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SHORT REPORT

Exclusion of the Ellis–van Creveld region on chromosome 4p16 in some families with asphyxiating thoracic dystrophy and short-rib polydactyly syndromes

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Ellis–van Creveld syndrome (EVC) is a relatively rare, usually non-lethal, autosomal recessive skeletal dysplasia characterized by short stature, polydactyly, cardiac and renal anomalies. Linkage analysis has localized the disease gene to chromosome 4p16, with the markers at loci D4S827 and D4S3135 defining the centromeric and telomeric limits of the linked interval, respectively. There has been long-term speculation that asphyxiating thoracic dystrophy (ATD) and the short-rib polydactyly syndromes (SRP) represent the severe end of the EVC disease spectrum. We performed linkage analysis using markers from the EVC region in seven families manifesting either ATD or SRP type III. In two of the families, one segregating ATD and one SRP kindred, linkage of the phenotype to the EVC region was excluded. In the other five families linkage of the phenotype to the EVC region could not be excluded, but the families were too small for linkage to the region to be established. The exclusion of the EVC region in ATD and SRP III families suggests that locus heterogeneity exists within the short-rib dysplasia (with and without polydactyly) group of disorders. *European Journal of Human Genetics* (2000) **8**, 645–648.

Keywords: Ellis–van Creveld; asphyxiating thoracic dystrophy; short-rib polydactyly; chromosome 4p16; dwarfism

Introduction

Ellis–van Creveld (EVC) syndrome is an autosomal recessive skeletal dysplasia which shares features with asphyxiating thoracic dystrophy (ATD) and the short-rib polydactyly syndromes (SRPs). Indeed, the most recent classification of the osteochondrodysplasias groups these disorders together as the short-rib dysplasias (with and without polydactyly) (International Working Group on Constitutional Diseases of Bone[1]). First described by Ellis and van Creveld in 1940,[2] the EVC syndrome consists of short stature, polydactyly, nail dystrophy, oral frenulum and cardiac malformations, frequently atrioventricular canal defects. The radiographic findings are very similar to ATD including a shortened ilia with a downward hook of the greater sciatic notches (trident pelvis). In the large Amish kindred ascertained by McKusick[3] linkage studies localized the gene for EVC to chromosome 4p16 (Francomano *et al*[4]). By haplotype analysis, Polymeropoulos *et al*[5] narrowed the disease gene interval to a region bounded by the markers at loci D4S827 and D4S3135. There was no evidence for locus heterogeneity among the four geographically diverse families studied. *HOX7* or *MSX1*, a homeobox gene, defined the telomeric limit of the linked interval and has been excluded as a candidate gene (Ide *et al*[6]). The candidate interval has been narrowed to approximately 1 megabase, but the disease gene has yet to be identified (Ho *et al*[7]).

Asphyxiating thoracic dystrophy (ATD) or Jeune syndrome is an autosomal recessive skeletal dysplasia with associated

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multisystemic involvement. It was first reported by Jeune in 1954 in two affected siblings,[8] and he coined the term, asphyxiating thoracic dystrophy. Long-term prognosis in ATD is usually limited, either as a result of respiratory insufficiency in infancy, or from renal failure in childhood. The radiographic findings include a small bell-shaped thorax, shortened tubular bones, trident pelvis, metaphyseal irregularities and occasional polydactyly.

The short-rib polydactyly syndromes (SRPs), also an autosomal recessive group of disorders, have been classified into four distinct groups (SRP types I, II, III, and IV) based on clinical, radiographic, and cartilage histomorphologic findings. Findings seen in all four forms include perinatal lethality, a very short narrow thorax with horizontal ribs, hydrops, shortened tubular bones, variable pre- and postaxial polydactyly and associated multisystem congenital anomalies. The initial subdivision of the short-rib polydactylys was based on what were believed to be distinct findings in a small number of cases (Saldino and Noonan,[9] Majewski *et al*,[10] Naumoff *et al*[11]). Therefore debate exists over whether this group of disorders should be separated into four separate entities, or two entities, one comprising SRP I and III and the other including SRP II and IV (Sillence[12]), or whether they represent variable expressivity (Francheschini *et al*[13]).

Because of the phenotypic and radiographic similarities (Maroteux and Savart,[14] Yang *et al*[15]), there has been longstanding speculation that the EVC, ATD and SRP syndromes are allelic. Under this hypothesis, the spectrum of severity is postulated to represent allelic heterogeneity. This hypothesis has been strengthened by ascertainment of cases in which the findings overlap. For example, Francheschini *et al*[13] reported a case of an affected individual who manifested findings consistent with SRP II, III and IV, and ATD, and Neri *et al*[16] reviewed seven 'transitional' cases and designated the group of conditions 'Oral–Facial–Skeletal (OFS) syndromes'. Further, cases have been ascertained in which the clinical and radiographic findings overlap between EVC and ATD, and between ATD and the SRPs (Rimoin and Lachman[17]). Therefore, to genetically test the hypothesis that ATD, SRP III and EVC syndromes were allelic, linkage to the EVC region on chromosome 4p was tested in seven families co-segregating either ATD (Figure 1a) or SRP (Figure 1b).

Materials and methods

Families were initially ascertained through the International Skeletal Dysplasia Registry (ISDR) with appropriate IRB approval. The SRP cases available for linkage analysis were SRP III, or the Verma–Naumoff type. Diagnoses were based on radiographic findings, clinical ascertainment and cartilage histomorphology. The patients were classified as ATD if the radiographic features included a bell-shaped thorax, trident appearance of the acetabular margin, handle-bar clavicles and mesomelic shortening. In two of the families, R99-031 and R96-155, the probands are both alive at ages 6 and 3, respectively. The proband in R99-031 has hepatic and renal complications associated with ATD. In the SRP cases, diagnosis was made primarily on radiographic grounds: short, narrow thorax, polydactyly, and shortened tubular bones with lateral metaphyseal spikes. Genotypes were determined for the probands, their parents and siblings. Marker order within the region was determined utilizing information from the EVC mapping report (Polymeropoulos *et al*[5]) and the genome databases: tel–D4S3023–D4S1013–D4S3135–D4S1013–D4S3135–D4S827–D4S500–D4S431–cen. Genotypes for the CEPH reference pedigrees at these loci are available at the GDB website.

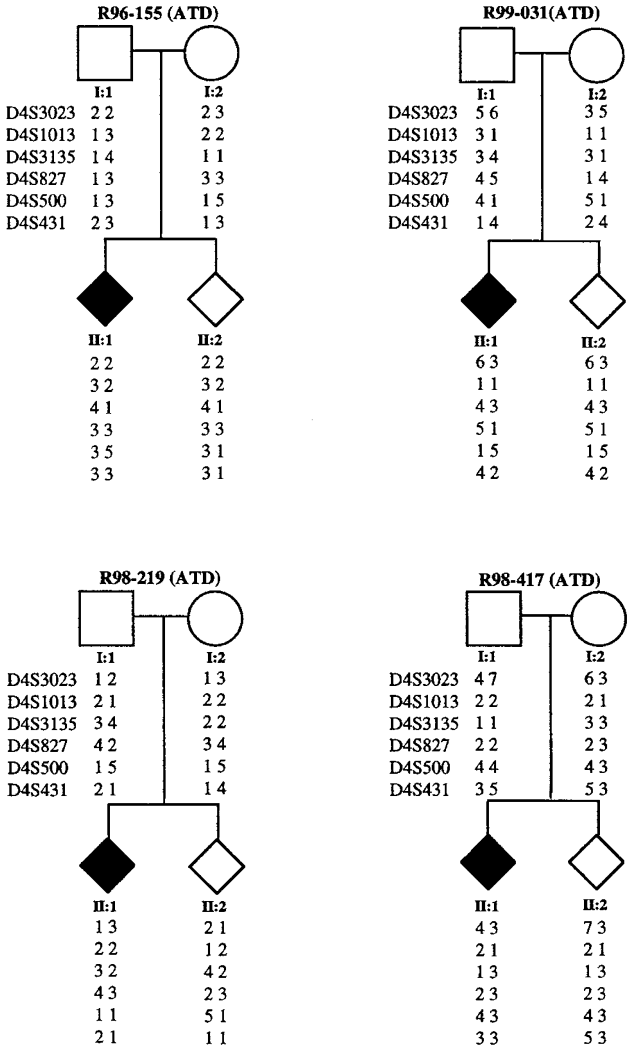

Figure 1a Haplotype analysis in ATD families. Solid symbols represent affected individuals. In generation II, the paternal genotypes are to the left, and the maternal genotypes are to the right.

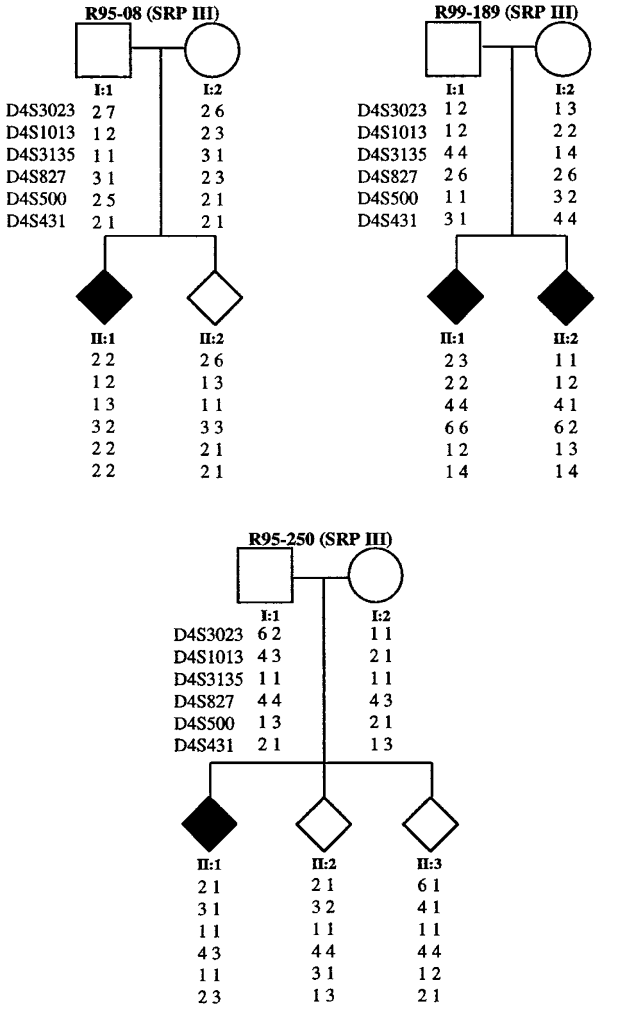

Figure 1b Haplotype analysis in SRP families. Solid symbols represent affected individuals. In generation II, the paternal genotypes are to the left, and the maternal genotypes are to the right.

Results and discussion

Haplotypes were determined by parsimony (Figures 1a and 1b). Under an autosomal recessive model, we could exclude linkage to the region if affected and unaffected individuals shared the same parental haplotypes, or if affected individuals in the same pedigree did not inherit identical parental haplotypes. In ATD family R99-031 (Figure 1a), the affected fetus and the unaffected siblings shared the same maternal and paternal haplotypes across the entire region. In SRP III family R99-189 (Figure 1b), the two affected siblings did not share haplotypes in the D4S3135–D4S827 interval, thereby excluding linkage to the region. In individual II-1, there was a recombination event on the paternal allele at the polymorphic locus D4S827. However, this is at the telomeric limit of the EVC interval, and recombination has been previously seen at that locus in EVC pedigrees (Polymeropoulos *et al*[5]). In ATD family R96-155 (Figure 1a), affected individual II-1 and the unaffected sibling, II-2, shared haplotypes in the EVC region, which would exclude the EVC interval. However, haplotype analysis revealed a recombinant event in individual II-1 on the maternal allele, either at the centromeric limit within the D4S827–D4S500 interval, or at the telomeric end within the D4S1035–D4S3023 interval. Because we could not determine the precise location of the recombination event, and the maternal genotypes at the markers for the loci defining the EVC limits were not informative, the EVC region could not be excluded in this family. In the other four families, linkage could not be excluded under an autosomal recessive model.

These data establish that at least some cases of ATD and SRP (type III) are not due to defects in the *EVC* disease gene. The ATD and SRP phenotypes in the cases excluded from the EVC region were not phenotypically distinct from typical cases described in the literature, or the other cases studied here. While the hypothesis that some cases of ATD and SRP may be allelic with EVC is still valid, it is clear that defects in a gene (or genes) other than the *EVC* gene can produce these severe dwarfing conditions.

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