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# Further Delineation of Deletion 1p36 Syndrome in 60 Patients: A Recognizable Phenotype and Common Cause of Developmental Delay and Mental Retardation

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## ABSTRACT

**OBJECTIVES.** Deletion 1p36 syndrome is a recently delineated disorder, considered to be the most common subtelomeric microdeletion syndrome (1 in 5000 newborns). 1p36.3 deletions account for 0.5% to 1.2% of idiopathic mental retardation; thus, knowledge about the condition is important for pediatricians caring for such patients. Despite 100 reported cases, little is known about its natural history. Our aim was to delineate the natural history of deletion 1p36 and develop complete and accurate information with which to answer families' questions in the clinical setting.

**PATIENTS AND METHODS.** We evaluated 60 patients with the 1p36 deletion syndrome (41 female, 19 male). All underwent physical and neurologic assessments, and most received a psychological evaluation. Standard cytogenetics, fluorescence in situ hybridization of the subtelomeric regions, or array comparative genomic hybridization were used for diagnosis.

**RESULTS.** Fourteen cases were detected by standard cytogenetics, and 46 were detected by fluorescence in situ hybridization of the subtelomeric regions or array comparative genomic hybridization. Occipitofrontal circumference was at  $\leq 2$ nd centile in 95%, and height and weight ranged between the  $< 3$ rd and 90th centiles. All patients had straight eyebrows, deep-set eyes, midface hypoplasia, broad nasal root/bridge, long philtrum, and pointed chin. Other features included micro-brachycephaly (65%), epicanthus (50%), large, late-closing anterior fontanel (77%), and posteriorly rotated, low-set, abnormal ears (40%). Brachy/camptodactyly and short feet were prominent. Seventy-one percent exhibited heart defects, including 23% with a "noncompaction cardiomyopathy." Fifty-two percent had eye/visual abnormalities, and 64% had visual inattentiveness. Twenty-eight percent had sensorineural deafness, 41% had skeletal anomalies, 25% had abnormal genitalia, and 22% had renal abnormalities. Eighty-eight percent had central nervous system anomalies, and 44% had seizures. All patients demonstrated developmental delay with poor/absent speech; 95% had hypotonia. Twenty-six percent were able to walk alone, and 47% had a behavior disorder. Constant developmental progress was observed in all cases over time. Noncompaction cardiomyopathy and most seizures were controlled by pharmacotherapy.

**CONCLUSIONS.** These 60 patients with deletion 1p36 represent the largest clinical series to date and provide new information on several aspects of this disorder, which is characterized by neurodevelopmental disability and a recognizable pattern of malformation.

**T**ERMINAL DELETION 1p36 syndrome was first reported in 1980<sup>1</sup> as the result of a malsegregation of a parental balanced translocation. However, it was only in 1997 that this newly emerging clinical entity was brought to the attention of clinical geneticists.<sup>2</sup> Monosomy 1p36 syndrome is now recognized as the most common terminal deletion syndrome, with an estimated incidence of 1 in 5000<sup>3</sup> to 1 in 10 000.<sup>2</sup> The disorder is a result of a partial loss of material from the short arm of chromosome 1, with the majority of cases being pure terminal deletions.<sup>4</sup>

**Key Words:** 1p36 deletion syndrome, monosomy 1p36, natural history

**Abbreviations:** FISH, fluorescence in situ hybridization; BAER, brainstem auditory evoked response; EEG, electroencephalographic

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To date, ~100 case reports have been published.<sup>2,4,5-10</sup> However, despite these clinical studies, few data on the natural history of deletion 1p36 syndrome exist. In practice, there tends to be the presentation of information in a pessimistic way, with some families being told that their child has very little chance, if any, for meaningful interaction with his or her relatives and peers, that there inevitably will be severe developmental delay, and that a serious seizure disorder is likely.

The purpose of this report is to more thoroughly delineate the natural history of deletion 1p36 syndrome for the development of accurate information that can be used to address families' questions in the clinical setting.

Accurate information is also of paramount importance to obstetricians, who assist families in making relevant decisions about management in pregnancy, and pediatricians, who help families adjust to the birth of children with the syndrome and provide longitudinal health care to affected patients over time.<sup>5</sup>

## PATIENTS AND METHODS

We have evaluated 60 patients with 1p36 deletion syndrome in different centers (41 female, 19 male). Age at first observation ranged between the newborn period and 24 years. Thirty of the patients have been followed from 3 months to 18 years. Fourteen cases were detected with a high-resolution G-banded karyotype (525–700 bands, one of which was detected prenatally by amniocentesis), whereas, the remaining 46 required either fluorescence in situ hybridization (FISH) of the subtelomeric regions or array comparative genomic hybridization. It is important to note that these 46 patients had been evaluated previously in different university hospitals, and the diagnosis had been missed by standard cytogenetic studies (performed between 1995 and 2005). All 14 cases detected by high-resolution G-banded karyotype were confirmed by using FISH probes in the subtelomeric 1p region. Of the 60 patients, 52 had a "pure" 1p36 deletion, whereas the other 8 had a more complex rearrangement. Age at diagnosis varied between 32 weeks' gestation and 24 years.

This investigation was approved by the institutional review board of the Stella Maris Clinical Research Institute.

## RESULTS

All patients were born at term, and most (96%) were small for gestational age. Parental ages were similar to that of the general population. Pregnancy and family history were generally unremarkable. Birth history was notable in 50% of the cases for varying degrees of perinatal distress.

The clinical findings of our patients are listed in Table 1.

All patients demonstrated a characteristic craniofacial appearance with remarkably similar features: straight eyebrows, deep-set eyes, midface hypoplasia, broad nasal root/bridge, long philtrum, and pointed chin. Other craniofacial features included microbrachycephaly (65%), epicanthal folds (50%), large, late-closing anterior fontanel (77%) (Fig 1), and posteriorly rotated, low-set, abnormal ears (40%) (Fig 2). Additional find-

**TABLE 1 Clinical Findings in 60 Patients With Deletion 1p36 Syndrome**

	n	%
Dysmorphic craniofacial features		
Microbrachycephaly	39	65
Large, late-closing anterior fontanel (N = 39)	30	77
Straight eyebrows	60	100
Deep-set eyes	60	100
Epicanthus	30	50
Broad nasal root/bridge	60	100
Midface hypoplasia	60	100
Posteriorly rotated/low-set/abnormal ears	20	40
Long philtrum	60	100
Pointed chin	60	100
Limbs/skeletal defects		
Brachydactyly/camptodactyly	48	80
Short feet	48	80
Skeletal anomalies (N = 32)	13	41
Visceral anomalies		
Congenital heart defects (N = 48)	34	71
Noncompaction cardiomyopathy (N = 48)	11	23
Dilated cardiomyopathy (N = 48)	2	4
Gastrointestinal anomalies (N = 18)	5	28
Anal anomalies	2	3
Genitourinary tract defects		
Renal abnormalities (N = 18)	4	22
Abnormalities of the external genitalia	15	25
Neurologic findings		
Congenital hypotonia	57	95
Seizures	26	44
EEG abnormalities (N = 34)	34	100
Brain abnormalities (US/CT/MRI) (N = 49)	43	88
Eye/vision problems (N = 44)	23	52
Visual inattention (N = 44)	28	64
Sensorineural deafness (N = 32)	9	28
Developmental findings		
Developmental delay	60	100
Mental retardation (formally evaluated)	52	100
Expressive language (poor/absent)	60	100
Behavior disorders	28	47

The total number of patients equals 60 unless otherwise noted. US indicates ultrasound; CT, computed tomography.

ings were brachydactyly and camptodactyly (Fig 3) and short feet (80%). Occipitofrontal circumference was at or below the 2nd centile in 78% of the sample, and height and weight ranged between the <3rd and 90th centiles. Only 2% had craniosynostosis. Cleft lip/palate was observed in 3 patients (5%) and associated with velopharyngeal insufficiency in 1.

Ocular malformations or functional visual problems were observed in 23 (52%) of the 44 patients for whom such information was available. These problems included strabismus (35%), refractive errors such as hypermetropia, myopia, or astigmatism (23%), nystagmus (26.5%), unilateral cataract (5.9%), retinal albinism (5.9%), and unilateral optic nerve coloboma (2.9%). Visual inattentiveness, such as absence of attentive visual behavior with fixation and following movements, was present in 28 (64%) of the 44 patients.

Hearing loss occurred in 15 (47%) of the 32 patients for whom such information was available and was sen-



**FIGURE 1**  
Patient 54 (7 years 6 months of age) showing microbrachycephaly, straight eyebrows, bilateral epicanthal folds, broad/flat nasal bridge, deep-set eyes, elongated philtrum, pointed chin, and hypotonic face.



**FIGURE 2**  
Right hand of patient 54 showing brachydactyly and fifth-finger clinodactyly with hypoplastic palmar and interphalangeal creases.

cluded unilateral renal pelvis with hydronephrosis of the upper pole, kidney ectopia with right kidney cyst, and unilateral pelvic ectasia. Abnormalities of the genitalia were present in 15 (25%) of the 60 patients and consisted of cryptorchidism (40%), hypospadias (20%), scrotal hypoplasia (13%), and micropenis (7%) in males and small labia minora (12%), clitoris hypertrophy (7%), and labia majora hypertrophy (2%) in females. Uterine hypoplasia was found in the only female known to have had a pelvic ultrasound.

sorineural in 9 (28%; bilateral in 7 of 9), conductive in 3 (9%), and mixed in the remaining 3 (9%). Testing was performed by brainstem auditory evoked responses (BAERs).

A variety of skeletal anomalies was observed in 13 (41%) of the 32 subjects for whom such information was available. These consisted of rib anomalies such as 11 ribs, or bifid/fused/enlarged ribs (16%), lower-limb asymmetry (6.5%), scoliosis (16%), congenital hip dysplasia (3%), valgus deformity of the femoral neck (3%), thinning of the long bones (3%), increased height of the vertebral bodies (3%), congenital bilateral talipes valgus (3%), bilateral calcaneovalgus (3%), and phalangeal hypoplasia of the hands with cone-shaped epiphyses of hands and feet (3%). Delayed bone age was found in 7 (22%) of the 32 cases. None of the patients demonstrated advanced bone age.

Renal abnormalities, observed in 4 (22%) of the 18 patients for whom such information was available, in-



**FIGURE 2**  
Patient 42 (3 years 6 months of age) showing low-set, posteriorly rotated, malformed left ear.

Gastroesophageal reflux was reported in 4 patients (7%) and was associated with hiatal hernia in 1 patient. Hypertrophic pyloric stenosis was present in 2 patients and associated in 1 patient with intestinal malrotation with malposition of the cecum, leading to a volvulus. Anteriorly placed anus was seen in 2 cases (3%) and imperforate anus in 1 case (2%). Hooked or bilobed gallbladder was reported in 3 (17%), congenital gallstones in 1 (5.5%), and a small spleen in 1 (5.5%) case. Sacral/coccygeal dimples were observed in 9 patients (15%), and congenital hypothyroidism was reported in 3 (15%) of the 20 patients in whom triiodothyronine, thyroxine, and thyrotropin levels had been evaluated periodically.

### Cardiac Abnormalities

Congenital heart defects were reported in 34 (71%) of the 48 patients for whom such information was available. These consisted of atrial septal defects (28%), ventricular septal defects (23%), patent ductus arteriosus (12.8%), valvular anomalies such as bicommissural aortic valve, pulmonic valve stenosis/dysplasia/atresia, and mitral valve insufficiency (20.5%), tetralogy of Fallot (7.7%), coarctation of the aorta (5.1%), infundibular stenosis of the right ventricle (2%), and Ebstein anomaly (2%).

Cardiomyopathy was observed in 13 patients (27%); it was of the "noncompaction" type in 11 (23%) patients and the dilated type in 2 (4%) patients.

### Neurologic Abnormalities

Twenty-six of our patients (44%) had seizures, with onset between 4 days and 2 years 8 months of age. Different seizure types occurred, including clonic (unilateral or bilateral), infantile spasms, complex partial, tonic/clonic, atypical absences, tonic, or tonic spasms.

Fifteen patients (25%) had infantile spasms, starting between 3 and 10 months of age, which were associated with a hypsarhythmic electroencephalogram (West syndrome) in 14 of them. In 8 patients the infantile spasms were preceded by focal or generalized clonic seizures that occurred between 1 and 7½ months earlier. The infantile spasms were well controlled by corticotropin in 11 patients (73.3%), whereas in 2 of them the West syndrome evolved into a Lennox-Gastaut-like electroclinical picture, with atypical absences, tonic spasms, and nocturnal tonic seizures. Of the remaining 2 patients, 1 continued having medically resistant tonic and multifocal seizures, and the other slowly improved over the following years.

Eleven patients had a variety of seizures (clonic, tonic, tonic/clonic, complex partial), starting between 2 weeks and 17 months of age, that were mostly controlled by standard antiepileptic drugs. In 21 patients seizures had stopped by 8 weeks to 6 years of age, and 5 of them have been off medication for a number of years.

Thirty-four of our patients, who received serial electroencephalographic (EEG) studies over time, showed a variety of abnormalities. These abnormalities included paucity of the usual rhythmic activities, mainly over the

posterior third of the head; hypsarhythmia; asymmetry of slow activities; focal and multifocal spikes; generalized slow spike and wave complexes; fast recruiting rhythms; and slow background activity.

Brain MRI studies (with T1, T2, and fluid-attenuated inversion recovery techniques) were performed on 49 patients. Findings included enlargement of the lateral ventricles (18 patients), cortical atrophy (10 patients), enlargement of subarachnoid spaces (11 patients), diffuse brain atrophy (5 patients), and enlargement of the frontotemporal opercula (2 patients). Focal pachygyria was observed in an additional patient and a coarse and nodular aspect of the cortex in another. White matter anomalies were observed in 8 patients and included delay in myelination in 4 of them, multifocal hyperintensity areas in T2-weighted images (which had led to a provisional clinical diagnosis of leukodystrophy before deletion 1p36 syndrome was diagnosed) in 1 of them, and periventricular leukomalacia in 3 of them. Two patients had a Chiari I malformation. Anomalies or morphologic variants of the commissural structures were seen in 8 patients, including hypoplasia, thinning, and total or partial broadness of the corpus callosum in 6 patients; cavum septum pellucidum in 2 patients; and cyst of the cavum vergae in 1 patient.

Computed tomography of the brain was performed on 8 patients and showed colpocephaly in 1 patient, mild ventriculomegaly in 1 patient, coronal and lambdoidal craniosynostosis in 1 patient, and normal structural development in 5 patients.

Central nervous system sonograms were conducted in 4 patients and demonstrated ventriculomegaly in 3 patients and agenesis of septum pellucidum in 1 patient.

Hypotonia was observed in 57 patients (95%). Seventy percent had histories of feeding problems, including poor suck and swallow.

### Developmental Outcome

All patients exhibited global developmental delay. Head control had been acquired between 5 and 15 months of age; 76.7% of patients were able to sit without support (range: 7 months to 3 years); and 26% were able to walk independently, usually with a broad-based gait (range: 2–7 years). The nonambulatory patients ranged in age from 14 months to 9 years.

Cognitive profile was assessed for 52 of the patients by using a number of psychological tests, depending on the age of the subject. Forty-six (88%) of these patients had severe-to-profound mental retardation; in the remaining 6 patients, impairment of cognitive function was moderate in 3 and mild in the other 3.

Expressive language was absent in 45 patients (75%), limited to a few isolated words in 10 patients (17%), and at the level of 2 word phrases in 5 patients (8%).

Behavior disorders were present in 28 patients (47%), including self-biting of hands and wrists (30%), temper tantrums (22%), reduced social interaction (52%), stereotypies such as holding hands in front of face, hand washing or flapping, head shaking or banging and rocking (34%), tendency to smell or beating or rolling objects in a repetitive and purposeless way (10%), and hyperphagia (13%).



**FIGURE 4**

Front and side views of some of our patients at different ages (from infancy to adulthood) showing how the characteristic craniofacial phenotype remains easily recognizable over time.

The patients with severe-to-profound mental retardation showed writing abilities limited to scribbling and occasionally helped with simple household tasks or with feeding and dressing and undressing themselves.

The follow-up of our patients, which spanned 18 years, showed a gradual acquisition of adaptive behaviors, improved social interaction, and attainment of gross and fine motor abilities. An improvement in the communicative skills and verbal comprehension with extension of the gesture repertoire and/or vowel production and a decreased occurrence of withdrawal behavior was also observed.

## DISCUSSION

Individuals with deletion 1p36 syndrome often face serious physical disabilities (eg, structural or functional heart abnormalities, seizures/epilepsy). Both physicians and parents have to deal with difficult decisions regarding the care and management of the child, such as, "how far should we go with the treatment of the cardiomyopathy in a child with severe mental retardation?" It is crucial, therefore, that current and accurate information be available in the medical literature.

Our experience with the natural history of deletion 1p36 syndrome in the cohort described herein expands the phenotype of the disorder, especially in certain areas.

All patients have the characteristic facial phenotype, which remains easy to recognize over time (Fig 4).

Seizures are observed in ~50% of cases.<sup>4,11</sup> Our patient sample illustrates that infantile spasms, associated with a hypsarhythmic electroencephalogram (West syndrome), represent the most frequent type of epileptic seizures, which occur in 25% of affected children, and are well controlled by corticotropin in the majority of them. On the whole, there seems to be an improvement of the seizures with time, although a few cases with intractable seizures have been reported.<sup>12</sup>

Previous reports in the medical literature have briefly summarized the EEG findings in patients with the deletion 1p36 syndrome.<sup>13,14</sup> Our data also show that patients with monosomy 1p36 syndrome have a variety of EEG

features, with the most common being hypsarhythmia and paucity of rhythmic activities. Focal and multifocal spikes, generalized spike/wave complexes, and fast recruiting rhythms do occur in some subjects. All such EEG findings tend to improve over time in all patients except for those rare subjects with difficult-to-treat epilepsy.

The brain neuroimaging findings observed in our cases extend the scant neuropathological data available in the literature on 1p36 deletion syndrome<sup>15-17</sup> and point out the possible occurrence, in such cases, of white matter lesions that mimic a leukodystrophy. Therefore, we suggest consideration of neuroimaging studies for all patients with deletion 1p36 syndrome to further expand the spectrum of underlying brain abnormalities.

In addition to seizures, cardiac abnormalities were commonly observed in our 1p36 deletion cohort. Congenital heart defects were documented in 71% of the patients and consisted primarily of septal defects, patent ductus arteriosus, and valvular abnormalities. An additional primary cardiac manifestation is cardiomyopathy of the left-ventricular noncompaction subtype. Although this has been sporadically reported in the literature,<sup>1,2,6,9,14</sup> our study illustrates that 27% of the children with deletion 1p36 syndrome manifested cardiomyopathy. The high incidence of heart disease warrants a thorough cardiac evaluation, including auscultation, electrocardiogram, and echocardiography, for all infants with 1p36 deletion syndrome.

Ballif et al<sup>18</sup> suggested that repetitive DNA-sequence elements may play an important role in generating and/or stabilizing terminal deletions of 1p36. It seems that the phenotypic features tend to vary with the size of the deletion and those with larger deletions show more phenotypic features,<sup>19</sup> whereas no obvious phenotypic differences could be observed from the parent-of-origin studies.<sup>4</sup> Candidate genes associated with an epilepsy phenotype<sup>14</sup> and clefting abnormalities<sup>20</sup> in monosomy 1p36 have been identified. More recently, haploinsufficiency of the *MMP23* gene, located at 1p36, has been proposed to be responsible for a large, late-closing ante-

rior fontanel; whereas its overexpression results in craniosynostosis.<sup>21</sup>

Chromosome 1p36 has been determined to be 1 of the major regions of interest in neuroblastoma,<sup>22–24</sup> with 3 patients with deletion 1p36 syndrome described in the literature developing neuroblastoma at ages 5, 8, and 9 months. Lately, a tumor suppressor gene has also been identified at human 1p36<sup>25</sup>; however, no individual in our study had a history of cancer.

The ophthalmologic problems observed in 52% of our patients, and the visual inattentiveness present in 64%, deserve close attention and require adequate diagnosis, follow-up, and treatment.

Hearing impairment, mostly of the sensorineural type, was observed in 47% of our sample and in an even higher percentage in a previous study.<sup>4</sup> Because it seems to be a component manifestation of monosomy 1p36 syndrome, we recommend audiological evaluation to exclude a possible hearing deficit, which, if not recognized, might worsen the child's prognosis.

Congenital hypothyroidism was observed in a minority of our cases, but because it is a treatable condition and it occurred in 20% of previously reported cases,<sup>4</sup> we suggest performing thyroid-function tests for all individuals with monosomy 1p36 syndrome.

We followed some of our patients for up to 18 years and could observe a clear improvement of their gross and fine motor abilities, adaptive behavior, and social interaction over time.

In the medical literature, very little attention has been devoted to the proper evaluation of cognitive function in patients with deletion 1p36 syndrome.<sup>2</sup> Our study illustrates that such patients tend to have a severe-to-profound degree of mental retardation, with absence of speech in most (none using nonverbal communication techniques) and behavioral disorders in just under 50%. Survival into adulthood seems to be the rule.

Our series consisted of 41 females and 19 males. A similar female predominance of cases has been noted in the literature.<sup>26</sup>

In the last 2 decades, guidelines for routine health supervision in the primary care setting have been proposed for children with various syndromes.<sup>27</sup> The pediatrician is the ideal practitioner to provide the medical home for children with deletion 1p36 syndrome. In this context, we suggest the following for health supervision and anticipatory guidance in the routine care of infants and children with deletion 1p36 syndrome.

### Infancy

We recommend cardiology consultation and focused examination of the heart; video-electroencephalography-polygraphy (if seizures are present); audiological screening (BAERs); ophthalmology consultation; swallowing study (if any feeding difficulties exist); thyroid-function screening; developmental testing/referral for early intervention; and genetic counseling.

### Childhood

We recommend cardiology follow-up (if a cardiac abnormality is present); video-electroencephalography-polyg-

raphy (if seizures are present); audiology follow-up (BAERs); thyroid-function screening; and continued developmental testing/appropriate school placement.

Participation in support groups is an important strategy for many parents in coping with a child with disabilities. There are 2 existing support organizations in North America for families of children with chromosome abnormalities: Chromosome Deletion Outreach, Inc ([www.chromodisorder.org](http://www.chromodisorder.org)), and MakingContact.org ([www.makingcontact.org](http://www.makingcontact.org)).

Deletion 1p36 syndrome is considered to be the most common terminal deletion syndrome<sup>28</sup> and is responsible for ~1% of all cases labeled as "idiopathic mental retardation."<sup>29</sup> Our experience suggests that there may be quite a number of unrecognized or misdiagnosed subjects in whom the standard karyotype testing has missed the terminal deletion or in whom an interstitial deletion<sup>4</sup> is missed by using only 1 subtelomeric FISH probe. This condition is far more common than many other better known multiple congenital anomalies/mental retardation syndromes. Thus, it is of the utmost importance for pediatricians to be aware of it and consider it whenever dealing with a patient who presents with infantile spasms associated with a hypsarhythmic electroencephalogram and/or a cardiomyopathy, particularly of the noncompaction type.

We emphasize the serious delay encountered in reaching the diagnosis in many patients because of the difficulty in clearly visualizing, by conventional cytogenetic analysis, the light-staining G-negative bands that constitute the 1p36 region. Therefore, we would alert clinicians to the need to pursue FISH with at least 2 subtelomeric region-specific probes (Vysis 1pSUBTEL probe, Vysis p58 probe [Des Plaines, IL]; D1Z2 Oncor probe or CEB108/T7 [Illkirch Graffenstaden, France]) or comparative genomic hybridization microarray in cases of suspected monosomy 1p36.

### CONCLUSIONS

The 1p36 deletion syndrome is a common clinically recognizable malformation syndrome, the diagnosis of which has significant implications for the affected child and his or her family. Furthermore, recognition of deletion 1p36 syndrome illustrates the importance and utility of the new molecular cytogenetic techniques in clinical practice.

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## Further Delineation of Deletion 1p36 Syndrome in 60 Patients: A Recognizable Phenotype and Common Cause of Developmental Delay and Mental Retardation

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