Autosomal Dominant Postaxial Polydactyly, Nail Dystrophy, and Dental Abnormalities Map to Chromosome 4p16, in the Region Containing the Ellis–van Creveld Syndrome Locus

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Summary

We have studied a four-generation family with features of Weyers acrofacial dysostosis, in which the proband has a more severe phenotype, resembling Ellis–van Creveld syndrome. Weyers acrofacial dysostosis is an autosomal dominant condition with dental anomalies, nail dystrophy, postaxial polydactyly, and mild short stature. Ellis–van Creveld syndrome is a similar condition, with autosomal recessive inheritance and the additional features of disproportionate dwarfism, thoracic dysplasia, and congenital heart disease. Linkage and haplotype analysis determined that the disease locus in this pedigree resides on chromosome 4p16, distal to the genetic marker *D4S3007* and within a 17-cM region flanking the genetic locus *D4S2366*. This region includes the Ellis–van Creveld syndrome locus, which previously was reported to map within a 3-cM region between genetic markers *D4S2957* and *D4S827*. Either the genes for the condition in our family and for Ellis–van Creveld syndrome are near one another or these two conditions are allelic with mutations in the same gene. These data also raise the possibility that Weyers acrofacial dysostosis is the heterozygous expression of a mutation that, in homozygous form, causes the autosomal recessive disorder Ellis–van Creveld syndrome.

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Introduction

Weyers acrofacial dysostosis (Curry-Hall syndrome; OMIM 193530 [http://www.ncbi.nlm.nih.gov/Omim/]) is an autosomal dominant condition characterized by hypotelorism, an abnormal mandible, incisors abnormal in shape and number, a single central incisor, conical teeth, postaxial polydactyly type A or type B, hypoplastic or dysplastic nails, and short stature. It was first reported in three unrelated cases (Weyers 1952), and three additional families have since been described (Curry and Hall 1979; Roubicek and Spranger 1984; Shapiro et al. 1984).

Ellis–van Creveld syndrome (OMIM 225500 [http://www.ncbi.nlm.nih.gov/Omim/]) (Ellis and van Creveld 1940) is a rare autosomal recessive disproportionate dwarfism that is most prevalent in the Amish population (McKusick et al. 1964). It is characterized by lip defects (oral frenula), dental abnormalities (neonatal teeth, hypodontia, and premature tooth loss), cardiac malformations (atrial septal defect and single atrium), genitourinary anomalies (epispadias and hypospadias), skeletal abnormalities (postaxial polydactyly type A, brachydactyly, fusion of the capitate and hamate, genu valgum, and distal limb shortening), and nail dysplasia (McKusick et al. 1964; Biggerstaff and Mazaheri 1968; Taylor et al. 1984). Weyers acrofacial dysostosis has some features in common with, but is distinct from, Ellis–van Creveld syndrome (table 1) (Gorlin et al. 1990, pp. 201–204). The two syndromes are dissimilar in mode of inheritance and phenotypic severity.

Linkage analysis of 12 families with Ellis–van Creveld syndrome previously mapped the locus to a 3-cM region between the genetic loci *D4S2957* and *D4S827* on chromosome 4p16.1 (Polymeropoulos et al. 1996). The maximum two-point LOD score (Z_{max}) observed was 6.91 (recombination fraction [θ] of .02) with a genetic marker for the *MSX1* homeobox gene. Subsequent sequencing of both *MSX1* exons in two patients and one obligate carrier of Ellis–van Creveld syndrome ruled out the pos-

Table 1

Phenotype of the Family and Related Syndromes

	Proband (IV:4)	Other Affected Family Members	Ellis–van Creveld Syndrome	Jeune Asphyxiating Thoracic Dysplasia	Weyers Acrofacial Dysostosis
Short stature	+	Mild	+	Mild	Mild
Abnormal frenula	+	+	+	−	+
Natal teeth	−	−	+	−	−
Hypodontia	+	+	+	−	+
Conical teeth	+	+	+	?	+
Mandibular anomalies	−	−	−	−	+/−
Retinal degeneration	−	−	−	+	−
Postaxial polydactyly	Hands and feet	Hands and feet	Hands; sometimes feet	+/−; if present, usually hands and feet	Hands and/or feet
Onychodystrophy	+	+	+	−	+
Thoracic dysplasia	+	−	+	+	−
Cardiac findings	Patent ductus arteriosus, ventricular septal defect	−	Atrial septal defect, atrioventricular septal anomaly	−	−
Hepatic/pancreatic abnormalities	−	−	−	+	−
Renal abnormality	−	−	−	+	−
Radiological findings	Flat acetabular roof with pointed pelvic prominence	−	Fifth carpal in distal row of wrist, multiple ossification centers in hamate, flat acetabular roof with pointed pelvic prominence	Flat acetabular roof with pointed pelvic prominence	−
Lethal in newborns	−	−	+/−	Often	−
Inheritance	?	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal dominant
Chromosomal linkage	4p16	4p16	4p16	?	4p16?

NOTE.—A plus sign (+) indicates present; a minus sign (−) indicates absent; a plus/minus sign (+/−) indicates sometimes present; and a question mark (?) indicates unknown.

sibility that mutations in the coding region are causative of this condition (Ide et al. 1996).

It has been suggested that isolated postaxial polydactyly, which occurs in these two conditions, may be a heterozygous manifestation of Ellis–van Creveld syndrome (Fryns 1991; Goldblatt et al. 1992). Another similar condition with postaxial polydactyly as a clinical feature is Jeune syndrome (OMIM 208500 [http://www.ncbi.nlm.nih.gov/Omim/]) (Jeune et al. 1955; Pirnar and Neuhauser 1966; Langer 1969). The pelvis and limbs are similar in Ellis–van Creveld and Jeune syndromes, but nail dystrophy, abnormal frenula, and cardiac abnormalities are not found in the latter condition. In addition, renal involvement is a frequent feature of Jeune syndrome and is not found in Ellis–van Creveld syndrome. Postaxial polydactyly also has been observed to segregate as a single trait. Linkage of an autosomal dominant form of postaxial polydactyly type A to chromosome 7p15-q11.23 recently was reported in a five-generation Indian family with no other clinical findings (Radhakrishna et al. 1997).

We have studied a family in which one individual (the proband) had findings that are most typical of Ellis–van Creveld syndrome. The paternal relatives, however, presented with postaxial polydactyly, short stature relative to unaffected sibs, and tooth abnormalities segregating in an autosomal dominant manner. These findings are similar to those reported for Weyers acrofacial dysostosis (Curry and Hall 1979; Roubicek and Spranger 1984; Shapiro et al. 1984). We performed linkage analysis of this condition and mapped it to chromosome 4p16 in a region that encompasses the locus for Ellis–van Creveld syndrome.

Patients and Methods

Patient Population

Genomic DNA was isolated from blood samples or lymphoblast cultures from 19 available family members, by use of the Blood and Cell Culture DNA kit (Qiagen). All these family members were examined clinically by one of the authors (A.E.G.).

Case Presentation

The proband (fig. 1; individual IV:4 in fig. 2) was the 7-lb 8-oz male product of an uncomplicated term pregnancy of a 29-year-old mother and her nonconsanguineous 28-year-old husband. The initial physical examination of the newborn was significant for a narrow chest, four-extremity postaxial polydactyly type A, short limbs, and swelling secondary to forceps delivery because of face presentation. As this swelling receded, examination of the upper lip revealed multiple frenula with shallow sulcus. Neonatal cardiology evaluation demonstrated a large patent ductus arteriosus that closed spontaneously at age 5 d and a small muscular ventricular septal defect. Radiographs were remarkable for short ribs and a flat acetabular roof with pointed pelvic prominence.

The proband was ventilator dependent for the first month of life but otherwise had an uncomplicated newborn course. He remained on oxygen supplementation by nasal cannula until 10 mo of age. At ~2 mo of age, the proband developed a hemangioma over the left chest that began to involute after his first birthday. By ~3 years of age, his fingernails and toenails had become dystrophic. He has decreased range of motion of the distal interphalangeal joints of his hands, and his thumbs appear to be mildly digitalized. Dental evaluation has revealed a number of symmetrically absent primary teeth and dental pitting. Renal evaluation demonstrated no structural or functional abnormalities. He generally has enjoyed excellent health and normal development. Height has been at slightly below but paralleling the 5th percentile, weight has been at approximately the 10th percentile, and head circumference has been at the 25th–50th percentile.

The proband's father has a history of postaxial polydactyly type A, radial fifth-digit clinodactyly, and onychodystrophy, as do at least seven other of the father's relatives (see fig. 2). Chromosome analysis was performed on the affected father (III:8 in fig. 2) and revealed a normal 46,XY karyotype. In the affected individuals, the polydactyly involves all four extremities, with the extra digits on the feet usually more fully formed than those on the hands. The individuals also may be slightly shorter in stature than their sibs. For instance, the proband's father (III:8) is 5 feet 9 inches tall, and his affected brothers are 5 feet 8 inches (III:4) and 5 feet 11 inches (III:6), whereas their unaffected brothers are 6 feet 2 inches (III:2) and 6 feet 4 inches (III:3) and their unaffected sister (III:1) is 5 feet 11 inches. Some of these affected individuals have unusual labial frenula or shallow labial sulci. Several, but not all, of the affected family members have had dental abnormalities: the paternal great-aunt (II:4) is reported to have conical-shaped teeth; the proband's father (III:8) has tooth agenesis; a paternal uncle (III:4) had a pear-shaped tooth that was removed; and a first cousin (IV:2) has bilateral fusion of primary mandibular canine and lateral incisors and several conical-shaped primary teeth. The same cousin also has a prominent raphe extending over the middle of her philtrum, from vermilion border to nasal root. The family history includes the proband's mother (III:9) being 5 feet 6 inches tall and having a history of urinary reflux. Her family's history is negative for short stature, polydactyly, onychodystrophy, congenital heart disease, or dental abnormalities.

PCR Amplification and Sequence Analysis

For the nine genetic markers listed in table 2, PCR was performed with DNA from each family member, in 10-μl reactions consisting of 100 ng genomic DNA, 50 mM KCl, 10 mM Tris-HCl, 200 μM each dNTP, 1.5 mM $MgCl_2$, 0.1 mg BSA/ml, 0.6 μmol each primer, 5–10 ng one $\gamma[^{32}P]$-dATP end-labeled primer, and 1.0 U *Taq* DNA polymerase (Boehringer Mannheim). Amplification parameters were as follows: 3 min at 94°C; 10 cycles of 40 s at 94°C, 40 s at the annealing temperature, and 40 s at 72°C; followed by 15 cycles of 40 s at 92°C, 40 s at the annealing temperature, and 40 s at 72°C; and a final extension of 3 min at 72°C. The annealing temperature for each genetic marker was as described in the Genome Database (http://www.gdb.org/), with the exceptions that the temperature for *D4S827* was increased from 62°C to 65°C and that for *D4S412* was decreased from 55°C to 50°C. The PCR products were separated on a 6.0% polyacrylamide sequencing gel and were detected by autoradiography.

The *MSX1* gene was sequenced by, first, amplification of both exons with two sets of PCR primers derived from the published sequence (Hewitt et al. 1991). To amplify exon 1, the forward primer 5′-CTGCTGACATGACTTCTTTGC-3′ and the reverse primer 5′-TGGGTTCTGGCTACTACCTG-3′, which amplify a 477-bp fragment, were used. PCR reactions for exon 1 were performed in 50-μl volumes consisting of 100–500 ng genomic DNA, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 200 μM each dNTP, 0.5 μM each primer, 5% dimethyl sulfoxide, and 1.25 U *Taq* DNA polymerase (Boehringer Mannheim). PCR parameters were 35 cycles of 1 min at 94°C, 1 min at 60°C, and 1 min at 72°C. Exon 2 was amplified with the forward primer 5′-GGCTGATCATGCTCCAATGCTT-3′ and the reverse primer 5′-TACAGCACCAGGGCTGGAGG-3′, yielding a 561-bp fragment. PCR reactions were performed as described for exon 1, with cycling parameters of 1 min at 95°C, 1 min at 66°C, and 2 min at 72°C. PCR products were run on 2% NuSieve gels (FMC BioProducts) and were extracted. The DNA, isolated with the Gel Extraction Kit (Qiagen), was directly se-

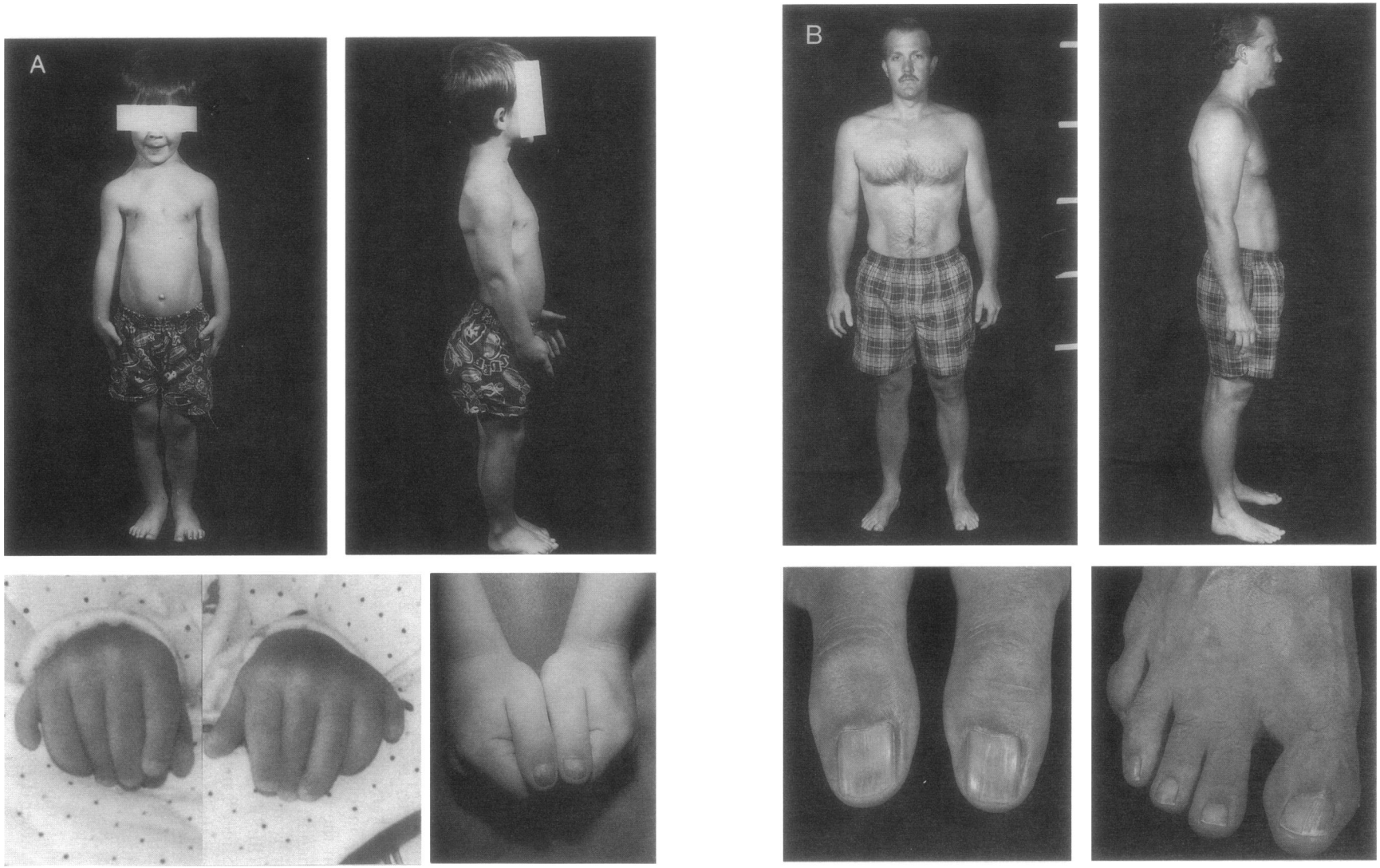

Figure 1 Clinical photographs of affected family members. *A*, Proband (IV:4 in fig. 2), front and lateral view. Note the short stature, abnormal configuration of the chest, hands with nail dysplasia of the thumbs (*bottom right*), and postaxial polydactyly in infancy (*bottom left*). *B*, Father of the proband (III:8 in fig. 2), front and lateral view. Note the proportional stature, normal chest, and onychodystrophy. His postaxial polydactyly had been surgically removed.

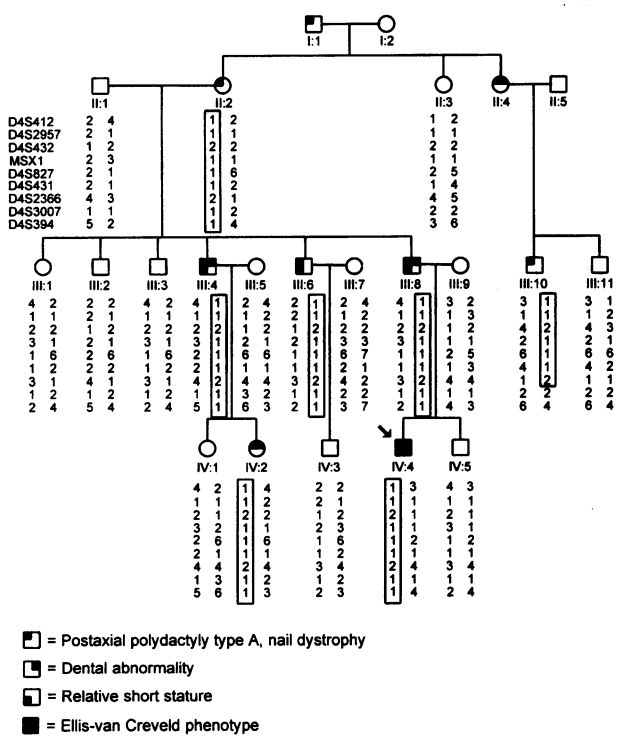

Figure 2 Linkage- and haplotype-analysis data for the studied family with features of Weyers acrofacial dysostosis and Ellis–van Creveld syndrome. For each individual evaluated, the alleles for the genetic markers are given below the symbol; individuals without assigned alleles were not available for analysis. The proband is indicated with an arrow. The boxed areas include the alleles that are either certainly or possibly inherited from an affected parent and show the largest possible region in which the disease locus may lie.

quenced by the Johns Hopkins Genetic Resources Core Facility, by use of the specific PCR primers.

Linkage and Haplotype Analysis

Nine genetic markers, spanning 10 cM (Polymeropoulos et al. 1996), were used for linkage analysis (table 2). The ILINK and MLINK options of the LINKAGE software package (version 5.1) (Ott 1991) were used to calculate LOD scores by use of an IBM personal computer. The disease was modeled as an autosomal dominant, fully penetrant disorder. The allele frequencies for each marker were set as equal. For the haplotype analysis, the order of the genetic markers was determined from the publicly available YAC physical map from the Stanford University Genome Center (ftp://shgc.stanford.edu/pub/hgmc/YAC_data) and from the order described elsewhere (Polymeropoulos et al. 1996).

Results

Phenotype of Family Members

As table 1 indicates, the proband and a number of his paternal relatives have features similar to those observed in Weyers acrofacial dysostosis, Ellis–van Creveld syndrome, and Jeune syndrome. Of these conditions, the proband most closely fits Ellis–van Creveld syndrome, on the basis of his short stature, four-extremity postaxial polydactyly type A, dystrophic nails, abnormal labial frenula and sulcus, hypodontia with poor enamel, thoracic dysplasia, congenital heart disease, neonatal pelvic x-ray significant for flat acetabular roof with pointed pelvic prominence, and survival postinfancy. If one assesses the family when the proband is excluded, however, the autosomal dominant mild short stature, four-extremity postaxial polydactyly type A, onychodystrophy, hypodontia, and abnormal frenula, with which the affected members present, closely resemble Weyers acrofacial dysostosis.

Linkage to Chromosome 4p16 and Haplotype Analysis

The proband in this family has features most consistent with Ellis–van Creveld syndrome. Therefore, we evaluated this family by using nine genetic markers from near the Ellis–van Creveld locus on chromosome 4p16.1 (table 2) (Polymeropoulos et al. 1996). Evidence for linkage to this region was observed, with LOD scores >3.00 and no recombination for two of the markers, *D4S827* and *D4S2366*. The highest two-point LOD score was 4.09 with the genetic marker *D4S2366*. One recombination event, between the genetic markers *D4S2366* and *D4S3007*, was detected in individual III:10 (fig. 2), defining the most proximal boundary for the region containing the disease locus. Recombinants that would have indicated the most distal boundary for the location of the gene were not detected within this 10-cM region. Using the LOD score 4.09, we calculated the 95% confidence interval for the disease locus to be 14 cM proximal and distal of *D4S2366*. However, the genetic distance between *D4S431* and *D4S3007*, which flank *D4S2366*, is only 3 cM (Polymeropoulos et al. 1996); thus, the recombinant (detected in individual III:10) limits the proximal boundary to a maximum of 3 cM from

Table 2

Linkage Analysis of Postaxial Polydactyly, Nail Dystrophy, and Dental Abnormalities to Chromosome 4p16

	LOD Score at θ =								
Marker	.00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D4S412	2.46	2.44	2.33	2.17	1.77	1.23	.59	2.46	.00
D4S2957	−.04	−.04	−.03	−.03	−.02	−.01	.00	.00	.50
D4S432	.25	.25	.25	.24	.20	.15	.08	.25	.04
MSX1	1.14	1.14	1.11	1.06	.90	.68	.38	1.14	.00
D4S827	3.22	3.16	2.93	2.63	1.98	1.27	.53	3.22	.00
D4S431	1.62	1.59	1.46	1.29	.92	.52	.16	1.62	.00
D4S2366	4.09	4.02	3.74	3.37	2.57	1.69	.75	4.09	.00
D4S3007	−∞	.26	.81	.92	.81	.54	.20	.92	.11
D4S394	−∞	1.73	2.20	2.19	1.82	1.27	.60	2.22	.07

D4S2366. Therefore, the region most likely to contain the gene is a 17-cM interval. This region encompasses the 3-cM critical region, between *D4S2957* and *D4S827*, for the Ellis–van Creveld syndrome locus, reported elsewhere (Polymeropoulos et al. 1996). Haplotype analysis provided similar results, with the critical region found to reside distal to *D4S3007* on the basis of recombination events detected in individual III:10 (fig. 2).

Sequencing of the MSX1 *Candidate Gene*

A candidate gene that maps within the critical region is the homeobox gene *MSX1*. The mouse homologue, *Hox-7*, is expressed in the neural crest, the developing mandible and teeth, the embryonic heart, and the limb buds (Robert et al. 1989), all of which are developmental regions affected in Ellis–van Creveld syndrome. In addition, a mutation in *MSX1* was recently reported in a family with selective tooth agenesis (Vastardis et al. 1996), which may be relevant to the dental abnormalities observed in both Ellis–van Creveld syndrome and Weyers acrofacial dysostosis. Both exons of *MSX1* from the proband (IV:4) and his affected paternal uncle (III:6) were sequenced. No mutations were detected, suggesting that changes in the *MSX1* coding region are not responsible for the clinical phenotype of this family. This result is consistent with the recent report that no mutations were detected in either of the two *MSX1* exons in patients with Ellis–van Creveld syndrome (Ide et al. 1996).

Discussion

We have studied a four-generation family segregating a condition with features of both Weyers acrofacial dysostosis and Ellis–van Creveld syndrome. The disorder in affected members of this family, including in the proband, demonstrated linkage to a chromosome 4p16 region estimated to be 17 cM and defined by recombination only proximally between loci *D4S3007* and *D4S2366*. The linkage-analysis data clearly show that, in this family, the candidate region for the condition encompasses the Ellis–van Creveld gene. The mapping of these two diseases to the same chromosomal region might represent any one of several phenomena. One possibility is that all affected members of this family have either an unreported autosomal dominant condition or Weyers acrofacial dysostosis with variable expression, with the proband being the most severely affected. Thus, the proband's condition would be a genocopy for Ellis–van Creveld syndrome. A second possibility is that the proband is a double heterozygote, with a mutation for the condition inherited from his father and a mutation for Weyers acrofacial dysostosis, Ellis–van Creveld syndrome, or Jeune syndrome inherited from his mother.

A final possibility is that the proband has Ellis–van Creveld syndrome and that his "affected" paternal relatives are symptomatic heterozygotes. Although some have questioned this interpretation (see OMIM 225500 [http://www.ncbi.nlm.nih.gov/Omim/]) because no heterozygous effects of Ellis–van Creveld syndrome were observed in the Amish population (McKusick et al. 1964), reports exist of several families in which heterozygotes exhibit findings similar to those in the family reported here (Fryns 1991; Goldblatt et al. 1992; Spranger and Tariverdian 1995). In fact, a similar family, consisting of a proband with Ellis–van Creveld syndrome and her father, who had features of Weyers acrofacial dysostosis (mild short stature, nail dysplasia, and teeth abnormalities but no polydactyly), has been reported (Spranger and Tariverdian 1995). The features observed in our proband's paternal relatives could be the phenotype resulting from one specific allele of the Ellis–van Creveld syndrome gene, an allele that differs from the allele affected in the Amish population. The proband may have inherited this allele from his father and a different mutant allele from his mother, leading to the full Ellis–van Creveld phenotype. Although no mutations were detected in the coding region of *MSX1* in the two members of this family who were tested, it is conceivable that mutations in the *MSX1* regulatory elements may be responsible for the condition in this family and, perhaps, for Ellis–van Creveld syndrome. Previous studies, using deletion analysis of the mouse *Msx1* promoter, identified regions that were important for distinct spatial and temporal expression patterns (MacKenzie et al. 1997).

Another candidate gene in the critical region for the condition in our family is that for fibroblast growth-factor receptor 3 (*FGFR3*). Mutations in *FGFR3* have been reported in patients with achondroplasia (Rousseau et al. 1994; Shiang et al. 1994), hypochondroplasia (Bellus et al. 1995), thanatophoric dysplasia (Tavormina et al. 1995; Rousseau et al. 1996), and craniofacial and limb abnormalities resembling Crouzon, Pfeiffer, or Saethre-Chotzen syndromes (Meyers et al. 1995; Bellus et al. 1996). *FGFR3* maps to chromosome 4p16.3 (Thompson et al. 1991) and is a potential candidate gene for the condition in this family or for Weyers acrofacial dysostosis, but it is distal to the critical region for the Ellis–van Creveld locus (Polymeropoulos et al. 1996). Other genes located on human chromosome 4p16 (those for dopamine receptor D1B [*DRD1B*], zinc finger protein–141 [*ZNF-141*], dopamine receptor D5 [*DRD5*], and protein S-100P [*S100P*]; the myosin light-chain regulatory gene [*MYL5*]; and homeobox gene H6 [*HMX1*]), identified in the syntenic region of mouse chromosome 5 (those for phosphodiesterase 6B, cGMP-specific, rod, beta [*PDEB*]; diacylglycerol kinase, delta

[*DAGK4*]; iduronidase, alpha-L [*IDUA*]; LDL-related protein-associated protein 1 [*LRPAP1;* alpha-2-macroglobulin receptor-associated protein]; G-protein-coupled receptor kinase-2 [*Drosophila*]–like [*GPRK2L*]; alpha-2C-adrenergic receptor [*ADRA2C*]; adducin, alpha subunit [*ADD1*]; huntingtin [*HD*]; and casein, beta [*CSN2*]) (DeBry and Seldin 1996; http://www.ncbi.nlm.nih.gov/Omim/Homology/), or associated with relevant mouse models are not obvious candidates, because their developmental expression patterns, function, or phenotypic effects differ significantly from the features present in the affected members of the family in this study.

The concept of a single gene causing both dominant and recessive conditions, as is possibly the case reported here, is not uncommon. Mutations in the genes for rhodopsin (Rosenfeld et al. 1992), von Willebrand factor (Zimmerman and Ruggeri 1987), thyroid hormone receptor–beta (Takeda et al. 1992), globin-beta (Thein et al. 1990), and collagen types 1A1 (Pruchno et al. 1991), 1A2 (De Paepe et al. 1997), and 7A1 (Christiano et al. 1993, 1994) have been found in both autosomal dominant and recessive diseases. For example, a much more severe osteogenesis imperfecta phenotype was found in two sibs homozygous for mutations in the collagen type 1A2 gene than was found in their heterozygous parents or sibs (De Paepe et al. 1997). This finding is similar to those for the family studied here, in which the heterozygous carriers are affected more mildly than the presumed homozygote (the proband). A potential mechanism for different mutations in the same gene, causing autosomal dominant and recessive inheritance patterns, is that certain mutations in the dominant form lead to dominant-negative effects, as is the case in generalized resistance to thyroid hormone (Takeda et al. 1992; Hayashi et al. 1994). In our family, a mutation in one gene may have a dominant-negative effect in the heterozygotes, leading to Weyers-acrofacial-dysostosis–like features, but this mutation in combination with a second mutation would lead to loss of function in the homozygote, resulting in the Ellis–van Creveld phenotype. Expression analysis and examination of the regulatory region of *MSX1* and of other candidate genes that later may be mapped to chromosome 4p16 in affected members of this family will help to determine the etiology of this condition.

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References

Bellus GA, Gaudenz K, Zackai EH, Clarke LA, Szabo J, Francomano CA, Muenke M (1996) Identical mutations in three different fibroblast growth factor receptor genes in autosomal dominant craniosynostosis syndromes. Nat Genet 14: 174–176

Bellus GA, McIntosh I, Smith EA, Aylsworth AS, Kaitila I, Horton WA, Greenhaw GA, et al (1995) A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet 10: 357–359

Biggerstaff RH, Mazaheri M (1968) Oral manifestations of the Ellis–van Creveld syndrome. J Am Dent Assoc 77: 1090–1095

Christiano AM, Greenspan DS, Hoffman GG, Zhang X, Tamai Y, Lin AN, Dietz HC, et al (1993) A missense mutation in type VII collagen in two affected siblings with recessive dystrophic epidermolysis bullosa. Nat Genet 4:62–66

Christiano AM, Ryynanen M, Uitto J (1994) Dominant dystrophic epidermolysis bullosa: identification of a gly-to-ser substitution in the triple-helical domain of type VII collagen. Proc Natl Acad Sci USA 91:3549–3553

Curry CJ, Hall BD (1979) Polydactyly, conical teeth, nail dysplasia, and short limbs: a new autosomal dominant malformation syndrome. Birth Defects 15:253–263

De Paepe A, Nuytinck L, Raes M, Fryns J-P (1997) Homozygosity by descent for a COL1A2 mutation in two sibs with severe osteogenesis imperfecta and mild clinical expression in the heterozygotes. Hum Genet 99:478–483

DeBry RW, Seldin MF (1996) Human/mouse homology relationships. Genomics 33:337–351

Ellis RWB, van Creveld S (1940) A syndrome characterized by ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis: report of three cases. Arch Dis Child 15:65–84

Fryns JP (1991) Postaxial polydactyly as heterozygote manifestation in Ellis–van Creveld syndrome? Am J Med Genet 39:500

Goldblatt J, Minutillo C, Pemberton PJ, Hurst J (1992) Ellis–van Creveld syndrome in a western Australian aboriginal community: postaxial polydactyly as a heterozygous manifestation? Med J Aust 157:271–272

Gorlin RJ, Cohen MM, Levin LS (1990) Syndromes of the head and neck, 3d ed. Oxford University Press, New York

Hayashi Y, Sunthornthepvarakul T, Refetoff S (1994) Mutations of CpG dinucleotides located in the triiodothyronine (T3)-binding domain of the thyroid hormone receptor (TR) beta gene that appears to be devoid of natural mutations may not be detected because they are unlikely to produce the clinical phenotype of resistance to thyroid hormone. J Clin Invest 94:607–615

Hewitt JE, Clark LN, Ivens A, Williamson R (1991) Structure and sequence of the human homeobox gene HOX7. Genomics 11:670–678

Ide SE, Ortiz de Luna RI, Francomano CA, Polymeropoulos MH (1996) Exclusion of the MSX1 homeobox gene as the gene for the Ellis–van Creveld syndrome in the Amish. Hum Genet 98:572–575

Jeune M, Beraud C, Carron R (1955) Dystrophie thoracique

asphyxiante de caractere familial. Arch Fr Pediatr 12: 886–891

Langer LO (1969) The thoracic-pelvic-phalangeal dystrophy. Birth Defects 5:55–64

MacKenzie A, Purdie L, Davidson D, Collinson M, Hill RE (1997) Two enhancer domains control early aspects of the complex expression pattern of Msx1. Mech Dev 62:29–40

McKusick VA, Egeland JA, Eldridge R, Krusen DE (1964) Dwarfism in the Amish. I. The Ellis–van Creveld syndrome. Bull Johns Hopkins Hosp 115:306–336

Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW (1995) Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 11:462–464

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Pirnar T, Neuhauser EBD (1966) Asphyxiating thoracic dystrophy of the newborn. Am J Roentgenol Radium Ther Nucl Med 98:358–364

Polymeropoulos MH, Ide SE, Wright M, Goodship J, Weissenbach J, Pyeritz RE, Da Silva EO, et al (1996) The gene for the Ellis–van Creveld syndrome is located on chromosome 4p16. Genomics 35:1–5

Pruchno CJ, Cohn DH, Wallis GA, Willing MC, Starman BJ, Zhang X, Byers PH (1991) Osteogenesis imperfecta due to recurrent point mutations at CpG dinucleotides in the COL1A1 gene of type I collagen. Hum Genet 87:33–40

Radhakrishna U, Blouin J-L, Mehenni H, Patel UC, Patel MN, Solanki JV, Antonarakis SE (1997) Mapping one form of autosomal dominant postaxial polydactyly type A to chromosome 7p15-q11.23 by linkage analysis. Am J Hum Genet 60:597–604

Robert B, Sassoon D, Jacq B, Gehring W, Buckingham M (1989) Hox-7, a mouse homeobox gene with a novel pattern of expression during embryogenesis. EMBO J 8:91–100

Rosenfeld PJ, Cowley GS, McGee TL, Sandberg MA, Berson EL, Dryja TP (1992) A null mutation in the rhodopsin gene causes rod photoreceptor dysfunction and autosomal recessive retinitis pigmentosa. Nat Genet 1:209–213

Roubicek M, Spranger J (1984) Weyers acrodental dysostosis in a family. Clin Genet 26:587–590

Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet J-M, Maroteaux P, Le Merrer M, et al (1994) Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature 371:252–254

Rousseau F, El Ghouzzi V, Delezoide AL, Legeai-Mallet L, Le Merrer M, Munnich A, Bonaventure J (1996) Missense FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD1). Hum Mol Genet 5:509–512

Shapiro SD, Jorgenson RJ, Salinas CF (1984) Brief clinical report: Curry-Hall syndrome. Am J Med Genet 17:579–583

Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, Winckur ST, et al (1994) Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78:335–342

Spranger S, Tariverdian G (1995) Symptomatic heterozygosity in the Ellis–van Creveld syndrome? Clin Genet 47:217–220

Takeda K, Sakurai A, DeGroot LJ, Refetoff S (1992) Recessive inheritance of thyroid hormone resistance caused by complete deletion of the protein-coding region of the thyroid hormone receptor-beta gene. J Clin Endocrinol Metab 74: 49–55

Tavormina PL, Shiang R, Thompson LM, Zhu Y-Z, Wilkin DJ, Lachman RS, Wilcox WR, et al (1995) Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat Genet 9:321–328

Taylor GA, Jordan CE, Dorst SK, Dorst JP (1984) Polycarpaly and other abnormalities of the wrist in chondroectodermal dysplasia: the Ellis–van Creveld syndrome. Radiology 151: 393–396

Thein SL, Hesketh C, Taylor P, Temperley IJ, Hutchinson RM, Old JM, Wood WG, et al (1990) Molecular basis for dominantly inherited inclusion body beta-thalassemia. Proc Natl Acad Sci USA 87:3924–3928

Thompson LM, Plummer S, Schalling M, Altherr MR, Gusella JF, Housman DE, Wasmuth JJ (1991) A gene encoding a fibroblast growth factor receptor isolated from the Huntington disease gene region of human chromosome 4. Genomics 11:1133–1142

Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE (1996) A human MSX1 homeodomain missense mutation causes selective tooth agenesis. Nat Genet 13:417–421

Weyers H (1952) Ueber eine korrelierte Missbildung der Kiefer und Extremitatenakren (Dysostosis acro-facialis). Fortschr Geb Roentgenstrahlen Nuklear Med 77:562–567

Zimmerman TS, Ruggeri ZM (1987) von Willebrand disease. Hum Pathol 18:140–152