalence of 1p36 deletion syndrome is estimated at between 1:5,000 and 1:10,000 births, with a 2:1 female to male ratio [Shapira et al 1997, Slavotinek et al 1999, Heilstedt et al 2003a, Battaglia et al 2008].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with copy number variance in the genes located within the 1p36 critical region.

Differential Diagnosis

The clinical phenotype and the facial gestalt of 1p36 deletion syndrome are characteristic. However, some individuals may be misdiagnosed because of features that overlap with the following disorders:

- **Rett syndrome** (OMIM 312750) is an X-linked dominant disorder that in girls is characterized by normal birth and apparently normal psychomotor development during the first six to 18 months of life followed by a short period of developmental stagnation and then by rapid regression in language and motor skills. The hallmark of the disease is the loss of purposeful hand use and its replacement with repetitive stereotyped hand movements. Autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, and acquired microcephaly also occur. The disease becomes relatively stable, but girls are likely to develop dystonia and foot and hand deformities as they grow older. Seizures occur in 50% of females with Rett syndrome; generalized tonic-clonic seizures and partial complex seizures are the most common. The incidence of sudden, unexplained death is increased. Males with a 46,XY karyotype may have such severe neonatal encephalopathy that they die before their second year. The diagnosis rests on clinical diagnostic criteria established for the classic syndrome and/or molecular testing of *MECP2*.
- **Angelman syndrome (AS)** is characterized by severe developmental delay/intellectual disability, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are common. The diagnosis rests on a combination of clinical features and molecular genetic testing and/or cytogenetic analysis. Consensus clinical diagnostic criteria for AS have been developed. Analysis of parent-specific DNA methylation imprints in the 15q11.2-q13 chromosome region detects approximately 78% of individuals with AS, including those with a deletion, uniparental disomy, or an imprinting defect; fewer than 1% of individuals have a cytogenetically visible chromosome rearrangement (i.e., translocation or inversion). *UBE3A* sequence analysis detects pathogenic variants in an additional approximately 11% of individuals. Accordingly, molecular genetic testing (methylation analysis and

UBE3A sequence analysis) identifies alterations in approximately 90% of individuals. The remaining 10% of individuals with classic phenotypic features of AS have a presently unidentified genetic mechanism and thus are not amenable to diagnostic testing.

- **Prader-Willi syndrome (PWS)** is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity (unless it is externally controlled). All individuals have some degree of cognitive impairment, with delay in motor milestones and language development. A specific behavior phenotype with temper tantrums, stubbornness, rigidity, stealing, lying, manipulative behavior, and obsessive-compulsive characteristics is common. Hypogonadism, present in both males and females, manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature with small hands and feet is common; characteristic facial features, strabismus, and scoliosis are often present, and non-insulin-dependent diabetes mellitus often occurs in obese individuals. Consensus clinical diagnostic criteria have been developed, but the mainstay of diagnosis is DNA-based methylation testing to detect abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR) on chromosome 15. This testing determines whether the region is maternally inherited only (the paternally contributed region is absent) and detects more than 99% of affected individuals. Methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially those who have atypical findings or are too young to manifest sufficient features to make the diagnosis on clinical grounds.
- **Smith-Magenis syndrome (SMS)** is characterized by distinctive facial features, developmental delay, cognitive impairment, and behavioral abnormalities. The facial appearance is characterized by a broad square-shaped face, brachycephaly, prominent forehead, synophrys, mildly upslanting palpebral fissures, deep-set eyes, broad nasal bridge, midfacial retrusion (formerly known as midfacial hypoplasia), short, full-tipped nose with reduced nasal height, micrognathia in infancy changing to relative prognathia with age, and a distinct appearance of the mouth, with fleshy everted vermilion of the upper lip. Individuals with SMS have a wide degree of variability in cognitive and adaptive functioning, with the majority of individuals with SMS functioning in the mild-to-moderate range of intellectual disability. The behavioral phenotype includes significant sleep disturbance, stereotypies, and maladaptive and self-injurious behaviors. Infants have feeding difficulties, failure to thrive, hypotonia, hyporeflexia, prolonged napping or need to be awakened for feeds, and generalized lethargy. SMS is caused by either detection of an interstitial deletion of 17p11.2 or by molecular genetic testing of *RAI1*. A visible interstitial deletion of chromosome 17p11.2 can be detected in all individuals with the common deletion by a routine G-banded analysis provided the resolution is adequate (550 band or higher). Molecular genetic testing of *RAI1*, the only gene in which mutation or deletion is known to account for a majority of features in SMS, is performed for individuals in whom a FISH- or aCGH-detectable deletion has been excluded.
- **Aicardi syndrome (AIS)** is characterized by a triad of features: agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. However, it is now well recognized that several other important findings are typically present in girls with Aicardi syndrome. Neurologic examination can reveal microcephaly, axial hypotonia, and appendicular hypertonia with spasticity. Moderate to severe global developmental delay and intellectual disability are expected. Many girls with Aicardi syndrome develop seizures prior to age three months, and most before age one year. Ongoing medically refractory epilepsy with a variety of seizure types develops over time. Costovertebral defects are common and can lead to marked scoliosis in up to one third of affected individuals. Other signs include characteristic facial features, gastrointestinal difficulties, small hands, vascular malformations and pigmentary lesions of the skin, increased incidence of tumors, lower growth rate after ages seven to nine years, and precocious or delayed puberty. Survival is highly variable, with the mean age of death about 8.3 years and the median age of death about 18.5 years.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with 1p36 deletion syndrome, the following evaluations are recommended:

- Measurements of growth parameters and plotting on standard growth charts

  Note: No growth charts are available specifically for 1p36 deletion syndrome.
- Physical and neurologic examination
- Evaluation of cognitive, language, and motor development and social skills
- Examination of the heart (auscultation, electrocardiogram, echocardiography) in infancy
- Waking/sleeping video-EEG-polygraphic studies (mainly in infancy) to detect infantile spasms with hypsarrhythmia
- Evaluation for feeding problems and gastroesophageal reflux with referral to a dysphagia team
- Ophthalmology consultation in infancy or at diagnosis even in the absence of overt anomalies
- Physical examination for skeletal anomalies (e.g., scoliosis, lower-limb asymmetry); if anomalies are present, referral for orthopedic and physical therapy evaluation
- Comprehensive otolaryngologic evaluation and audiologic screening (brain stem auditory evoked responses) as early as possible to allow appropriate interventions
- Renal function testing and renal ultrasonography in infancy to detect structural renal anomalies
- Periodic thyroid function screening
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Intellectual disability. Enrollment in a personalized rehabilitation program with attention to motor development, cognition, communication, and social skills is appropriate [Battaglia et al 2008]. Use of sign language enhances communication skills and does not inhibit the appearance of speech. Early intervention and, later, appropriate school placement are essential.

Seizures. Up to 25% of persons with 1p36 deletion syndrome develop infantile spasms associated with a hypsarrhythmic EEG; the spasms are responsive to ACTH.

In most individuals, all seizure types are well controlled by standard antiepileptic drugs (AEDs), provided that the first-choice drug is started as early as possible.

Feeding difficulties. Feeding therapy with attention to oral motor skills is appropriate. Special feeding techniques or devices, e.g., the "Haberman feeder," can be used for feeding a hypotonic infant/child without a cleft palate or those with an unrepaired cleft palate. Gavage feeding is recommended for those with poorly coordinated swallow. Gastroesophageal reflux should be addressed in a standard manner. In one study, a few individuals with 1p36 deletion syndrome were managed with gastrostomy [Heilstedt et al 2003b].

Congenital heart defects are usually not complex and are amenable to repair. "Non-compaction" cardiomyopathy responds well to the standard pharmacotherapy (e.g., furosemide, captopril, digoxin) [Battaglia et al 2008].

Ophthalmologic abnormalities are treated in the standard manner. Visual inattentiveness, reported in up to 64% of individuals with 1p36 deletion syndrome, can be treated with an appropriate rehabilitation program [Bolognini et al 2005, Battaglia et al 2008].

Skeletal abnormalities (e.g., scoliosis, lower-limb asymmetry) need to be addressed on an individual basis. Early treatment (both physical therapy and surgery) is suggested.

Hearing loss is treated with a trial of hearing aids.

Other. Structural anomalies (e.g., gastrointestinal, renal) should be addressed in a standard manner. Hypothyroidism is treated in a standard manner.

Surveillance

Systematic follow up allows for adjustment of rehabilitation and treatment as skills improve or deteriorate and medical needs change [Battaglia et al 2008].

Evaluation of Relatives at Risk

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

1p36 deletion syndrome can be the result of an inherited or *de novo* chromosome abnormality.

Risk to Family Members

Parents of a proband

- The parents of a proband with 1p36 deletion syndrome are unaffected but may carry a balanced rearrangement involving 1p36 (see Table 1).
- Sixty percent of *de novo* deletions occur on the maternally derived chromosome
- In approximately one third of individuals with a derivative chromosome 1, the derivative chromosome 1 results from malsegregation of a balanced parental translocation.

- Parents of individuals with 1p36 deletion syndrome should have cytogenetic analysis looking for a translocation involving 1p36. CMA would not be recommended for this as the rearrangement would be expected to be balanced, and thus not detected.
- Subtelomeric analysis of both parents of a proband with an apparently *de novo* deletion is appropriate to detect the presence of a cryptic balanced translocation involving chromosome 1 in a parent [Heilstedt et al 2003b].

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the parents.
- If the deletion in the proband is *de novo*, the risk to the sibs of a proband should be the same as the general population risk. Of note, apparent germline mosaicism has been reported in one family [Gajecka et al 2010].
- If a parent is a balanced translocation carrier, the risk to sibs of being affected with 1p monosomy (i.e., 1p36 deletion syndrome) or 1p trisomy is increased over the general population risk.

Offspring of a proband. No individual with 1p36 deletion syndrome is known to have reproduced.

Other family members of a proband. If a parent carries a chromosome rearrangement, his or her family members are also at risk of carrying the rearrangement.

Carrier Detection

If a parent of the proband has a balanced chromosome rearrangement, at-risk family members can be tested by the method used to identify the rearrangement in the parent (i.e., chromosome analysis or subtelomeric FISH analysis).

Related Genetic Counseling Issues

Specific counseling issues. Specific empiric risks for translocations involving 1p and another chromosome are unknown.

Family planning

- The optimal time for determination of genetic risk 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 known to be or at risk of being carriers of a chromosome rearrangement.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancy. In families who have had a child with 1p36 deletion syndrome or in which one parent is known to be a carrier of a chromosome rearrangement, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **My46 Trait Profile**
  1p36 deletion syndrome

- **Chromosome Disorder Outreach (CDO)**
  PO Box 724
  Boca Raton FL 33429-0724
  Phone: 561-395-4252 (Family Helpline)
  Email: info@chromodisorder.org
  www.chromodisorder.org
- **Unique: The Rare Chromosome Disorder Support Group**
  G1 The Stables
  Station Road West
  Oxted Surrey RH8 9EE
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org; rarechromo@aol.com
  www.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 A. 1p36 Deletion Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
Not applicable	1p36	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 1p36 Deletion Syndrome (View All in OMIM)

607872	CHROMOSOME 1p36 DELETION SYNDROME

Molecular Pathogenesis

No genes have been conclusively determined to be associated with the clinical features that characterize 1p36 deletion syndrome.

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Chapter Notes

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Revision History

- 8 August 2019 (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
- 6 June 2013 (me) Comprehensive update posted live
- 1 February 2008 (me) Review posted live
- 24 August 2007 (ab) Original submission

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