A novel acropectoral syndrome maps to chromosome 7q36


Abstract

F syndrome (acropectoral syndrome) is a dominantly inherited skeletal dysplasia affecting the hands, feet, sternum, and lumbosacral spine, which has previously been described in only two families. Here we report a six generation Turkish family with a related but distinct dominantly inherited acropectoral syndrome. All 22 affected subjects have soft tissue syndactyly of all fingers and all toes and 14 also have preaxial polydactyly of the hands and/or feet. In addition, 14 have a prominent upper sternum and/or a blind ending, inverted U shaped sinus in the anterior chest wall. Linkage studies and haplotype analysis carried out in 16 affected and nine unaffected members of this family showed that the underlying locus maps to a 6.4 cM interval on chromosome 7q36, between EN2 and D7S2423, a region to which a locus for polydactyly and sternal defects respectively, suggesting that misregulation of SHH may underlie the unusual combination of abnormalities in this family. A recently proposed candidate gene for 7q36 linked preaxial polydactyly is LMBRI, encoding a novel transmembrane receptor which may be an upstream regulator of SHH.

Case reports

All 22 living affected subjects were assessed clinically and radiographs of the hands and feet were obtained in 13 cases. All 22 subjects were found to have partial or complete soft tissue webbing between all fingers and all toes. The most lateral three or four toes were also often adducted and flexed at the interphalangeal joints. Eight had preaxial polydactyly in the hands (unilateral in two, bilateral in six), ranging in severity from broad or bifid distal phalanges in the thumbs to duplication of an entire biphalangeal or triphalangeal thumb, in two cases with an associated extra metacarpal, lying in a soft tissue web between the thumb and index finger. Fourteen had preaxial...
polydactyly in the feet (unilateral in one, bilateral in 13), consisting of a small extra biphalangeal toe, in most cases with an associated rudimentary extra metatarsal, lying in a soft tissue web between the hallux and second toe. In some cases, this was accompanied by hypoplasia of the head of the first metatarsal and absence of both phalanges of the hallux. In addition, 14 had a sternal abnormality, consisting of a pectus carinatum deformity of the upper sternum and/or a pectus excavatum deformity of the lower sternum, producing a blind ending, inverted U shaped sinus in the anterior chest wall. A thoracic CT scan of V.38, who was typically affected, showed an increase in the anterior-posterior diameter of the upper chest, with no underlying bony defect in the sternum. There were no other skeletal or extraskeletal abnormalities.

The novel acropectoral syndrome in this family, comprising total soft tissue syndactyly, preaxial polydactyly, and sternal deformity, is remarkably similar to F syndrome. It differs in that the carpal, metatarsal, and tarsal synostoses and the vertebral anomalies found in F syndrome are absent. In addition, the soft tissue syndactyly is more extensive than in F syndrome and the preaxial polydactyly occurs in the feet as well as in the hands. These limb abnormalities are also very similar to those that occur in several dominantly inherited types of preaxial polydactyly, especially preaxial polydactyly type II (PPD2, OMIM 174500, characterised by duplication of an opposable triphalangeal thumb), preaxial polydactyly type III (PPD3, OMIM 174600, characterised by duplication of a non-opposable triphalangeal index finger), and triphalangeal thumb-poly syndactyly (TPT-PS, OMIM 190605, characterised by duplication of a triphalangeal thumb, syndactyly of fingers 3 to 5, and variable syndactyly and preaxial or postaxial

![Figure 1 Pedigree of the affected family. The 28 clinically affected subjects (22 living and six dead) are represented by filled symbols.](http://jmg.bmj.com/Downloadedfrom)
polydactyly in the feet). In nine unrelated families with PPD2/3 and two unrelated families with TPT-PS, the underlying locus has been mapped to chromosome 7q36. Although none of the affected subjects in any of these families had the sternal deformity seen in the family we report here, the similarity in limb phenotype prompted us to investigate whether the underlying locus in our family might map to the same chromosomal region.

Methods
Karyotyping in two affected family members did not show any chromosomal abnormality. We therefore carried out linkage and haplotype analysis on a subset of 16 affected and nine unaffected family members (fig 4), using seven highly polymorphic microsatellite repeats that map to chromosome 7q36 (table 2). Information about these markers and their relative positions was obtained from the Genome Database (http://gdbwww.gdb.org/). Marker D7S594 was reported by Hing et al and the dinucleotide repeat within the EN2 gene was reported by Tsukurov et al. Genomic DNA was extracted from whole venous blood by standard methods and the markers were amplified by PCR and analysed by polyacrylamide gel electrophoresis, as described previously. Two point linkage analysis was performed using the MLINK program of the LINKAGE package (version 5.1). Lod scores were calculated assuming acropectoral syndrome is an autosomal dominant trait with a gene frequency of 0.0001 and complete penetrance. The mutation rate was set at zero and equal recombination rates between males and females were assumed. Marker allele frequencies were kept equal.

Results
The results of two point linkage analysis and haplotype analysis are shown in table 2 and fig 4, respectively. A maximum lod score of 4.00 at 4.00.
Acropectoral locus on 7q36

Deformity in V.41.

Subjects. (A) Upper sternum deformity in IV.15, showing blind ending, inverted U shaped sinus. (B) Upper sternum

Recombination events were, however, observed between the phenotype and D7S2423 in another affected subject (VI.17). The locus for acropectoral syndrome thus lies in an interval flanked by EN2 and D7S2423, a genetic distance of approximately 6.4 cM. All 16 affected subjects shared a common haplotype for markers D7S550 and D7S559, which was not seen in any of the nine unaffected subjects. This haplotype differs from that segregating with PPD2/3 and TPT-PS in previously reported families, including a Turkish TPT-PS family, suggesting that the phenotype in the family we describe results from an independent mutational event.

Discussion

Previous studies of phenotypic variation in PPD2/3 and TPT-PS families linked to 7q36, as well as in families not subjected to linkage analysis and in isolated cases (reviewed by Kantaputra and Chalidapong) have suggested that PPD2/3, TPT-PS, tibial hypoplasia/aplasia with polydactyly (OMIM 18870), and Haas type syndactyly (syndactyly type IV, OMIM 186200) are all different manifestations of the same genetic entity. Our results support this suggestion. Haas type syndactyly is characterised by skin syndactyly of all fingers, variable skin syndactyly of the toes, and variable polydactyly, and we have found that skin syndactyly of all fingers and all toes with variable preaxial polydactyly is linked to 7q36. In addition, our findings extend the range of associated abnormalities to include sternum deformity, and suggest that F syndrome may also be part of the same phenotypic spectrum.

Three mouse mutant strains with limb abnormalities closely related to these human phenotypes map to a region on proximal mouse chromosome 5 that is syntenic to human chromosome 7q36. Hemimelic extra-toes (Hx), a spontaneous semidominant mutation, produces triphalangeal first digits, preaxial polydactyly, and shortening of the radius and tibia in both heterozygotes and homozygotes. All four limbs are affected, the hindlimbs more severely than the forelimbs. Hammertoe (Hm), another spontaneous semidominant mutation, produces persistent interdigital webbing in all four limbs, more extensive in homozygotes than in heterozygotes, resulting in marked flexion of digits 2-5. Hx and Hm are extremely closely linked, with only a single recombination in 3664 meioses, suggesting that they may represent different mutations in the same gene or regulatory region. Sasquatch (Ssq) is a semidominant mutation generated by the random insertion of an enhancer-reporter construct in proximal mouse chromosome 5. Heterozygotes have preaxial polydactyly in the hindlimbs, while homozygotes also have tibial hemimelia and preaxial polydactyly in the forelimbs.

The supernumerary anterior digits in preaxial polydactyly and the alteration of digit identity from anterior to more posterior in triphalangeal thumb both result from a disturbance of anterior-posterior patterning in the developing limb. One of the key determinants of anterior-posterior patterning is the secreted signalling molecule Sonic hedgehog (Shh). Expression of Shh is normally confined to the zone of polarising activity at the posterior margin of the developing limb. Artificially induced expression of Shh at the anterior margin causes mirror image duplications of the anterior digits, and an ectopic anterior domain of Shh expression has been identified in many mouse mutants with triphalangeal first digits.
preaxial polydactyly, and tibial hemimelia. These include not only \( Hx \)\(^22 \) and \( Ssq \)\(^19 \), but also Extra toes (\( Xt \)), Strong's luxoid (\( lst \)), Carter's lux-\( lx \), Recombination induced mutant 4 (\( \text{Rim4} \)), and \( X \) linked polydactyly (\( Xpl \)\(^22\)\(^23 \)), as well as transgenic mice misexpressing \( \text{Hoxb8} \), \( \text{Hoxd12} \), or \( \text{dHAND} \) throughout their limbs. Interestingly, in \( Xt \) mice\(^28\)\(^29 \) and transgenic mice misexpressing \( \text{Hoxd12} \) in lateral plate mesoderm,\(^30 \) ectopic \( \text{Shh} \) expression also results in sternal abnormalities, ranging from mildly split sternebrae to sternal agenesis with open ribcage. In \( Xt \) and \( lst \) mice, ectopic \( \text{Shh} \) expression is caused by loss of function mutations in \( \text{Gli3} \)\(^28 \) and \( \text{Alx4} \)\(^30 \) respectively, transcription factors which normally down-regulate \( \text{Shh} \), while in the transgenic mice it is caused by misexpression of \( \text{Hoxb8} \), \( \text{Hoxd12} \), or \( \text{dHAND} \), transcription factors which normally upregulate \( \text{Shh} \). In \( Ssq \) mice, however, the construct insertion site lies only about 800 kb distal to the \( \text{Shh} \) gene itself, raising the possibility that a long distance regulatory element of \( \text{Shh} \) might be directly disrupted.\(^19 \)

The chromosome 7q36 PPD2/3 and TPT-PS critical region has recently been narrowed down to a 450 kb interval, approximately 0.8-1.25 Mb distal to the human \( \text{SHH} \) gene.\(^31 \) This interval includes one known gene, \( \text{HLXB9} \), which is mutated in Currarino syndrome, and three novel transcripts, \( \text{C7orf2} \), \( \text{C7orf3} \), and \( \text{C7orf4} \), encoding putative proteins of unknown function. No mutations have

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Figure 4 Partial pedigree showing the 16 affected and nine unaffected subjects in whom linkage and haplotype analysis was carried out and the haplotypes obtained. The seven microsatellite markers mapping to chromosome 7q36 are ordered from centromere to telomere.

Table 2 Pairwise lod scores between chromosome 7q36 markers and the acropectoral locus at various recombination fractions. The markers are ordered from centromore to telomere.
been identified in transcripts of any of these candidate genes in patients with PDDP/3 or TPT-PS.31

The Hx and Hm critical region on mouse chromosome 5 has also recently been narrowed down to a 295-570 kb interval, approximately 1.2 cM distal to the mouse Shh gene.32 The mouse homologues of HLBx9 and C7orf3 lie outside this interval, and there appears to be no mouse homologue of C7orf4. The interval does, however, include the mouse homologue of C7orf2, which has been named Lmbr1. Not only is this gene expressed in the developing mouse limb, but its expression pattern is dramatically altered in the limbs of Hx mice. From E11.5 to 12.5, the period during which morphological abnormalities first appear in Hx limbs, there is transient loss of Lmbr1 expression, occurring first in the hindlimbs (more severely affected) and later in the forelimbs (less severely affected). No mutations have been identified in the coding sequence of Lmbr1 in either Hx or Hm mice, however, suggesting that Hx (and probably Hm as well) is caused by a mutation in a regulatory region of Lmbr1.3 It will be interesting to see if the Sio phenotype results from a similar regulatory mutation in Lmbr1, rather than a regulatory mutation in Shh, as originally proposed.3,33 These exciting new findings strongly suggest that PDDP/3 and TPT-PS are caused by regulatory mutations in the human LMBR1 gene (C7orf2), and we are currently screening for such a mutation in the family we report here. When taken together with previous data and our own, they also suggest that Lmbr1 may be a novel upstream regulator of Shh expression both in the developing limb and in lateral plate mesoderm.

**Note added in proof**

A homozygous loss of function mutation in LMBR1 has now been shown to be responsible for the congenital limb malformation achondroplasia, confirming the gene’s importance in human limb development.35

The first two authors contributed equally to this work. We thank all the members of the family for their participation in this study.

5 Radhakrishna U, Blouin JL, Solanki JV, Dhoriani GM, Oostra BA, Heutink P. Clinical and genetic studies on 12 preaxial polydactyly families and 125.}

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