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Brachydactyly and Mental Retardation: An Albright Hereditary Osteodystrophy–like Syndrome Localized to 2q37

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Summary

We report five patients with a combination of brachymetaphalangia and mental retardation, similar to that observed in Albright hereditary osteodystrophy (AHO). Four patients had cytogenetically visible de novo deletions of chromosome 2q37. The fifth patient was cytogenetically normal and had normal bioactivity of the α subunit of Gs (Gsα), the protein that is defective in AHO. In this patient, we have used a combination of highly polymorphic molecular markers and FISH to demonstrate a microdeletion at 2q37. The common region of deletion overlap involves the most telomeric 2q marker, D2S125, and extends proximally for a maximum distance of 17.6 cM. We suggest this represents a consistent phenotype associated with some deletions at 2q37 and that genes important for skeletal and neurodevelopment lie within this region. Screening for deletions at this locus should be considered in individuals with brachymetaphalangia and mental retardation. Furthermore, 2q37 represents a candidate region for type E brachydactyly.

Introduction

The delineation of dysmorphic mental retardation syndromes on the basis of a constellation of physical and biochemical features has proved valuable in identifying individuals whose disorder has a common underlying etiology. In a number of these dysmorphic syndromes, the finding of patients with de novo cytogenetic abnormality has contributed to the localization and subsequent characterization of the underlying molecular genetic defect (Ewart et al. 1993; Reiner et al. 1993).

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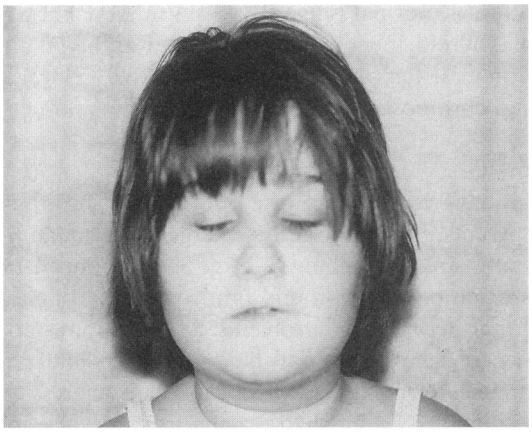
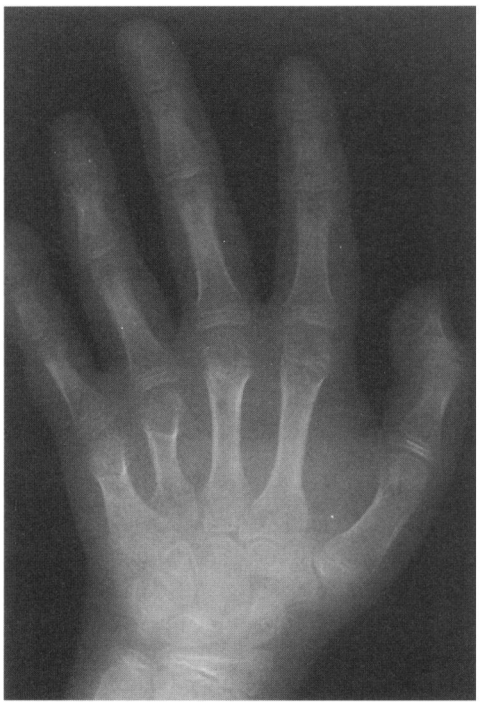
The physical feature *brachymetaphalangia* refers to shortening of either the metacarpals and phalanges of the hands or of the equivalent bones in the feet. The combination of brachymetaphalangia and mental retardation occurs in Albright hereditary osteodystrophy (AHO) (Albright et al. 1942), a dysmorphic syndrome that is also associated with cutaneous ossification (in ≤60% of cases [reviewed by Fitch 1982]); round face; and short, stocky build. Affected individuals with AHO may have either pseudohypoparathyroidism (PHP), with end organ resistance to parathyroid hormone (PTH) and certain other cAMP-dependent hormones, or pseudo-pseudohypoparathyroidism (PPHP), with normal hormone responsiveness (Albright et al. 1952). The molecular defect has been identified as a reduction in membrane levels of the α subunit of Gs (Gsα), which transduces signals between hormone receptors and adenylyl cyclase (reviewed by Schwindinger and Levine 1994). Deactivating mutations have been reported in the Gsα gene on chromosome 20q13 (Oude Luttikhuis et al. 1994).

As part of a study of individuals with AHO in the United Kingdom, we have identified a group of patients with many features of AHO but normal Gsα levels, indicating an alternative etiology. All have normal prometaphase karyotypes. Independently, four patients ascertained through the clinical genetics services in Newcastle and Leicester, because of mental retardation and dysmorphic features that included brachymetaphalangia, were found to have cytogenetically visible terminal 2q deletions. Furthermore, Phelan et al. (1993) recently reported two unrelated patients with terminal 2q deletions and AHO phenotypes. Because of this evidence of an emerging clinical grouping, we proceeded to characterize the molecular extent of our identified cytogenetic deletions and, in addition, screened our patients with AHO features and normal Gsα levels for submicroscopic deletions within this chromosomal region. In one, we have identified a maternally derived microdeletion, using markers that map to 2q37.3. The combination of clinical and molecular findings confirms that there is a specific AHO-like syndrome associated with some deletions of 2q37. Patients LC, JD, and CH have been previously described elsewhere (Oley et al. 1992).





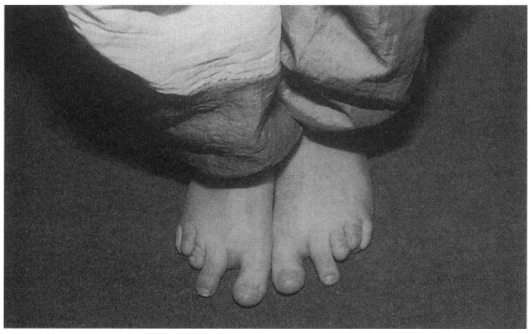


Figure 1 *Top,* KW at 12 years of age, showing round face, short neck, and small nose with low flattened nasal bridge. *Middle,* Plain radiograph of hand from KW at 12 years of age, illustrating both shortening of the distal phalanx of thumb and of fourth and fifth metacarpals and cone-shaped third metacarpal epiphysis. *Bottom,* Feet of KW, showing marked third- and fourth-metatarsal shortening.

Patients and Methods

Patient 1 (KW)

KW is a 12-year-old female, the first child of healthy unrelated parents, born by breech delivery at 36 wk gestation, weighing 2.34 kg, with Apgar scores of 5 at 1 min and 8 at 5 min. All developmental milestones were delayed, and she now attends a special school, with severe learning difficulties. She has had intermittent grand mal seizures from the age of 5 years, despite normocalcemia throughout. Electroencephalography was consistent with primary generalized epilepsy. A computed-tomography head scan showed narrowing of the front of the skull, with a degree of craniosynostosis. From the age of 7 years, she rapidly gained weight, while remaining short in stature. Her bone age at 10 years was delayed, assessed by carpal index as 8 years. She has a left amblyopia secondary to strabismus and astigmatism.

Presently, her height is 126 cm (<3d percentile), weight 36.4 kg (25th percentile), and occipitofrontal circumference (OFC) 50 cm (<3d percentile). She has a round face, with low, flattened nasal bridge and dental crowding but no cutaneous or intracranial calcification (fig. 1, *top*). She has shortened fourth and fifth metacarpals with overlying knuckle dimples and shortened terminal phalanges (fig. 1, *middle*). Her feet are small and broad, with marked shortening of the third and fourth metatarsals (fig. 1, *bottom*). She has a moderately severe lumbar lordosis.

Investigations revealed that plasma calcium, phosphate, urea, creatinine, magnesium, vitamin D, and intact PTH were all within normal limits, as were thyroid function, thyrotropin-releasing hormone, and luteinizing-hormone-releasing-hormone (LHRH) tests. Response to exogenous PTH was normal, with a 90-fold rise in urinary cAMP/creatinine. Gsα levels, the average from two separate assays, were 90%, 125%, and 99% of a healthy unrelated control, in the patient, father, and mother, respectively. Chromosomes were 46,XX normal female, with no visible deletion on 2q on prometaphase spreads.

Patient 2 (LC)

LC is a 12-year-old boy, born to healthy unrelated parents after a normal pregnancy and delivery, weighing 3.5 kg. All developmental milestones were delayed, and he now attends a special school, with moderate learning difficulties. He had surgery for strabismus at age 12 years. Flexural eczema and sparse white hair were present from birth, with subsequent intermittent hair loss and total scalp alopecia from 5 years of age. There is a paternal history of atopy.

Presently, he is prepubertal, with a height of 149.5 cm (50th percentile), weight 56.8 kg (97th percentile), and OFC 53 cm (25th–50th percentile). He has no scalp hair and sparse eyebrows and eyelashes, but his nails, teeth, and sweating are normal. He has a round face, prominent ears with large fleshy lobes, prominent columella, bilaterally

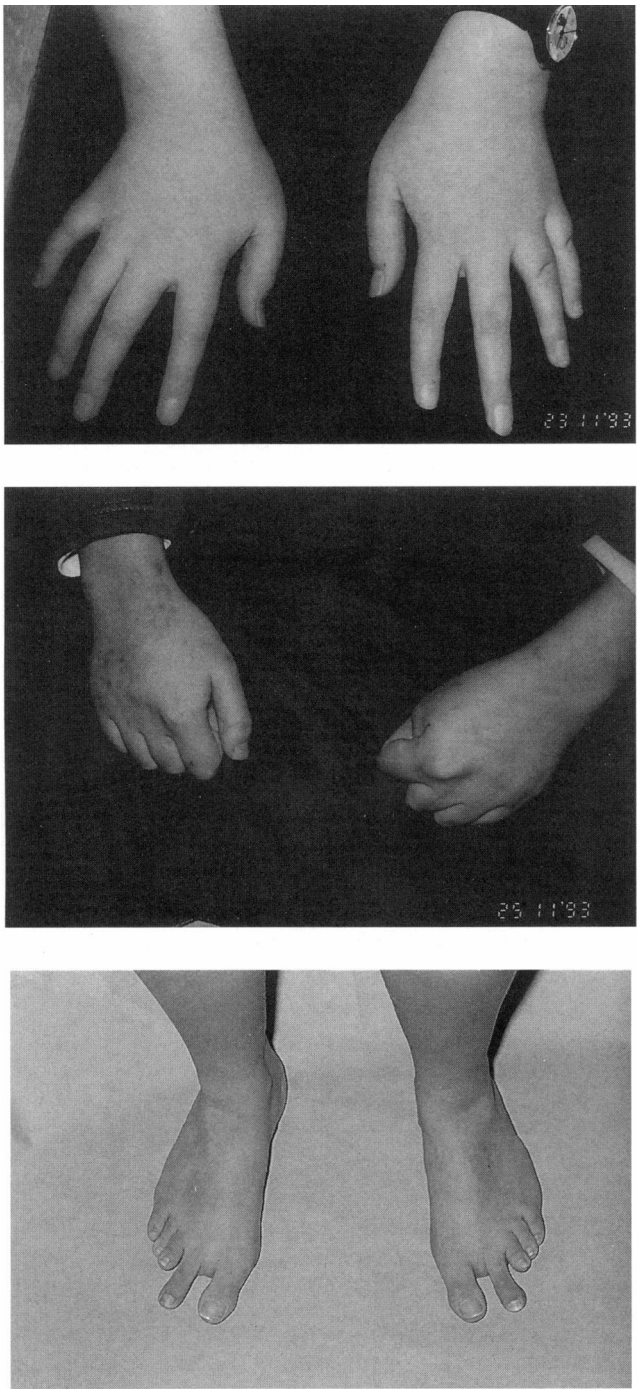


Figure 2 *Top,* Hands of LC, demonstrating shortening of the fourth and fifth metacarpals and proximally placed thumbs. *Middle,* Fist of JD, illustrating knuckle dimples overlying the shortened third, fourth, and fifth metacarpals and the short distal phalanx of the thumb. *Bottom,* Feet of RA, showing marked third-, fourth-, and fifth-metatarsal shortening.

shortened fourth and fifth metacarpals (fig. 2, *top*), proximally placed thumbs, and small feet with short fourth and fifth toes.

Plasma calcium, albumin, urea, and creatinine were within normal limits, while phosphate was slightly raised, at 1.68 mM (normal range 0.8–1.44 mM). PTH was not tested. Thyroid function was normal. Karyotype analysis on peripheral lymphocytes was 46,XY,del (2)(q37), and parental chromosomes were normal.

Patient 3 (JD)

JD is a 14-year-old girl, the only child of healthy unrelated parents, born at term by emergency cesarean section for fetal distress, weighing 3.4 kg. She responded rapidly to resuscitation for profound bradycardia and apnea and had no further neonatal problems. All developmental milestones were delayed. She now has moderate mental retardation and major behavioral problems with aggression and self-mutilation. She has had eczema from infancy and has slow-growing fine scalp hair. Pubertal development has been normal.

Presently, her height is 150 cm (10th percentile), weight 50 kg (25th–50th percentile), and OFC 54 cm (50th percentile). She has a mild left ptosis, upslanting palpebral fissures, frontal bossing, prominent columella, and prominent large ears with fleshy earlobes. She has marked shortening of the third, fourth, and fifth metacarpals (fig.2, *middle*) and third and fourth metatarsals bilaterally. Skeletal survey showed a thoracic kyphoscoliosis and bilateral coxa valga.

Investigation revealed normal renal function, corrected plasma calcium, phosphate, and intact PTH. Routine chromosomal analysis showed an abnormal 46,XX,del (2)(q37) karyotype. Parental chromosomes were normal.

Patient 4 (CH)

CH is a 20-year-old female, the youngest of three children, born uneventfully to healthy unrelated parents and weighing 4.09 kg. Severe eczema was present from the neonatal period. Developmental milestones were delayed, and poor height and weight gain were noted. Skeletal survey at this time showed a slightly advanced bone age, some epiphyseal irregularity, and flattened vertebrae T12 and L1 with anterior beaking.

Between 12 and 17 years of age, she received growth hormone for short stature, with an initial improvement in growth velocity. Detailed endocrine assessment at 20 years of age confirmed growth hormone deficiency, with maximal levels of 2.3 mU/L during insulin-induced hypoglycemia but a normal cortisol response. Thyroid function has remained normal. Menarche occurred at 14 years of age but with amenorrhea for the last 4 years. Gonadotrophin response to LHRH was normal but with undetectable estradiol and progesterone. Pelvic ultrasound demonstrated a small uterus, and the left ovary was visualized. Plasma calcium, phosphate, urea, creatinine, and intact PTH were all normal.

At 20 years of age, she has moderate learning difficulties. Her height is 139.7 cm (<3d percentile), weight 50 kg (10th–25th percentile), and OFC 54 cm (25th percentile).

She has very fine scalp hair, sparse eyebrows and lashes, flexural eczema, keratoconus, and minimal development of secondary sexual characteristics. Her face is round, with a beaked nose, prominent columella, and low-set prominent ears with fleshy earlobes. She has shortening of the first, fourth, and fifth metacarpals and of the first metatarsal, fourth, and fifth toes and a hypoplastic left ulna. Blood chromosome analysis showed 46,XX,del (2)(q37.1), while parental chromosomes were normal.

Patient 5 (RA)

RA is a 15-year-old girl, the first child of healthy unrelated parents, born at 36 wk gestation, following a normal pregnancy and delivery, weighing 2.45 kg. Bilateral dislocating hips associated with acetabular dysplasia were noted soon after birth. Other skeletal abnormalities include dislocated radial heads, bowing of the radius and ulna, mild lumbar scoliosis, and joint laxity at the wrists, fingers, knees, and ankles. Additional findings on skeletal survey are mild dysplasia of the distal femoral epiphyses, metacarpal and metatarsal shortening, and a normal bone age. Dentition is normal, and there in no skin laxity. Myopia and an alternating divergent squint were noted at 2 years of age, but fundal examinations have been normal. Menarche was at 14 years of age. Developmental milestones were mildly delayed, and she currently attends a special school, with moderate learning difficulties. Her mother has myopia and short stature but no skeletal abnormalities.

Presently, her height is 135.6 cm (<3d percentile), weight 35.2 kg (<3d percentile), and OFC 53.2 cm (10th percentile). She has frontal bossing, deep set eyes, a flat midface, mild micrognathia, and prominent upper lip. Secondary sexual characteristics are normal. She has bilateral shortening of the third through fifth metacarpals, with knuckle dimples, and shortening of the third through fifth metatarsals and toes. Excoriated eczematous lesions were noted over the dorsum of hands and flexural surfaces. Metabolic investigations, including serum calcium, were normal. Karyotyping of cultured lymphocytes showed 46,XX,del(2) (q37.2 or q37.3). Parental chromosomes were normal. The clinical features of these patients are summarized in table 1.

Measurement of Gsα Bioactivity

Between 2 and 5 ml of venous blood in citrate anticoagulant were frozen on dry ice and stored at −70°C. Measurement of erythrocyte Gsα bioactivity was by cyc-reconstitution assay, as described by Bourne et al. (1983), and membranes were provided by Dr. C. Van Dop. Purification of [^{32}P]cAMP was as described by Salomon et al. (1974), using Dowex Alumina chromatography and [^{3}H]cAMP to monitor recovery. Sample eluates were counted in 8 ml of scintillation fluid (Universol ES), in a dual channel scintillation counter. Values are the mean of duplicates, corrected for cAMP recovery and expressed as a percentage of the [^{32}P]cAMP production in a concurrent sample from an unrelated healthy control.

Genetic Marker Studies

Genomic DNA from patients and their parents was prepared from peripheral blood lymphocytes or lymphoblastoid cell lines by standard methods. Markers CEB11, D2S3, and D2S90 (CEB1) were typed by Southern analysis of unamplified DNA digested with *Msp*I or *Hin*fI (D2S90 and CEB11) or with *Pst*I (D2S3), using standard methods. D2S90 was additionally typed by Southern analysis of PCR product made by 23 cycles of amplification in a reaction volume of 22 μl containing 200 ng of genomic DNA, 1 μM each of forward and reverse primers, and 45 mM Tris HCl (pH 8.8); 11 mM ammonium sulphate; 4.5 mM $MgCl_2$; 6.7 mM 2-mercaptoethanol; 4.4 μM EDTA (pH 8.0); 1 mM each of dATP, dCTP, dGTP, dTTP; 113 μg of BSA/ml; and 1 U of *Taq* polymerase. Primer sequences were as follows: forward, 5′ GGT CTA GAG CTC TGC TGA GTC AGA GTC AGC CAG 3′ (Buard and Vergnaud 1994); and reverse, 5′ GGC CTT CTC CCT GTA ACC AGT TAC 3′ (J. Buard, personal communication), and annealing temperature was 68°C.

Dinucleotide repeats AFM259yc9 (D2S206), AFM182ya5 (D2S140) and AFM356te5 (D2S395), AFM275yf5 (D2S336), AFM269yd9 (D2S331), and AFM112yd4 (D2S125) were amplified by PCR, using standard methods. Primer sequences were as described by Gyapay et al. (1994), and annealing temperatures were as follows: AFM259yc9, 53°C; AFM182ya5, 56°C; AFM356te5, 62°C; AFM275yf5 and AFM269yd9, 60°C; and AFM112yd4, 55°C. Samples were mixed with an equal volume of formamide denaturing buffer (95% formamide, 20 mM EDTA, and 0.05% each of bromophenol blue and xylene cyanol FF), were denatured, and were run on a 6% acrylamide (19:1 acrylamide:bisacrylamide) gel containing 1 × Tris-borate EDTA and 8 M urea. PCR products were visualized by incorporation of α-[^{32}P] dCTP and autoradiography or by silver staining of unlabeled products. A deletion was scored if no allele from one parent was seen in the proband. Band intensities were not scored for dosage.

FISH Using D2S90/CEB11 in KW

Metaphases were prepared from a lymphoblastoid cell line, by standard methods. The cosmid CEB1 (containing the VNTR at D2S90) was labeled with biotin-11-dUTP by nick-translation using a concentration of DNAase I sufficient to produce labeled fragments 300–600 bp in length (Buckle and Rack 1993). One hundred nanograms of conjugated probe and 2.5 μg of competitor DNA were denatured in hybridization mix for 5 min at 95°C and preannealed for 10 min at 37°C. Slides were denatured at 70°C in 70% formamide and 2 × SSC, were washed in 2 × SSC, and were dehydrated through an alcohol series. Hybridization was carried out at 42°C overnight, and the

Table 1

Summary of Clinical Features and Comparison among Subjects with AHO

AHO Characteristic	KW (12)	LC (12)	JD (14)	CH (20)	RA (15)
Short stature	+	–	–	+	+
Stocky build	+	+	+	+	–
Mild/moderate MR	+	+	+	+	+
Soft-tissue ossification	–	–	–	–	–
Brachymetaphalangia	+	+	+	+	+
Seizures	+	–	–	–	–
Endocrine:					
PHP: resitance to PTH and other hormones	–	–	–	–	–
PPHP: normal endocrine responses	+	+	+	Deficient growth hormone, estradiol, and progesterone	+
Other	Strabismus	Eczema, fine hair, self-mutilation, thoracic kyphoscoliosis, coxa valga	Strabismus, eczema, sparse hair, alopecia, proximally placed thumbs	Eczema, sparse hair, hypoplastic ulna, keratoconus,	Congenital dislocating hips, dislocated radial heads, bowed radius and ulna, joint laxity, myopia, strabismus

NOTE.—Subject ages (in years) are given in parentheses. A plus sign (+) indicates that a subject is positive for a characteristic, and a minus sign (–) indicates that a subject is negative for a characteristic.

slides were then washed in 2 × SSC for 10 min and in 0.1 × SSC for 40 min. Probes were detected by alternate layers of fluorescein isothiocyanate–conjugated avidin (5 μg/ml; Vector Laboratories) and biotinylated anti-avidin (5 μg/ml; Vector Laboratories). After a final wash in PBS, the slides were counterstained in antifade (Vector Laboratories) containing 0.5 μg of propidium iodide/ml. A confocal laser microscope (Biorad MRC 600) was used for image collection and analysis.

Results

Analysis of Microsatellite Markers

A total of 13 polymorphic markers mapping within 2q37 were analyzed, and the results are summarized in figure 3,

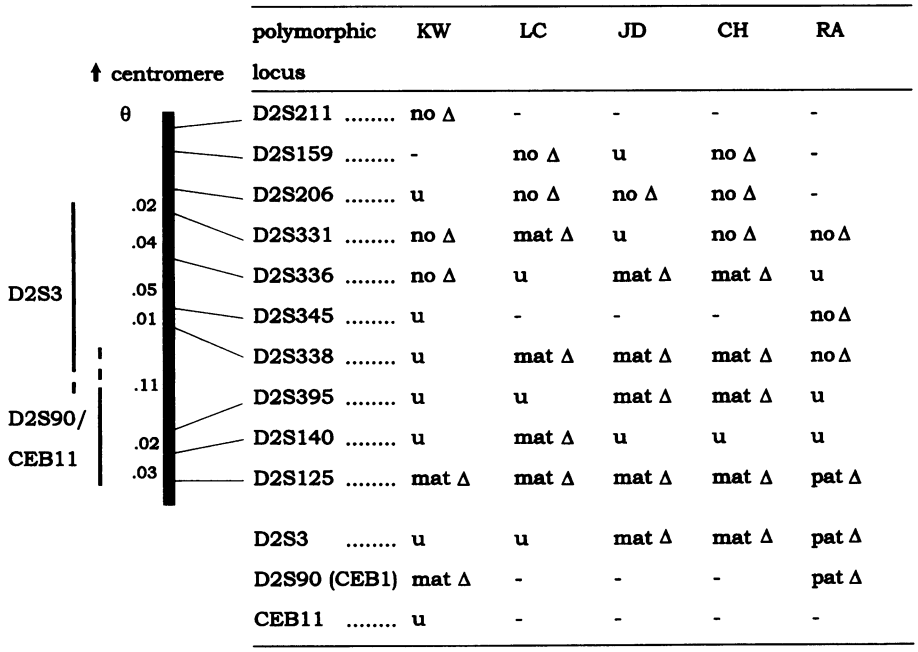


Figure 3 Summary of results from analysis of 2q polymorphic markers, with a representation of current ordering and recombination distances between microsatellite loci (Gyapay et al. 1994). Current ordering for D2S90/CEB11 and D2S3 is tel–D2S125–D2S140–D2S90/CEB11–D2S3–D2S206–cen (Third Chromosome 2 Workshop, 1994), but linkage relationships with the remaining microsatellites within this region are not known. A dash (–) indicates the locus was not analyzed, and "u" indicates uninformative analyses. Maternal and paternally derived deletions are represented by "mat Δ" and "pat Δ," respectively.

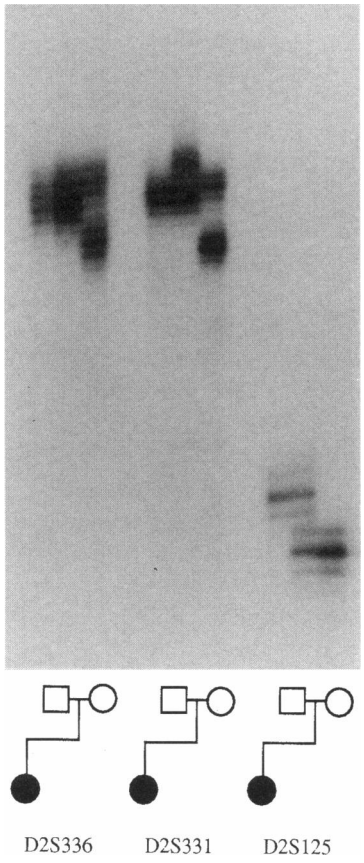


Figure 4 Microsatellite analyses at three loci in KW and parents. KW is heterozygous at D2S336 and D2S331 but has no maternally derived allele at D2S125, consistent with a maternal deletion at this locus.

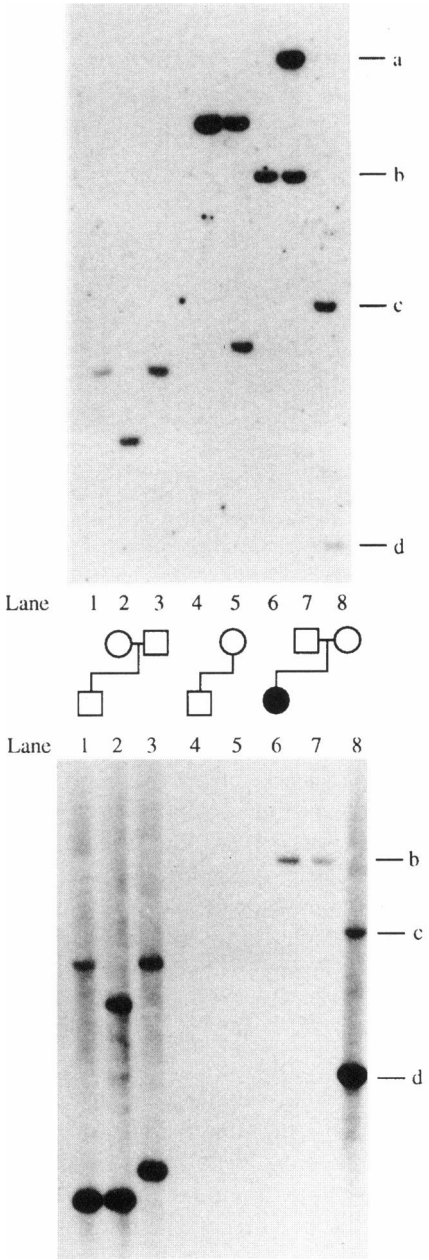


Figure 5 Analyses at D2S90 in KW (lanes 6–8) and two unrelated families. *Upper panel,* Southern analysis of genomic DNA digested with *Hin*fI, demonstrating heterozygosity in both parents (father ab, mother cd) but a single paternally derived allele, b, in KW. *Lower panel,* Southern analysis of products of PCR amplification across D2S90 in the same individuals, excluding the presence of a mutated small allele at this locus in KW.

which summarizes the data and shows current ordering of the markers analyzed (Gyapay et al. 1994). All five patients have overlapping deletions within 2q37. Four have maternal deletions, and paternity therefore has not been tested. In patient RA, paternity has been confirmed by analysis at nine independent microsatellite loci. D2S338 marks the centromeric boundary of the common region of deletion. The proximal extent of the deletion cannot presently be defined for KW, within the 22-cM region between D2S125 and D2S336 (fig. 4). Similarly, no informative marker telomeric to D2S90 and D2S125 has yet been found.

Analysis of D2S90 in KW

Both parents were heterozygous for alleles at D2S90; however, only a single paternally derived allele was detected in KW. Owing to the high mutation rate at this locus (15% in sperm, 0.4% in ova [Vergnaud et al. 1991]), the presence of a small allele undetected by Southern analysis was excluded by PCR amplification across the repeat (fig. 5). This confirmed the presence of a single paternally derived allele. To exclude both uniparental isodisomy and mutation of the maternal allele to a size indistinguishable from the paternal allele, FISH using D2S90 was performed (fig. 6), which confirmed the deletion of this locus in 25/25 cells examined.

Discussion

We report five unrelated patients with overlapping deletions, involving chromosome 2q37, in whom the salient

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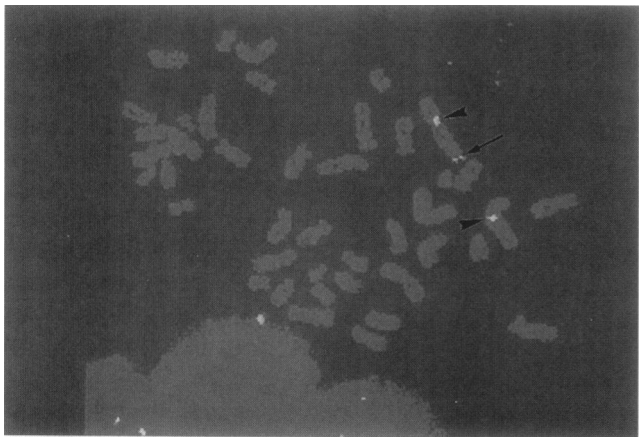

Figure 6 FISH using the D2S90 cosmid and a chromosome 2 centromere probe to metaphase chromosomes from KW. Fluorescent signals are present on both chromosome 2 centromeres (*arrow heads*). Signals from the D2S90 probe are present on only one chromosome 2 (*arrow*).

consistent clinical features are brachymetaphalangia and mental retardation. In four, cytogenetic deletions had been detected. In KW, despite the absence of cytogenetic abnormality, we were prompted to search for microdeletions at 2q37, by her AHO phenotype with normal erythroctye Gsα levels, rendering the Gsα locus on 20q13 unlikely to be of etiological importance. The deletion in KW is the only 2q37 microdeletion described to date. It is not as yet possible to determine whether this represents an interstitial deletion or a healing of a terminal deletion through telomere repair or capture. The minimum region of deletion overlap in our five patients involves D2S125, the most telomeric 2q marker described, and extends proximally for a maximum distance of 17.6 cM.

Our patients and those in the preliminary report by Phelan et al. (1993) have, in common, metacarpal and metatarsal shortening, moderate mental retardation, short stature, round faces, short necks, and shortened noses with flat nasal bridges. Neither our patients nor, apparently, those of Phelan et al. manifested any endocrine abnormality compatible with PHP. Taken together, these data suggest that a gene(s) important for skeletal morphogenesis and neurodevelopment lies within the region identified in this study. The possibility exists that protein(s) encoded by genes at 2q37 act through a Gsα-transduced pathway. This may result in the phenotypic similarity to Gsα-deficient AHO, but without hormone resistance, since other Gsα-transduced pathways would remain intact. It is noteworthy therefore that the gene for one G-protein–coupled receptor, human RDC1 (GPRN1), has been mapped to 2q37 (Libert et al. 1991). Alternatively, the phenotypic abnormalities may result from haploinsufficiency for developmental genes acting through an unrelated pathway—for example, the homeobox gene GBX2, which has recently been mapped to 2q37 (Matsui et al. 1993).

Eight children with isolated deletions involving 2q37 have been reported elsewhere (Young et al. 1983; Sanchez and Pantano 1984; Gorski et al. 1989; Coldwell et al. 1992; Lin et al. 1992; Stein et al. 1992; Waters et al. 1993; Wang et al. 1994). The oldest, at 8 years, had certain features in common with our patients—namely, seizures, small nose with depressed nasal bridge, and developmental delay—but no brachymetaphalangia was noted (Stein et al. 1992). Of the remainder, the oldest was 4 years 10 mo (Lin et al. 1992). This child was described as having small hands and feet. Another child, at 9 mo of age, was said to have hypoplastic second phalanges of the fingers and a hypoplastic first phalanx of the big toe (Sanchez and Pantano 1984). Metacarpal and metatarsal shortening was not described; however, in AHO, these clinical features have been shown to evolve with age, because of both reduced longitudinal growth and premature epiphyseal fusion, and thus such features may not be apparent in young children. Three of the reported cases had cutaneous syndactyly (Young et al. 1983; Sanchez and Pantano, 1984; Wang et al. 1994), as has been described in several children with more centromeric distal 2q deletions (reviewed by Ramer et al. 1989). Syndactyly was not present in any of the patients we describe; however, an additional feature noted in all four of our cytogenetic deletion cases was that of cutaneous eczema, also recorded in the report by Gorski et al. (1989) of a 21-mo-old boy with 46,XY,del(2q37).

Other conditions in which brachymetaphalangia is a major feature include brachydactyly type E and acrodysostosis, both of which may be difficult to distinguish from PPHP and have been suggested to belong to the same disease spectrum (Ablow et al. 1977; Poznanski et al. 1977). In type E brachydactyly, short stature may also be present. In acrodysostosis, cutaneous ossification is absent, metacarpal shortening is usually more generalized, and nasal hypoplasia is more severe. We are not aware that Gsα levels have been measured in such patients. Clearly, 2q37 is an alternative candidate region for these disease loci.

We now suggest there are three groups of patients in whom cytogenetic and molecular investigation of 2q37 may be valuable: those with brachymetaphalangia and mental retardation; those with the AHO phenotype but normal Gsα levels; and those with type E brachydactyly or acrodysostosis. Further studies of these three groups are now indicated and may help to define the critical region of 2q37, as well as the range of clinical manifestations of this new chromosomal deletion syndrome.

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