

Original articles

A novel acropectoral syndrome maps to chromosome 7q36

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Abstract

F syndrome (acropectorovertebral 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 preaxial polydactyly and triphalangeal thumb-polysyndactyly has previously been mapped. Our findings expand the range of phenotypes associated with this locus to include total soft tissue syndactyly and sternal deformity, and suggest that F syndrome may be another manifestation of the same genetic entity. In mice, ectopic expression of the gene *Sonic hedgehog (Shh)* in limb buds and lateral plate mesoderm during development causes preaxial 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 *LMBR1*, encoding a novel transmembrane receptor which may be an upstream regulator of *SHH*.

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Keywords: preaxial polydactyly; sternal deformity; F syndrome; chromosome 7q36

F syndrome or acropectorovertebral syndrome (OMIM 102510) is a rare, dominantly inherited skeletal dysplasia affecting the distal limbs,

sternum, and lumbosacral spine. It was first described in 1969 in eight members of a four generation American family whose surname began with the letter F¹ and has only once been reported since, in an Italian father and daughter.² In the hands, the malformation primarily involves the thumbs and index fingers, which are short, deformed, often partially duplicated, and joined by soft tissue webbing and sometimes a bony bridge. The capitate and hamate are invariably fused and other carpals are frequently fused as well. In the feet, there is soft tissue webbing between the toes, especially the first and second, occasional postaxial polydactyly, and hypoplasia, deformity, and fusion of the metatarsals, especially the first and second and the fourth and fifth. The talus and navicular are invariably fused, and there are also extensive fusions of most other tarsals. In the chest, there is characteristically a prominent upper sternum, with pectus excavatum of the lower sternum, while in the spine there is often spina bifida occulta of L5 and/or S1. The minor craniofacial anomalies and mild intellectual impairment observed in some affected members of the original family probably do not form part of the syndrome.

Here we report a large six generation Turkish family (fig 1) with a related but distinct combination of distal limb and sternal abnormalities, also inherited in an autosomal dominant fashion. The phenotype in this family is illustrated in figs 2 and 3, and summarised in table 1.

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

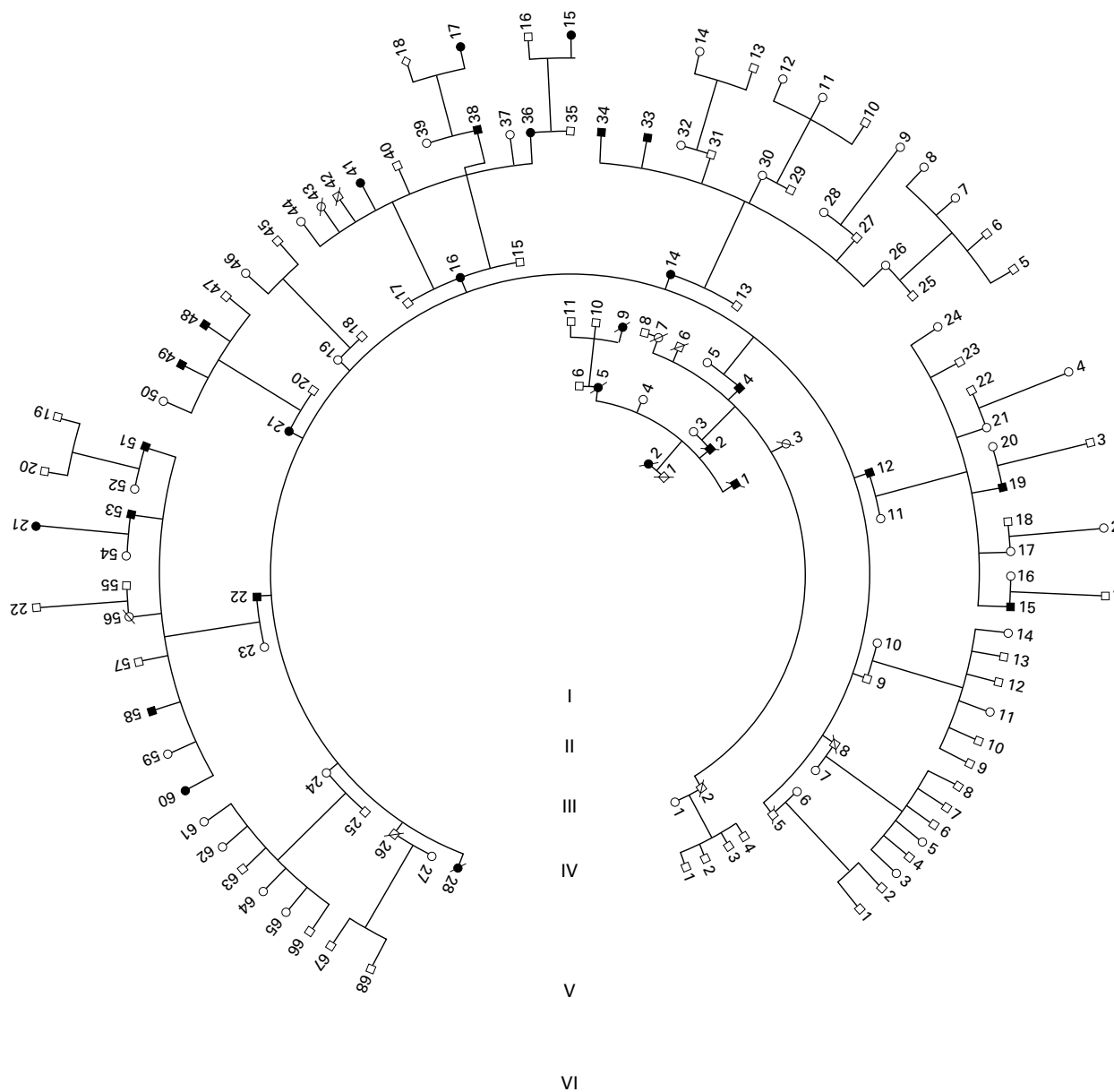


Figure 1 Pedigree of the affected family. The 28 clinically affected subjects (22 living and six dead) are represented by filled symbols.

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 extraskelatal 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-polysyndactyly (TPT-PS, OMIM 190605, characterised by duplication of a triphalangeal thumb, syndactyly of fingers 3 to 5, and variable syndactyly and preaxial or postaxial

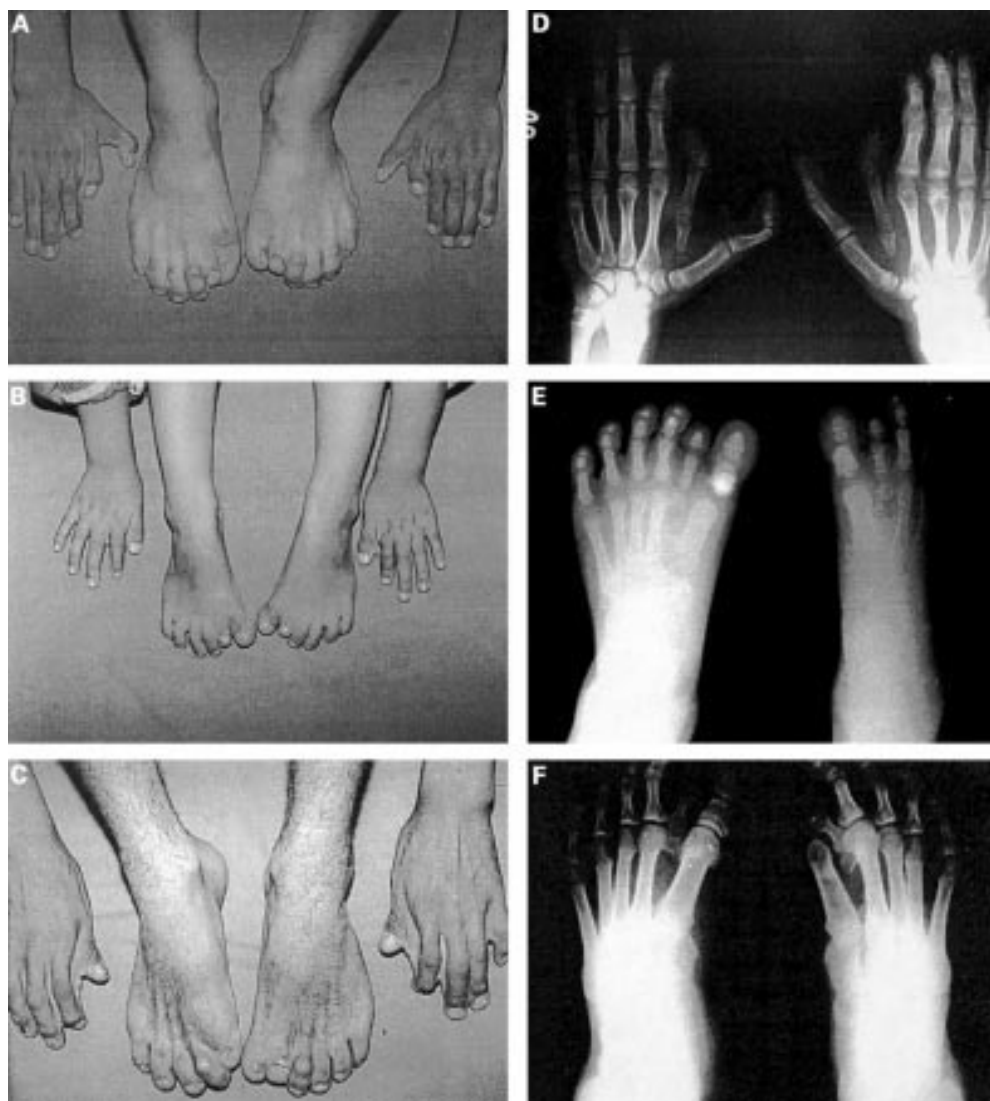


Figure 2 Limb abnormalities in three typically affected subjects. Hand and foot photographs of (A) V.34, (B) VI.21, and (C) V.58, showing partial or complete skin syndactyly between all digits of all four limbs, preaxial polydactyly in the feet, and, in V.34 only, preaxial polydactyly in the hands. (D) Radiograph of the hands of V.34, showing bilateral triphalangeal thumbs and bilateral extra triphalangeal digits with rudimentary extra metacarpals in the first web spaces. (E) Radiograph of the feet of VI.21, showing bilateral, small, extra biphalangeal digits with rudimentary extra metatarsals in the first web spaces. (F) Radiograph of the feet of V.58, showing bilateral rudimentary extra digits in the first web spaces, and, on the left, absence of both phalanges of the hallux, with hypoplasia of the head of the first metatarsal.

polydactyly in the feet). In nine unrelated families with PPD2/3³⁻⁷ and two unrelated families with TPT-PS,^{8,9} 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 Data-Base (<http://gdbwww.gdb.org>). Marker

D7S594 was reported by Hing *et al*¹⁰ and the dinucleotide repeat within the *EN2* gene was reported by Tsukurov *et al*.⁸ Genomic DNA was extracted from whole venous blood by standard methods¹¹ and the markers were amplified by PCR and analysed by polyacrylamide gel electrophoresis, as described previously.¹² Two point linkage analysis was performed using the MLINK program of the LINKAGE package (version 5.1).¹³ 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

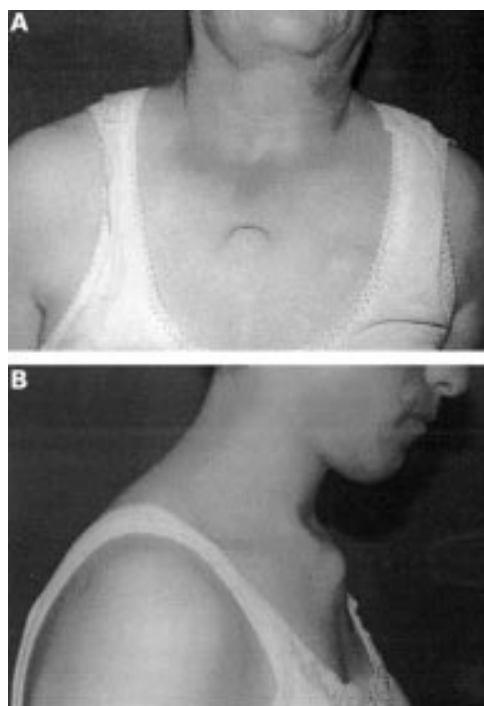


Figure 3 Sternal abnormalities in two typically affected subjects. (A) Upper sternum deformity in IV.15, showing blind ending, inverted U shaped sinus. (B) Upper sternum deformity in V.41.

Table 1 Clinical findings in the 22 affected subjects

Subject	Syndactyly of all fingers and toes	Preaxial polydactyly		Sternal deformity
		Hands	Feet	
III.4*	+	-	B	+
IV.12*	+	B	B	+
IV.14*	+	-	B	+
IV.15*	+	B	B	+
IV.20*	+	B	B	+
IV.21*	+	-	B	+
V.15	+	-	-	-
V.19	+	-	-	+
V.33*	+	B	B	-
V.34*	+	B	B	-
V.36	+	L	L	+
V.38*	+	-	-	+
V.41*	+	-	B	+
V.48	+	L	B	+
V.49	+	-	-	+
V.51	+	-	-	+
V.53	+	-	-	-
V.58*	+	-	B	-
V.60*	+	-	B	-
VI.15	+	-	-	+
VI.17	+	-	-	-
VI.21*	+	B	B	-

Asterisks indicate the 13 subjects for whom hand and foot radiographs were obtained. B = bilateral, L = left sided.

$\theta=0.00$ was obtained for marker D7S550, showing linkage of acropectoral syndrome to chromosome 7q36. No recombination was seen with markers D7S550 and D7S559. Recombination events were, however, observed between the phenotype and *EN2* in one affected subject (V.58), and 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,⁹ 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,^{6,9} as well as in families not subjected to linkage analysis and in isolated cases (reviewed by Kantaputra and Chalidapong¹⁴) 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 sternal 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)*,^{15,16} 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)*,¹⁷ 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,¹⁸ suggesting that they may represent different mutations in the same gene or regulatory region. *Sasquatch (Ssq)*¹⁹ 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,^{20,21} and an ectopic anterior domain of *Shh* expression has been identified in many mouse mutants with triphalangeal first digits,

Table 2 Pairwise lod scores between chromosome 7q36 markers and the acropectoral locus at various recombination fractions. The markers are ordered from centromere to telomere

Marker	Recombination fraction (θ)							
	0.00	0.01	0.05	0.10	0.15	0.20	0.30	0.40
NOS	−∞	−0.06	1.72	2.20	2.28	2.18	1.67	0.87
D7S637	1.71	1.70	1.64	1.54	1.40	1.25	0.90	0.48
EN2	−∞	3.04	3.44	3.34	3.09	2.77	1.96	0.98
D7S550	4.00	3.97	3.77	3.46	3.09	2.68	1.75	0.74
D7S559	2.71	2.67	2.51	2.30	2.07	1.84	1.32	0.71
D7S2423	−∞	−1.40	−0.72	−0.44	−0.29	−0.19	−0.08	−0.02
D7S594	−∞	−4.15	−1.93	−0.99	−0.50	−0.21	0.08	0.12

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 luxate (lx)*, *Recombination induced mutant 4 (Rim4)*, and *X linked polydactyly (Xpl)*,^{22, 23} as well as transgenic mice misexpressing *Hoxb8*,²⁴ *Hoxd12*,²⁵ or *dHAND*^{26, 27} throughout their limbs. Interestingly, in *Xt* mice^{28, 29} and transgenic mice misexpressing *Hoxd12* in lateral plate mesoderm,²⁵ ectopic *Shh* expression also results in sternal abnormalities, ranging from

mildly split sternebrae to sternal agenesis with open ribcage. In *Xt* and *lst* mice, ectopic *Shh* expression is caused by loss of function mutations in *Gli3*²⁸ and *Alx4*³⁰ respectively, transcription factors which normally down-regulate *Shh*, while in the transgenic mice it is caused by misexpression of *Hoxb8*, *Hoxd12*, or *dHAND*, transcription factors which normally upregulate *Shh*. In *Ssq* mice, however, the construct insertion site lies only about 800 kb distal to the *Shh* gene itself, raising the possibility that a long distance regulatory element of *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 *SHH* gene.³¹ This interval includes one known gene, *HLXB9*, which is mutated in Currarino syndrome, and three novel transcripts, *C7orf2*, encoding a putative transmembrane receptor, and *C7orf3* and *C7orf4*, encoding putative proteins of unknown function. No mutations have

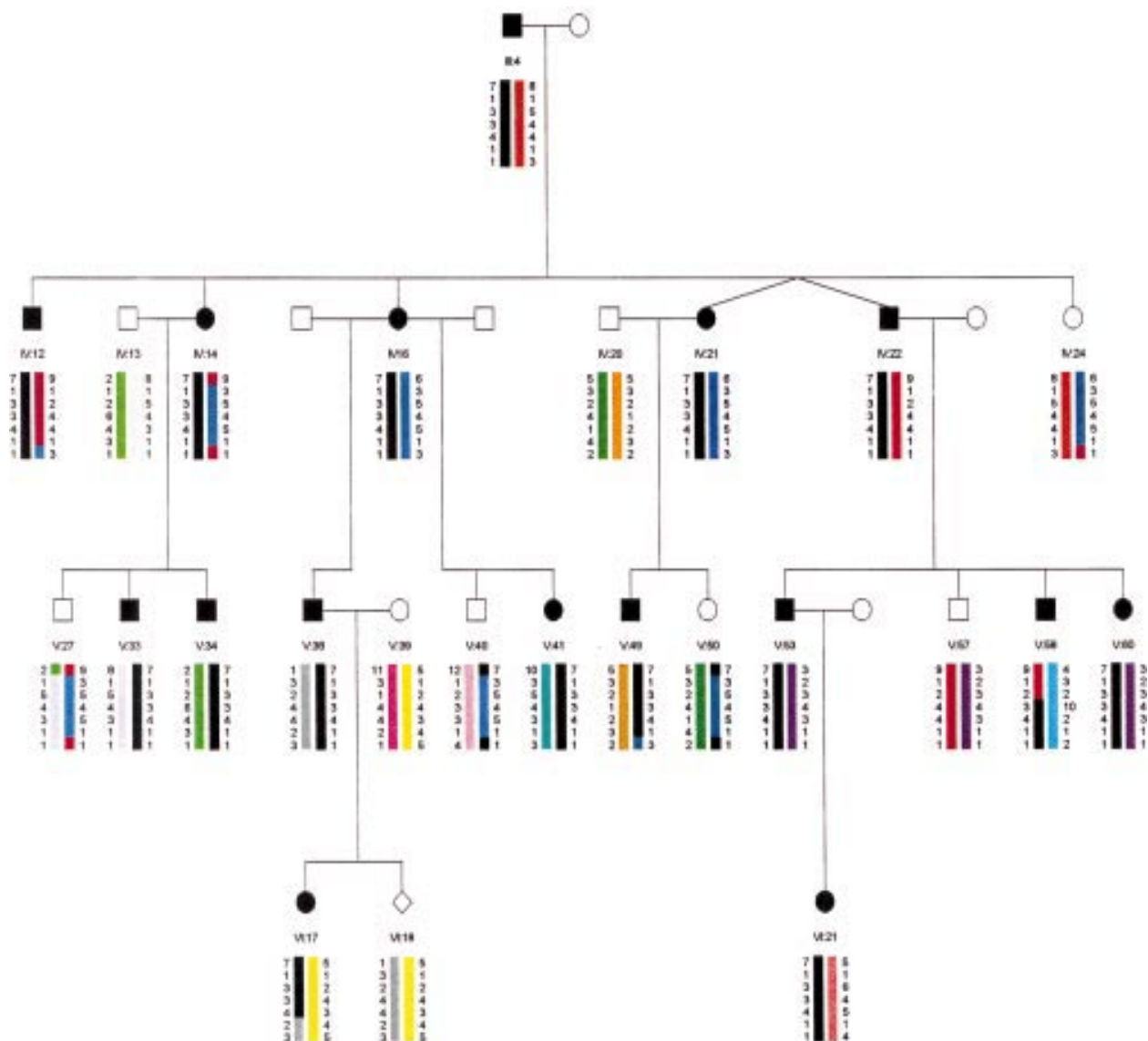


Figure 4 Partial pedigree showing the 16 affected and nine unaffected subjects in whom linkage and haplotype analysis was carried out and the haplotypes obtained. The seven microsatellite markers mapping to chromosome 7q36 are ordered from centromere to telomere.

been identified in transcripts of any of these candidate genes in patients with PPD2/3 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 *HLXB9* 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*.³² It will be interesting to see if the *Ssq* phenotype results from a similar regulatory mutation in *Lmbr1*, rather than a regulatory mutation in *Shh*, as originally proposed.¹⁹ These exciting new findings strongly suggest that PPD2/3 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 acheiropodia, confirming the gene's importance in human limb development.³³

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

- 1 Grosse FR, Herrmann J, Opitz JM. The F-form of acro-pectoro-vertebral dysplasia: the F-syndrome. *Birth Defects* 1969;V:48-63.
- 2 Camera G, Camera A, Pozzolo S, Costa M, Mantero R. F-syndrome (F-form of acro-pectoro-vertebral dysplasia): report on a second family. *Am J Med Genet* 1995;57:472-5.
- 3 Heutink P, Zguricas J, van Oosterhout L, Breedveld GJ, Testers L, Sandkuijl LA, Snijders PJ, Weissenbach J, Lindhout D, Hovius SE, Oostra BA. The gene for triphalangeal thumb maps to the subtelomeric region of chromosome 7q. *Nat Genet* 1994;6:287-92.
- 4 Hing AV, Helms C, Slaugh R, Burgess A, Wang JC, Herman T, Dowton SB, Donis-Keller H. Linkage of preaxial polydactyly type 2 to 7q36. *Am J Med Genet* 1995;58:128-35.
- 5 Radhakrishna U, Blouin JL, Solanki JV, Dhoriani GM, Antonarakis SE. An autosomal dominant triphalangeal thumb: polysyndactyly syndrome with variable expression in a large Indian family maps to 7q36. *Am J Med Genet* 1996;66:209-15.
- 6 Zguricas J, Heus H, Morales-Peralta E, Breedveld G, Kuyt B, Mumcu EF, Bakker W, Akarsu N, Kay SP, Hovius SE, Heredero-Baute L, Oostra BA, Heutink P. Clinical and genetic studies on 12 preaxial polydactyly families and refinement of the localisation of the gene responsible to a 1.9 cM region on chromosome 7q36. *J Med Genet* 1999;36:32-40.
- 7 Dobbs MB, Dietz FR, Gurnett CA, Morcuende JA, Steyers CM, Murray JC. Localization of dominantly inherited isolated triphalangeal thumb to chromosomal region 7q36. *J Orthop Res* 2000;18:340-4.

- 8 Tsukurov O, Boehmer A, Flynn J, Nicolai JP, Hamel BC, Traill S, Zaleske D, Mankin HJ, Yeon H, Ho C, Tabin C, Seidman JG, Seidman C. A complex bilateral polysyndactyly disease locus maps to chromosome 7q36. *Nat Genet* 1994;6:282-6.
- 9 Balci S, Demirtas M, Civelek B, Piskin M, Sensoz O, Akarsu AN. Phenotypic variability of triphalangeal thumb-polysyndactyly syndrome linked to chromosome 7q36. *Am J Med Genet* 1999;87:399-406.
- 10 Hing AV, Helms C, Donis-Keller H. VNTR and microsatellite polymorphisms within the subtelomeric region of 7q. *Am J Hum Genet* 1993;53:509-17.
- 11 Teo HL. Manual DNA extraction protocol. *The Probe* 1995; Autumn:3.
- 12 Weber JL, May PE. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am J Hum Genet* 1989;44:388-96.
- 13 Lathrop GM, Lalouel JM. Easy calculations of lod scores and genetic risks on small computers. *Am J Hum Genet* 1984;36:460-5.
- 14 Kantaputra PN, Chalidapong P. Are triphalangeal thumb-polysyndactyly syndrome (TPTPS) and tibial hemimelia-polysyndactyly-triphalaengeal thumb syndrome (THPTTS) identical? A father with TPTPS and his daughter with THPTTS in a Thai family. *Am J Med Genet* 2000;93:126-31.
- 15 Dickie MM. New mutation: hemimelic extra toes, *Hx*. *Mouse News Lett* 1968;38:24.
- 16 Knudsen TB, Kochhar DM. The role of morphogenetic cell death during abnormal limb-bud outgrowth in mice heterozygous for the dominant mutation Hemimelia-extra toe (*Hmx*). *J Embryol Exp Morphol* 1981;65(suppl):289-307.
- 17 Green MC. New mutation: hammer-toe, *Hm*. *Mouse News Lett* 1964;31:27-8.
- 18 Sweet HO. *Hm* and *Hx* are not alleles. *Mouse News Lett* 1982;66:66.
- 19 Sharpe J, Lettice L, Hecksher-Sorensen J, Fox M, Hill R, Krumlauf R. Identification of *sonic hedgehog* as a candidate gene responsible for the polydactylous mouse mutant *Sasquatch*. *Curr Biol* 1999;9:97-100.
- 20 Riddle RD, Johnson RL, Laufer E, Tabin C. Sonic hedgehog mediates the polarizing activity of the ZPA. *Cell* 1993;75:1401-16.
- 21 Chang DT, Lopez A, von Kessler DP, Chiang C, Simandl BK, Zhao R, Seldin MF, Fallon JF, Beachy PA. Products, genetic linkage and limb patterning activity of a murine hedgehog gene. *Development* 1994;120:3339-53.
- 22 Masuya H, Sagai T, Wakana S, Moriwaki K, Shiroishi T. A duplicated zone of polarizing activity in polydactylous mouse mutants. *Genes Dev* 1995;9:1645-53.
- 23 Masuya H, Sagai T, Moriwaki K, Shiroishi T. Multigenic control of the localization of the zone of polarizing activity in limb morphogenesis in the mouse. *Dev Biol* 1997;182:42-51.
- 24 Charite J, de Graaff W, Vogels R, Meijlink F, Deschamps J. Regulation of the *Hoxb-8* gene: synergism between multimerized cis-acting elements increases responsiveness to positional information. *Dev Biol* 1995;171:294-305.
- 25 Knezevic V, De Santo R, Schughart K, Huffstadt U, Chiang C, Mahon KA, Mackem S. *Hoxd-12* differentially affects preaxial and postaxial chondrogenic branches in the limb and regulates *Sonic hedgehog* in a positive feedback loop. *Development* 1997;124:4523-36.
- 26 Fernandez-Teran M, Piedra ME, Kathiriyai IS, Srivastava D, Rodriguez-Rey JC, Ros MA. Role of *dHAND* in the anterior-posterior polarization of the limb bud: implications for the *Sonic hedgehog* pathway. *Development* 2000;127:2133-42.
- 27 Charite J, McFadden DG, Olson EN. The bHLH transcription factor *dHAND* controls *Sonic hedgehog* expression and establishment of the zone of polarizing activity during limb development. *Development* 2000;127:2461-70.
- 28 Hui CC, Joyner AL. A mouse model of Greig cephalopolysyndactyly syndrome: the *extra-toes* mutation contains an intragenic deletion of the *Gli3* gene. *Nat Genet* 1993;3:241-6.
- 29 Mo R, Freer AM, Zinyk DL, Crackower MA, Michaud J, Heng HH, Chik KW, Shi XM, Tsui LC, Cheng SH, Joyner AL, Hui C. Specific and redundant functions of *Gli2* and *Gli3* zinc finger genes in skeletal patterning and development. *Development* 1997;124:113-23.
- 30 Qu S, Tucker SC, Ehrlich JS, Levorse JM, Flaherty LA, Wisdom R, Vogt TF. Mutations in mouse *Aristales-like4* cause *Strong's luxoid* polydactyly. *Development* 1998;125:2711-21.
- 31 Heus HC, Hing A, van Baren MJ, Joosse M, Breedveld GJ, Wang JC, Burgess A, Donnis-Keller H, Berglund C, Zguricas J, Scherer SW, Rommens JM, Oostra BA, Heutink P. A physical and transcriptional map of the preaxial polydactyly locus on chromosome 7q36. *Genomics* 1999;57:342-51.
- 32 Clark RM, Marker PC, Kingsley DM. A novel candidate gene for mouse and human preaxial polydactyly with altered expression in limbs of *Hemimelic extra-toes* mutant mice. *Genomics* 2000;67:19-27.
- 33 Ianakiev P, van Baren MJ, Daly MJ, Toledo SP, Cavalcanti MG, Neto JC, Silveira EL, Freire-Maia A, Heutink P, Kilpatrick MW, Tsipouras P. Acheiropodia is caused by a genomic deletion in *C7orf2*, the human orthologue of the *Lmbr1* gene. *Am J Hum Genet* 2001;68:38-45.