Am. J. Hum. Genet. 61:642–650, 1997

Chromosome 1p36 Deletions: The Clinical Phenotype and Molecular Characterization of a Common Newly Delineated Syndrome

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Summary

Deletions of the distal short arm of chromosome 1 (1p36) represent a common, newly delineated deletion syndrome, characterized by moderate to severe psychomotor retardation, seizures, growth delay, and dysmorphic features. Previous cytogenetic underascertainment of this chromosomal deletion has made it difficult to characterize the clinical and molecular aspects of the syndrome. Recent advances in cytogenetic technology, particularly FISH, have greatly improved the ability to identify 1p36 deletions and have allowed a clearer definition of the clinical phenotype and molecular characteristics of this syndrome. We have identified 14 patients with chromosome 1p36 deletions and have assessed the frequency of each phenotypic feature and clinical manifestation in the 13 patients with pure 1p36 deletions. The physical extent and parental origin of each deletion were determined by use of FISH probes on cytogenetic preparations and by analysis of polymorphic DNA markers in the patients and their available parents. Clinical examinations revealed that the most common features and medical problems in patients with this deletion syndrome include large anterior fontanelle (100%), motor delay/hypotonia (92%), moderate to severe mental retardation (92%), growth delay (85%), pointed chin (80%), eye/vision problems (75%), seizures (72%), flat nasal bridge (65%), clinodactyly and/or short fifth finger(s) (64%), low-set ear(s) (59%), ear asymmetry (57%), hearing deficits (56%), abusive behavior (56%), thickened ear helices (53%), and deep-set eyes (50%). FISH and DNA polymorphism analysis showed that there is no uniform region of deletion but, rather, a spectrum of different deletion sizes with a common minimal region of deletion overlap.

Received March 4, 1997; accepted for publication June 6, 1997.

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0002-9297/97/6103-0022$02.00

Introduction

Deletion of the distal band(s) of some chromosomes has long been recognized as the cause of certain genetic disorders with congenital abnormalities and mental retardation; examples include Wolf-Hirschhorn syndrome (4p monosomy) (Wolf et al. 1965; Leao et al. 1967) and cri-du-chat syndrome (5p monosomy) (Lejeune et al. 1963), although, by high-resolution chromosomal banding techniques, distal deletions for virtually all chromosomes have been identified in patients. Deletion of the distal short arm of chromosome 1 (1p36 deletion) is a recently identified chromosomal syndrome that we believe has been previously underascertained by cytogenetic analysis. This may be due to the difficulty in clearly visualizing by conventional cytogenetics the light-staining G-negative bands constituting the 1p36 region.

Partial monosomy of chromosome 1p36 was first reported in 1980 in an infant who had inherited an unbalanced-translocation product from a parent who carried a balanced 1;15 translocation (Hain et al. 1980). This child, as well as several subsequently reported individuals (Desangles et al. 1983; Barbi et al. 1992; Reish et al. 1995), had partial monosomy 1p36 in addition to partial trisomy of another chromosomal region (double-segmental imbalance), because of inheritance of unbalanced-translocation products from a parent. These patients were easily identified cytogenetically because of their other segmental imbalance. However, delineation of the clinical effects of 1p36 monosomy, separate from the effects of the other chromosomal imbalances, was not possible. Other patients with de novo–derivative chromosomes involving deletion of distal 1p have also been described, but, similarly, they are not ideal for delineation of the features of the 1p36 deletion syndrome, because of additional chromosomal imbalance (Yunis et al. 1981; Steele et al. 1984; Reish et al. 1995). Since 1987, 14 cases of presumed pure (single-segmental imbalance) de novo deletion of 1p36, as well as 1 case of a pure 1p35 deletion, have been reported; these cases have been useful for initial characterization of the monosomy 1p36 phenotype (Magenis et al. 1987; Wenger

et al. 1988; Wargowski et al. 1991; Wexler et al. 1991; Keppler-Noreuil et al. 1995; Reish et al. 1995; Sandlin et al. 1995).

In delineating the clinical features of 1p36 deletions, previous clinical summaries have not confined their characterization of the deletion phenotype to patients with pure 1p36 deletions (Keppler-Noreuil et al. 1995; Reish et al. 1995; Sandlin et al. 1995); they have included the phenotypic features and clinical manifestations of patients with double-segmental imbalances. This approach may provide a general gestalt of the physical features and medical problems associated with 1p36 deletions; however, assessment of the frequency of each particular phenotypic feature and definition of the isolated 1p36 deletion phenotype have been confounded by the effects of other chromosomal imbalance.

Herein we describe the clinical features of 13 patients with isolated deletion of the distal short arm of chromosome 1. In order to define the clinical phenotype of patients with this chromosomal deletion syndrome, we compare the phenotypes of our patients with those of four patients previously described with presumedly pure 1p36 deletions (Keppler-Noreuil et al. 1995; Reish et al. 1995) and with that of one patient with a 1p35 deletion (Wenger et al. 1988). By excluding the patients with double-segmental imbalance, we can assess the variability of features that appear specific to patients with the 1p36 deletion.

It has been suggested that the phenotypic variability among patients with the 1p36 deletion syndrome, particularly with regard to growth, may be due to the parental origin of the deletion and to the effects of imprinted genes (Wargowski et al. 1991; Keppler-Noreuil et al. 1995). Conversely, phenotypic variability may be due to submicroscopic differences in the physical extent of each deletion resulting in the loss of different contiguous dosage-sensitive genes, or due to the unmasking of certain recessive alleles. In order to investigate these possibilities, our 13 patients with pure 1p36 deletions, as well as 1 patient with distal 1p monosomy in conjunction with minimal distal 22q trisomy, have been studied with DNA polymorphisms and FISH, to determine the parental origin of each deleted chromosome, as well as to define the extent of each deletion interval. The results indicate that no parent-of-origin effect is obvious and that the physical extent of deletions of 1p36 is quite variable.

Subjects, Material, and Methods

Patients and Cell Lines

During 1993–96, 13 patients referred, for cytogenetic studies, to the Kleberg Cytogenetics Laboratory (Baylor College of Medicine) and to the Hermann Hospital Cytogenetics Laboratory (The University of Texas Medical School) were identified as having 1p36 deletions, by G-banded chromosome analysis performed on peripheral blood lymphocytes; 1 additional patient was ascertained prenatally, by chromosome analysis performed on amniocytes, and was confirmed postnatally, by analysis of peripheral blood lymphocytes, to have a 1p36 deletion. Blood samples were subsequently collected from all 14 patients and their available parents, and lymphoblastoid cell lines were established by methods described elsewhere (Watt and Stephen 1986). The protocols were approved by the institutional review board of Baylor College of Medicine, and informed consent was obtained from the parents or guardians of all patients.

Thorough clinical characterization of the patients was performed after the cytogenetic diagnosis was established, in order to document features for table 1; all of the features listed within table 1 were part of a checklist utilized by the examiner. The checklist was compiled on the basis of features reported previously in the literature, as well as on the basis of features observed in our patients. All patients presented in this report were examined by one of the authors (patients 2–14 were examined by S.K.S., and patient 1 was examined by F.G.). Eight of the 14 patients have been examined (by S.K.S.) on more than one occasion, in order to document any changes in their features.

FISH

Metaphase chromosome preparations of peripheral blood lymphocytes from the 14 patients and available parents were studied by FISH using four probes mapping to 1p36.3: p1-79 (ATCC), p58 (Oncor), 1A9, and 13P11. A FISH probe mapping to the centromere of chromosome 1, D1Z5 (Oncor), was used as a control. Probe p1-79 (also known as "D1Z2") binds to a distal 1p hypervariable repeated sequence (Buroker et al. 1987). Probe p58 (also known as "CDC2L1" or "PITSLRE") identifies a cell cycle–regulated kinase gene with homology to human CDC2 (Bunnell et al. 1990). BAC probe 1A9 (Shizuya et al. 1992) and PAC probe 13P11 (Ning et al. 1996) are clones of chromosome 1–specific sequences that contain the DNA polymorphisms D1S214 and D1S1615, respectively. All FISH analyses were performed according to methods described elsewhere (Shaffer et al. 1994).

Polymorphic Marker Analysis

Total cellular DNA was prepared from either peripheral blood lymphocytes or lymphoblastoid cell lines (Spence et al. 1987). As many as 12 dinucleotide or tetranucleotide polymorphisms located in chromosome 1p36 were analyzed on the 14 patients and their available parents (Shaffer et al. 1993). To establish which polymorphic loci were deleted, alleles were compared between each patient and available parents

Table 1

Clinical Features of Pure 1p36 Deletion Patients

Feature	Report (n = 13)	Previous Reports (n = 5)	Total (%)
Clinical:			
Growth delay (postnatal)	8/8	3/5	11/13 (85)
Normal prepubertal height (at age >1 year)	0/7	2/5	2/12 (17)
Precocious puberty	2/3	1/1	3/4 (75)
Obesity	1/8	1/5	2/13 (15)
Motor delay/hypotonia	8/8	4/5	12/13 (92)
Mental retardation (moderate-severe)	7/8	5/5	12/13 (92)
Abusive behavior[a]	3/7	2/2	5/9 (56)
Seizures[b]	9/13	4/5	13/18 (72)
Hearing deficits	4/8	1/1	5/9 (56)
Eye/vision problems	6/8	3/4	9/12 (75)
Infant feeding problems	7/13	1/4	8/17 (47)
Dysmorphic:			
Microcephaly (postnatal)	4/9	1/4	5/13 (38)
Brachycephaly	5/13	1/1	6/14 (43)
Large anterior fontanelle	8/8	3/3	11/11 (100)
Low anterior hairline	5/13	0/0	5/13 (38)
Small ears	4/13	2/4	6/17 (35)
Large ears	1/13	0/4	1/17 (6)
Thickened ear helices	7/13	1/2	8/15 (53)
Ear-pinna dysplasia	3/13	1/1	4/14 (29)
Ear asymmetry	7/13	1/1	8/14 (57)
Low-set ear(s)	6/13	4/4	10/17 (59)
Posteriorly rotated ear(s)	3/13	0/4	3/17 (18)
Short palpebral fissures	3/13	2/4	5/17 (29)
Palpebral fissures (up)	6/13	1/4	7/17 (41)
Palpebral fissures (down)	4/13	2/4	6/17 (35)
Deep-set eyes	6/13	1/1	7/14 (50)
Hypotelorism	4/13	0/0	4/13 (31)
Hypertelorism (apparent)	2/13	0/0	2/13 (15)
Flat nasal bridge	9/13	2/4	11/17 (65)
Flat nose	5/13	0/1	5/14 (36)
High nasal bridge	3/13	1/1	4/14 (29)
Long-appearing philtrum	4/13	0/4	4/17 (24)
Prognathism	3/8	1/1	4/9 (44)
Pointed chin	10/13	2/2	12/15 (80)
Small hands/feet	1/13	2/2	3/15 (20)
Fifth finger short/clinodactyly	8/13	1/1	9/14 (64)
Scrotal hypoplasia	1/6	0/1	1/7 (14)
Congenital:			
CT/MRI anomaly[c]	2/10	0/1	2/11 (18)
Cleft lip/palate	2/13	0/5	2/18 (11)
Infantile cardiomyopathy	2/6	2/3	4/9 (44)
Congenital heart defect (minor)	2/13	1/5	3/18 (17)
Cryptorchidism	1/6	1/1	2/7 (29)

NOTE.—Data are proportion or percentage of patients in whom the feature either could be directly assessed or was specifically noted in a clinical report.

[a] Includes hand biting, banging or throwing objects, striking people, and episodes of violent physical activity.

[b] Includes simple and complex partial seizures, myoclonus, and infantile spasms (modified hypsarrhythmia).

[c] Includes lateral ventricle asymmetry, ventricular enlargement, and focal atrophy.

(except patient 3, in whom heterozygosity for a marker was used to indicate lack of deletion). The marker order on the genetic map was based on mapping data obtained from Chromosome 1 World Wide Web (1997) resources (http://www.med.upenn.edu/~poncol/chr1/resources.html) and from radiation-hybrid mapping data for 1p35-36 (Jensen et al., 1997).

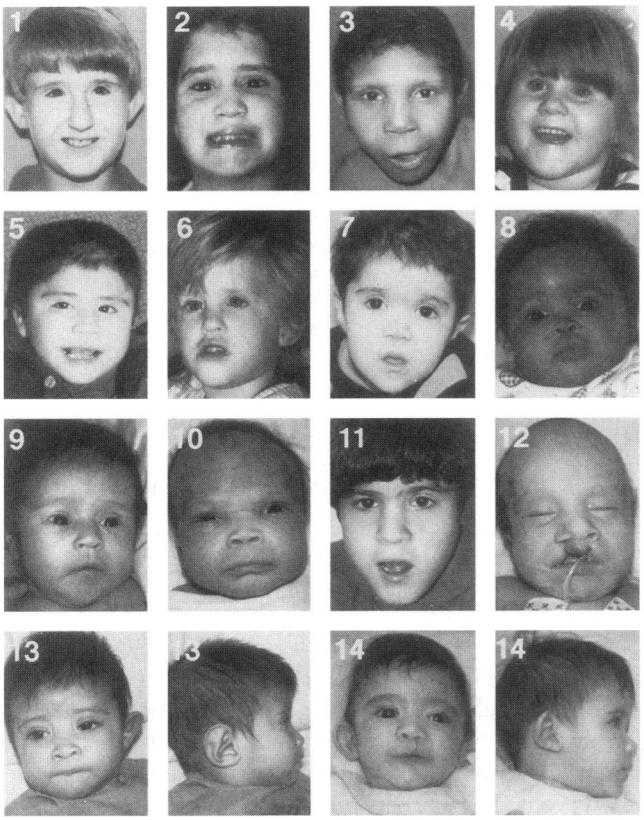

Figure 1 Patients with chromosome 1p36 deletions. Panel numbers in the upper-left-hand corners are patient numbers. Frontal views are shown for all patients, and lateral views are shown for patients 13 and 14.

Results

Clinical Features of 1p36 Deletion Patients

The 14 patients with 1p36 deletion are shown in figure 1. Patient 13 has a presumed double-segmental imbalance (1p36 monosomy and minimal 22q13.3 trisomy) and is not included in the clinical characterization of pure 1p36 deletions. The frequencies of clinical features of the remaining 13 patients are listed in table 1, along with data from reports describing 5 other patients with similar single-segmental imbalances: 4 individuals with 1p36 deletions (Keppler-Noreuil et al. 1995; Reish et al. 1995) and 1 individual with a 1p35 deletion (Wenger et al. 1988). Patients with pure 1p36 deletions reported by others in abstracts alone (Magenis et al. 1987; Wargowski et al. 1991; Wexler et al. 1991; Sandlin et al. 1995) were not included in this comparison, because of lack of a complete phenotypic description and photographs.

Cytogenetic and FISH Analyses of 1p36 Deletion Syndrome Patients

The 1p36 deletions in the 14 patients were ascertained by 600–800-band–resolution cytogenetic analysis, and the results are summarized in table 2, along with the age at diagnosis and the indication for referral for cytogenetic studies. Partial G-banded karyotypes showing pairs of chromosomes 1 from several deletion patients are shown in figure 2*A*. Cytogenetic studies of the mothers ($n = 14$) and available fathers ($n = 9$), in conjunction with FISH using probes p1-79 and p58, showed no rearrangements involving distal 1p for the parents of 13 of the 14 patients. The one exception was the father of patient 13, who was found to carry a presumed balanced translocation with breakpoints in 1p36.2 and 22q13.3.

Metaphase cells from the 14 patients with 1p36 deletions were analyzed by FISH using probes p1-79, p58, 1A9, and 13P11; a representative example of the FISH analysis for 1 patient is shown in figure 2*B*. All 14 patients were deleted for probe p58, 13 of 14 patients were deleted for probe p1-79, 5 of 14 patients were deleted for probe 1A9, and 2 of 14 patients were deleted for probe 13P11 (results are summarized in fig. 3). Patient 4 (not deleted for p1-79) is presumed to have an interstitial deletion, within 1p36.3, that preserves the more telomeric region of the chromosome (containing p1-79) but that still deletes the region containing p58. These results from patient 4 suggest that p1-79 is distal to p58 on chromosome 1.

Molecular Polymorphism Analysis of 1p36 Deletion Syndrome Patients

Between 6 and 12 dinucleotide- and tetranucleotide-repeat polymorphic markers that map to distal 1p36 were examined for each family. Representative results of markers analyzed for families 8 and 9 are shown in figure 4. A summary of the results of the marker analyses is shown in figure 3. A significant difference in parental origin of the de novo–deleted chromosome 1 was observed with 17% paternally derived and 83% maternally derived deletions ($\chi^2_1 = 5.3$, $.01 < P < .05$). On the basis of the polymorphic marker and FISH results, the size of the deletion region was found to vary between the patients. By combining the FISH analyses using probes p1-79, p58, 1A9, and 13P11 with the polymorphic marker analyses, the deletions could be arrayed, with many patients having deletions of different size but all of them containing a minimal deletion interval, in distal 1p36, that encompassed marker D1S243 and probe p58 (fig. 3). On the basis of the markers used in the present study, patient 4 appeared to have the smallest deletion, and patient 13 had the largest deletion.

Discussion

Thirteen patients with pure chromosome 1p36 deletions have been evaluated for their clinical phenotypes (table 1). These 13 patients with single-segmental imbalance, as well as 1 patient with a double-segmental imbalance (patient 13), have been evaluated for the size and

Table 2

Cytogenetic Analysis of 1p36 Deletion Patients

Patient	Age at Diagnosis	Referral Indication	Karyotype
1	11 years 3 mo	Developmental delay; dysmorphism	46,XY,del(1)(p36.22)
2	10 years 9 mo	Developmental delay; dysmorphism	46,XX,del(1)(p36.2)
3	4 years 10 mo	Developmental delay; dysmorphism	46,XY,del(1)(p36.2)
4	5 years 11 mo	Possible Prader-Willi syndrome	46,XX,del(1)(p36.31)
5	2 years 9 mo	Seizures; developmental delay	46,XY,del(1)(p36.23)
6	2 years 9 mo	Developmental delay; growth delay	46,XX,del(1)(p36.2)
7	2 years 2 mo	Developmental delay	46,XY,del(1)(p36.2)
8	Prenatal	Abnormal maternal serum alpha-fetoprotein	46,XX,del(1)(p36.22)
9	2 wk	Seizures	46,XX,del(1)(p36.2)
10	4 d	Dysmorphic features	46,XY,del (1)(p36.2)
11	10 years 1 mo	Possible Rubinstein-Taybi syndrome	46,XX,del(1)(p36.22)
12	4 d	Multiple congenital anomalies	46,XY,del(1)(p36.2)
13	7 mo	Seizures; dysmorphism	46,XY,der(1)t(1;22)(p36.2;q13.3)pat
14	6 mo	Multiple congenital anomalies	46,XX,del(1)(p36.2)

parental origin of their deletions (fig. 3). Cytogenetic and molecular studies have determined that, in the 13 patients with pure 1p36 deletions, the deletions are de novo and do not appear to include other chromosomal segmental imbalance. Although the fathers of five of the patients were not available for testing by cytogenetic analysis or FISH in order to exclude a paternal translocation, in each of these cases the origin of the deleted chromosome was found, by molecular studies, to be maternal, thus confirming that each deletion was a de novo event. The patients reported here represent a useful resource for delineation of the clinical phenotype, because they represent a substantial cohort of pure single-segmental imbalance for 1p36 deletions. Patient 13 (with presumed double-segmental imbalance), who was excluded from the clinical characterization of the syndrome (table 1) but was included in the molecular studies (fig. 3), is of interest because, by cytogenetic and FISH analysis, he appeared to have a pure 1p36 deletion. However, only after the cytogenetic and FISH studies performed on his parents identified his father as a translocation carrier was the cytogenetic interpretation for him changed to 46,XY,der(1)t(1;22)(p36.2;q13.3)pat. Therefore, it is prudent to perform cytogenetic and FISH evaluation of the parents of all 1p36 deletion patients, in order to exclude the possibility that a patient has an unbalanced-translocation product inherited from a parent who carries a balanced translocation.

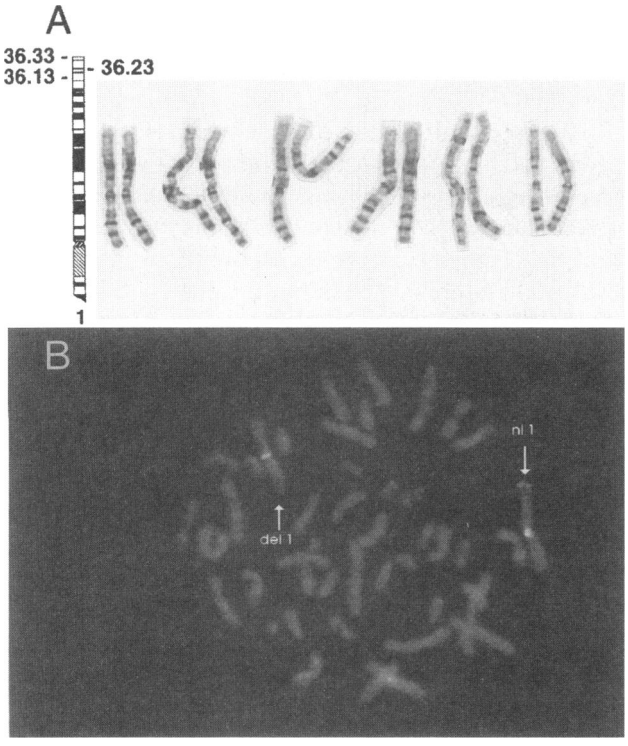

Figure 2 Cytogenetic analysis and FISH analysis for 1p36 deletions. *A*, Ideogram of chromosome 1p and pairs of chromosome 1 from several deletion patients. For each pair, the deleted chromosome 1 is on the right. From left to right, the pairs of chromosome 1 correspond to patients 10, 10, 11, 9, 4, and 8. *B*, FISH analysis from patient 11 is shown; both the normal (nl) and deleted (del) chromosome 1 show hybridization with the control probe at the centromere (D1Z5), but one chromosome (del 1) of the pair is deleted for the distal 1p36 probe, p1-79.

The 1p36 deletion syndrome appears to be more common than most other deletion syndromes. Population studies have shown that, for other deletion syndromes, the incidence is estimated to be 1/45,000 for 5p monosomy (Niebuhr 1978), 1/25,000 for Prader-Willi syndrome (Butler 1990), and ≥1/4,000 for the 22q11 deletion involved in DiGeorge/velo-cardio-facial syndrome (Burn et al. 1995). With regard to the incidence of 1p36 deletion syndrome, six of our patients were born in 1996 in Harris County (Texas), where there are ~60,000 births/year (Texas Department of Health 1995 statistics). Therefore, the incidence of monosomy 1p36 appears to be >1/10,000, since it is likely that not all cases

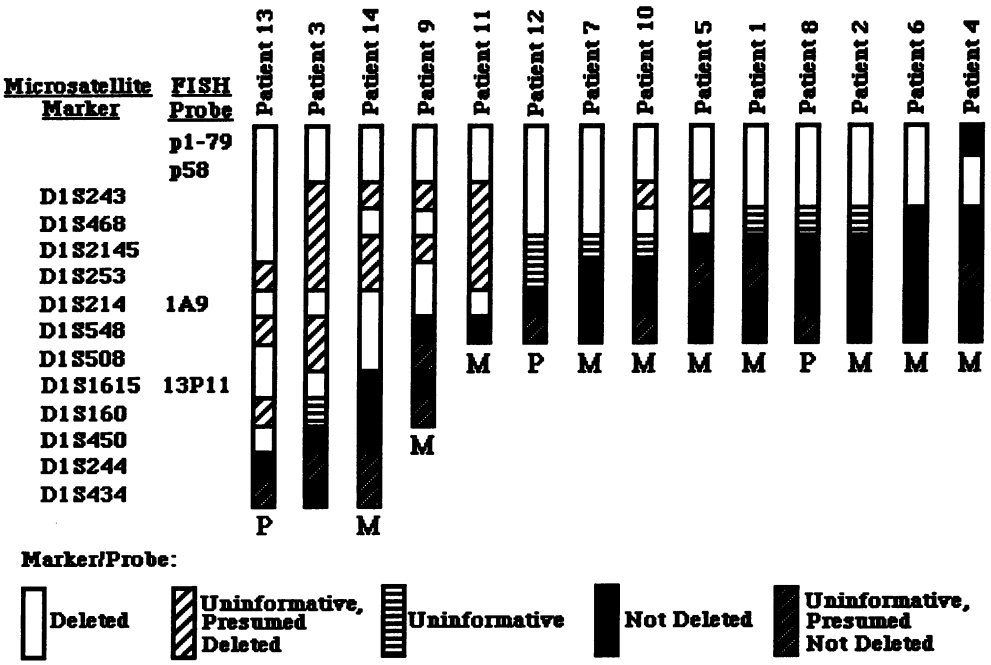

Figure 3 Natural 1p36 deletion panel, for 14 patients, from analysis of microsatellite markers and FISH probes. Polymorphic markers and FISH probes are listed at the left, in order, from distal (*top*) to proximal in chromosome 1p36. The 14 deletion patients are listed at the top of the figure, over each deletion panel. The deletion size decreases from left to right. Beneath each deletion panel is an indication of whether the deletion is paternally derived (P) or maternally derived (M). Since parental samples were not available for the analysis of patient 3, the indicated deleted regions were determined by analysis with FISH probes, and the nondeleted regions were inferred from heterozygosity for the microsatellite markers.

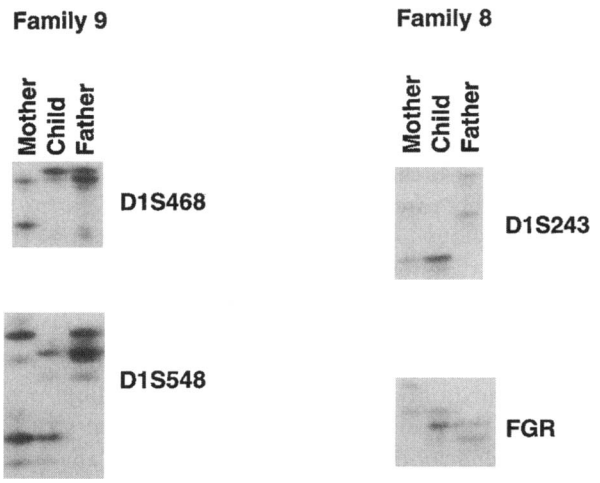

Figure 4 Polymorphic marker analysis for 1p36 deletion patients. Fully informative analyses of two chromosome 1p36 markers are shown for patients 8 and 9 and their parents. Patient 9 demonstrates inheritance of only one allele (from her father) for marker D1S468 and therefore has a deletion for this marker on the maternally derived chromosome. At locus D1S548, patient 9 is heterozygous, since she has inherited a different allele from each parent, indicating no deletion for this marker. Patient 8 has a deletion on the paternally derived chromosome, since she has inherited only one allele (from her mother) for marker D1S243. Patient 8 is heterozygous for the marker FGR, indicating no deletion for this marker. Marker FGR, although analyzed for many of the patients, is not shown in figure 3 because it maps outside the deletion region.

in the catchment area have yet been ascertained. This estimate may seem high, but 1p36 deletions are likely being underascertained in most cytogenetics laboratories. Of our 14 patients, 6 had prior cytogenetic studies in which the deletion was not identified. Three of these six patients had their initial cytogenetic study performed in 1996 (one in each of three different cytogenetics laboratories), and two of these three patients (13 and 14) have large deletions that were not detected in the initial cytogenetic studies.

For individuals with monosomy for 1p36, moderate to severe mental retardation, hypotonia, and developmental delay are found almost universally. Full-scale IQ scores are generally <60 (on the basis of testing performed on our six oldest patients; the other patients were too young for adequate testing). Although gross and fine motor skills are moderately delayed, speech development is more significantly impaired. The vast majority (85%) of individuals have significant growth retardation. However, several reports note that a few individuals had infantile feeding problems and poor weight gain but developed obesity and/or macrosomia in childhood, like patients with Prader-Willi syndrome (Wenger et al. 1988; Wargowski et al. 1991; Keppler-Noreuil et al. 1995); in each of these cases, the diagnosis of Prader-Willi syndrome was suggested before the correct cytogenetic diagnosis of monosomy 1p36 was made. Previous reports (Wargowski et al. 1991; Kep-

pler-Noreuil et al. 1995; Sandlin et al. 1995) have suggested that two distinct clinical phenotypes constitute this deletion syndrome: (1) growth failure associated with hirsutism, specific craniofacial features (small face, midface hypoplasia, short up-slanting palpebral fissures, epicanthal folds, deep-set eyes, small nose, and micrognathia), and cleft lip and/or cleft palate and (2) normal growth parameters or obesity associated with other craniofacial features (tall forehead, broad face, bitemporal narrowing, normal palpebral fissures, hypertelorism, sparse eyebrows, flat nasal bridge, broad nasal root, and prominent jaw or prognathism). Our experience, based on detailed clinical assessment of the 14 patients reported here, is that each of the craniofacial features of these two supposed clinical phenotypes occurs in a proportion of the patients but that these features do not separate the patients into two distinguishable groups. In addition, it does not appear that differing craniofacial features are due to the size of the chromosomal deletion. Patients with both small and large deletions may have very similar craniofacial features (compare patients 4 and 9 [fig. 1], who have developed a closer resemblance as patient 9 has grown older), whereas patients with similar-size deletions may have quite different phenotypes (compare patients 1 and 2 [fig. 1], whose photographs were obtained at the same age). The phenotypic variability among these patients may represent ethnic differences, may reflect natural variation in the genetic background, or may be associated with deletion of specific regions of the genetic map.

At birth, all of our patients had normal measurements for weight, length, and head circumference, but the vast majority (85%) became growth retarded at age >1 year. Several older patients had normal growth parameters at the time of ascertainment (in our series, patients 2 and 11), and a few patients had infantile feeding problems but developed childhood obesity similar to what occurs in Prader-Willi syndrome (in our series, patient 4). The two older patients with normal growth parameters at the time of ascertainment (both of whom were girls 10–11 years of age) previously had been <3d centile for height and weight but subsequently had early pubertal growth spurts that increased their height and weight to the normal range. As these two patients are followed, it is expected that they will complete puberty early (they are already Tanner IV–V at age 10–11 years and started menses at age 10 years), plateau in their growth, and attain adult heights that are <3d centile. Thus, the category of patients with "normal growth" or obesity may in fact represent hypothalamic/pituitary dysfunction that manifests as precocious puberty in some patients and as obesity in others. We did not observe a correlation between these growth anomalies and particular craniofacial features, as has been suggested in other reports (Keppler-Noreuil et al. 1995).

Previous reports (Keppler-Noreuil et al. 1995) have also suggested that congenital heart defects and cardiomyopathy are common features of this deletion syndrome, but we did not find congenital heart defects to be common in our cohort. Two of our patients (patients 12 and 14) had infantile cardiomyopathy, and none of our patients had significant congenital heart defects (one had a patent ductus arteriosus, and one had mild left-pulmonary-artery-branch stenosis). Other reports have described patients with infundibular stenosis, tetralogy of Fallot, and ventricular septal defects (Yunis et al. 1981; Magenis et al. 1987; Biegel et al. 1993), but in the first case there was other chromosomal segmental imbalance, and in the other two cases the deletion breakpoints were judged to be more proximal (1p36.13 and 1p36.1, respectively) than those in the patients described here. Therefore, we do not consider significant cardiac defects to be a common feature of this deletion syndrome. However, infantile cardiomyopathy occurred in two of our patients, as well as in two other patients with pure 1p36 deletions (Keppler-Noreuil et al. 1995), and may occur in ≤44% of patients.

It has been suggested that cleft lip or cleft lip/palate occurs in ≤40% of patients with this condition (Keppler-Noreuil et al. 1995). Two of our patients had clefting defects (patient 14 had cleft lip, and patient 12 had cleft lip/palate), which suggests a lower incidence (closer to 10%) for this congenital anomaly.

Although there is clinical variability between the patients with the 1p36 deletion syndrome, this condition has a recognizable phenotype that is unique enough to consider it as a newly delineated syndrome; in our patient series, the diagnosis was made by the geneticist and/or neurologist, on the basis of clinical examination, before the cytogenetic result was available, for patients 11–14; the other 10 patients were diagnosed retrospectively after chromosome analysis (except for patient 8, who was diagnosed by prenatal testing). The prospective diagnosis for patients 11–14 was possible because each patient had many of the most common features listed in table 1, as well as having had some of the other less common features (i.e., cleft lip/palate, infantile cardiomyopathy, and infant feeding problems). On the basis of the clinical assessments of our entire patient cohort and those reviewed in the literature who have single-segmental imbalance, we suggest that the most common features that constitute this deletion syndrome include large anterior fontanelle (100%), motor delay/hypotonia (92%), moderate to severe mental retardation (92%), growth delay (85%), pointed chin (80%), eye/vision problems (75%), seizures (72%), flat nasal bridge (65%), clinodactyly and/or short fifth finger(s) (64%), low-set ear(s) (59%), ear asymmetry (57%), hearing deficits (56%), abusive behavior (56%), thickened ear helices (53%), and deep-set eyes (50%). All other craniofacial features occur in <50% of the patients and do not separate into consis-

tent patterns of anomalies. Eye/vision problems among our patients include strabismus, 6th-nerve palsy, amblyopia, refractive errors (including hyperopia, myopia, and/or astigmatism), anomalous optic disks, and lacrimal defects. Hearing deficits include both conductive and sensorineural abnormalities. Seizures occur in infancy in more than two-thirds of patients but have two patterns of clinical outcome. One group of patients has a few seizures in infancy, with normal electroencephalograms (EEGs), that may receive transient therapy with anticonvulsants, but has no recurrence of the seizures at age >1 year (in our series, patients 1, 4, 8, and 10). The other group of patients also has infantile seizures, but these patients have abnormal EEGs and require anticonvulsants for treatment of chronic seizures (in our series, patients 5, 9, and 11–14).

Previous reports (Wargowski et al. 1991; Keppler-Noreuil et al. 1995) have suggested that the differences in the clinical phenotype of the patients with 1p36 deletions may be due to the effects of imprinted genes. However, since 10 of our 13 patients (77%) have deletions that arose on the maternal chromosome, we have no evidence for imprinted genes contributing to the phenotypic variability. In other words, in patients with a paternally inherited deletion there were no clinical features identified that were not also observed in individuals in whom the deletion was maternally derived, and vice versa. This is not to say that there cannot be imprinted loci in the deletion region that alter the probability or nature of the phenotype, since the current patient sample size may yet be too small to allow this to be detected.

FISH and molecular analyses have shown that the deletion size varies among the patients. It is conceivable that phenotypic variability, such as appears to be the case for the development of chronic seizures, may be due to dosage-sensitive genes that map to certain deletion intervals. The present sample size of 14 patients is yet too small for a formal analysis to assign the majority of features to specific deletion intervals. Other investigators have used panels of natural deletions or duplications to assign phenotypic features to the physical map, such as in Down syndrome (Korenberg et al. 1994), cri-du-chat syndrome (Church et al. 1995; Gersh et al. 1995), and Langer-Giedion syndrome (Ludecke et al. 1995). A similar approach should prove useful for molecular characterization of the distal 1p36 deletion phenotype and for ultimate isolation of genes implicated in this syndrome.

Acknowledgments

We are indebted to the clinical genetics and pediatric neurology physicians and fellows at Texas Children's Hospital, Baylor College of Medicine, and The University of Texas, Houston, who provided the initial medical evaluation of many of the patients described here and who submitted samples for cytogenetic analysis: Drs. Carlos Bacino, Claudia Benton, Chester Brown, Ian Butler, William Craigen, Marvin Fishman, Gisele Greenhaw, Jacqueline Hecht, Katherine Hegmann, Gail Herman, William Horton, Stefan Kochanek, Michael Levin, Avi Orr-Urtreger, Diana Rodriguez, Helen Ross, David Stockton, and Elaine Wendt. We thank Kay Atkins and Jill Johnston (Kleberg Cytogenetics Laboratory) and Wilbur Harrison (Hermann Hospital Cytogenetics Laboratory) for FISH analysis of the patients and their parents. We thank John Bargerstock and Stella Madu in the Mental Retardation Research Center tissue-culture core (Baylor College of Medicine) for establishing lymphoblastoid cell lines. We thank Dr. Peter S. White (Children's Hospital of Philadelphia) for providing information on marker order in distal 1p36, on the basis of radiation-hybrid mapping, and for useful discussions. We are grateful to the families for participating in these studies.

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