

# Chromosome 1p36 deletions

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**Creation date: September 2003**

**Scientific editor: Professor Alain Verloes**

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## Abstract

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## Abstract

*Monosomy 1p36 has been increasingly recognized as a distinct chromosome deletion syndrome in the past few years. It is considered to be one of the commonest chromosome deletion syndromes, with an estimated incidence of 1 in 5,000 to 1 in 10,000 live births. The breakpoints for this cytogenetic syndrome have been variable and have ranged from bands 1p36.13 to 1p36.33. Developmental delay affects the majority of children with 1p36 monosomy and is usually severe. Behavioral difficulties and self-injury have been described. Hypotonia and feeding problems with oropharyngeal dysphasia are frequent; seizures have been a frequent and debilitating problem. Other dysmorphic, cardiac, visual and auditive features are been described. The management of 1p36 monosomy includes a comprehensive evaluation for the major clinical complications with an echocardiogram and ophthalmologic examination.*

**Keywords:** monosomy 1p36, deletion 1p36, developmental delay, mental retardation, seizures

## Disease name and synonyms

A deletion of chromosome band 1p36 can also be termed "monosomy 1p36". The monosomy can be "pure" or can be found in connection with additional chromosomal imbalance. This review is confined to the phenotype associated with "pure" 1p36 monosomy. Over 40 patients have been reported in the medical literature.

## Diagnosis criteria / definition

The breakpoints for this cytogenetic syndrome have been variable and have ranged from bands 1p36.13 to 1p36.33 with the majority in band 1p36.2 (see section on molecular characterization). The deletion has been detected by amniocentesis, high-resolution G-banding, chromosome-specific fluorescence *in-situ* hybridization (FISH) with probes for 1p and by subtelomeric probe screening. The last two methods are the most common and confirmation of deletions that are identified using G-banding with FISH is considered mandatory. The use of

subtelomeric probes may be insufficient to detect interstitial deletions of 1p36 and it has been suggested that both probes D1Z2 and p58 be used as some patients have been deleted for only one of these probes.

## Differential diagnosis

The differential diagnosis of a chromosomal phenotype includes other segmental aneusomy syndromes. Prader-Willi syndrome has been considered in a minority of patients because of obesity and hyperphagia.

## Frequency

The incidence of monosomy 1p36 has been estimated to be 1 in 5,000 to 1 in 10,000 liveborn children. However, a higher incidence is plausible due to under-ascertainment before the development of FISH and subtelomeric probes screening. To date, more females than males have been reported.

### Clinical description

Developmental delay affects the majority of children with 1p36 monosomy and is usually severe. In four out of six children in whom IQ could be assessed, levels of <60 were achieved with more severe impairment for speech compared to motor development (Shapira *et al.*, 1997). Reports of a milder learning disability in children with smaller deletions have suggested that there may be a correlation between deletion size and mental ability that requires further investigation. Behavioral difficulties and self-injury have been described. Hypotonia (87%) and feeding problems with oropharyngeal dysphasia were frequent (Heilstedt *et al.*, 2003).

Seizures have been a frequent and debilitating problem in children with 1p36 deletions. Up to 72% of patients have had seizures (Shapira *et al.*, 1997) and 15/31 (48%) had chronic seizures requiring continuing anticonvulsant treatment (Slavotinek *et al.*, 1999; Heilstedt *et al.*, 2003). There does not appear to be one seizures type that is predominant and generalized tonic-clonic seizures, myoclonic seizures, simple and complex partial seizures, right sided focal seizures and infantile spasms have been reported (Slavotinek *et al.*, 1999; Heilstedt *et al.*, 2003). In some children, epilepsy commenced in infancy but ceased in the first few years of life (Slavotinek *et al.*, 1999). Therapy with anticonvulsant medications is most commonly tried and carbamazepine and valproate were the commonest medications in one study (Heilstedt *et al.*, 2001). A hemispherectomy has been performed for management in one child (Wexler, 1991). Interestingly, the seizure phenotype in patients with 1p36 monosomy has been associated with hemizygoty for the voltage-gated K<sup>+</sup> channel  $\beta$ -subunit gene, *KCNAB2* (Heilstedt *et al.*, 2001). 8/9 (89%) patients deleted for this gene had severe seizures including infantile spasms as compared with only 4/15 (27%) of patients who were not deleted for this gene (Heilstedt *et al.*, 2001).

Deletions of 1p36 cause growth retardation with microcephaly that can be prenatal or postnatal in onset and may be extreme. In one study, postnatal growth retardation was found in 11/13 (85%; Shapira *et al.*, 1997). In contrast, several children have had overgrowth and hyperphagia with a clinical presentation similar to Prader-Willi syndrome. These children have not shown any other clinically distinguishing features and the cause of the macrosomia is unknown. Developmental delay has also been severe in the patients with the Prader-Willi like phenotype (Keppler-Noreuil *et al.*, 1995; Eugster *et al.*,

1997). Puberty has been reported to be both early and delayed (Slavotinek *et al.*, 1999).

The facial features in 1p36 monosomy have been considered to be characteristic, although few patients have been diagnosed solely on the basis of craniofacial dysmorphism. The phenotype includes microcephaly, brachycephaly (18/30 or 60%), frontal bossing, deep-set eyes (24/30 or 80%), short, narrow and slanting palpebral fissures, a flat nose (20/30 or 67%) and nasal bridge (23/30 or 77%), midface hypoplasia, anomalous, low-set (7/30 or 23%) and small ears, a small mouth with down-turned corners and a pointed chin (20/30 or 67%; percentages from Heilstedt *et al.*, 2003). Some authors have considered that horizontal or straight eyebrows are useful for diagnosis (Alain Verloes, personal communication). Reported digital findings were fifth finger brachydactyly (26/30 or 87%), clinodactyly (12/30 or 40%; percentages from Heilstedt *et al.*, 2003) or camptodactyly. Distinguishing findings were a large or late closing anterior fontanelle (up to 85% of patients) and facial asymmetry (Slavotinek *et al.*, 1999; Heilstedt *et al.*, 2003).

Structural cardiac malformations were present in 43% of patients and patent ductus arteriosus (5/30 or 17%), Tetralogy of Fallot, septal defects and Ebstein anomaly have been described (Slavotinek *et al.*, 1999; Heilstedt *et al.*, 2003). Infantile dilated cardiomyopathy was reported in 7/30 subjects (23%) and has responded to treatment in some cases (Heilstedt *et al.*, 2003). Cerebral anomalies have included cerebral atrophy and ventricular dilatation with hydrocephalus.

Visual abnormalities have been wide-ranging, including strabismus (9/30 or 30%), sixth nerve palsy, refractive errors with hypermetropia in 20/30 (67%), anomalous optic discs and optic atrophy, cataracts, nystagmus (4/30 or 13%) and lacrimal defects. Visual inattentiveness (defined as an absence of attentive visual behavior such as fixation and following movements) was noted in 30% (Heilstedt *et al.*, 2003).

Sensorineural or conductive hearing loss is common (23/28 or 82%) and has ranged from a mild, high frequency sensorineural loss at 6-8 kHz in 37% of patients to a severe loss at all frequencies in 40% of patients (Heilstedt *et al.*, 2003). Conductive loss is relatively rare (3% of patients; Heilstedt *et al.*, 2003).

Orofacial clefting has been noted in 17-40% and has involved the lip and/or palate or uvula (Slavotinek *et al.*, 1999; Heilstedt *et al.*, 2003). Two patients had hypothyroidism that required supplementation and four patients had elevated

levels of thyroid stimulating hormone with low T4 levels (total 6/30 = 20%; Heilstedt *et al.*, 2003).

Genital hypoplasia (cryptorchidism, small scrotum and small genitalia) has been reported in males but structural renal abnormalities were rare in both sexes. Musculoskeletal findings were infrequent but have included kyphosis and/or scoliosis, joint contractures, hip dysplasia and rib anomalies.

Three children with a 1p36 deletion or a translocation breakpoint in this chromosome band have developed neuroblastoma and there is strong evidence that a tumor suppressor gene maps between chromosome bands 1p36.1 to 1p36.3. However, screening for neuroblastoma has not routinely been performed in children with 1p monosomy. In a study of 30 subjects up to 13 years of age, none had developed cancer (Heilstedt *et al.*, 2003).

### Molecular characterization

In the largest study of 60 deletions, 43 patients (72%) had terminal deletions (defined as absence of the most distal, known unique 1p subtelomeric sequence and without replacement by another chromosome end; Heilstedt *et al.*, 2003). 4/60 (7%) were interstitial deletions and 10 patients (17%) had a derivative chromosome 1 with replacement of the 1p telomere by another chromosome end (Heilstedt *et al.*, 2003). Three subjects had more complex chromosome rearrangements involving the 1p telomere (5%). In those in whom the parental origin of the deletion could be determined, 24/40 (60%) had a maternally inherited deletion and 16/40 (40%) had a paternally derived deletion. There was no discernable clinical difference between the maternal and paternal deletions.

Interestingly, the size of the maternal deletions was significantly smaller than the size of the paternal deletions with 75% of the maternal breakpoints occurring less than 5.0 Mb from the 1p telomere and 62.5% of the paternal breakpoints more than 5.0 kb from the 1p telomere ( $p=0.2$ ; Heilstedt *et al.*, 2003). Most breakpoints clustered between 4.0 and 4.5 kb from the chromosome telomere and 40% of all breakpoints were 3.0 to 5.0 kb from the telomere (Heilstedt *et al.*, 2003). The breakpoint range extended from 0.5 Mb to more than 10.5 Mb from 1pter in three patients, making a common mechanism for these deletions unlikely as previously demonstrated for other chromosome deletion syndromes (Heilstedt *et al.*, 2003).

A phenotype/genotype correlation has been attempted (Heilstedt *et al.*, 2003) with the critical

region for clefting and hypothyroidism extending more proximally to the critical region for cardiomyopathy, hearing loss and hypotonia (Heilstedt *et al.*, 2003).

### Management

The management of 1p36 monosomy includes a comprehensive evaluation for the major clinical complications with an echocardiogram and ophthalmologic examination. A full audiological evaluation should be performed including testing at high frequencies with follow up as some patients have had progressive hearing loss. An electroencephalogram and cranial magnetic resonance imaging (MRI) are also warranted. Testing for thyroid dysfunction with T4, free T4 and TSH levels at birth, six months of age and annually has been recommended (Heilstedt *et al.*, 2003). Palatal evaluation and swallow-function studies should be included in the initial evaluation.

Developmental assessments with speech, physical and occupational therapist interventions are required. Developmental pediatricians, cardiologists, neurologists, cleft lip and palate specialists, orthopedists, otolaryngologists and nutritionists should also be involved as appropriate.

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