

# Acropectorovertebral dysgenesis (F syndrome) maps to chromosome 2q36

H Thiele, C McCann, S van't Padje, G C Schwabe, H C Hennies, G Camera, J Opitz, R Laxova, S Mundlos, P Nürnberg

*J Med Genet* 2004;41:213–218. doi: 10.1136/jmg.2003.014894

The F form of acropectorovertebral dysgenesis, also called F syndrome, is a rare dominantly inherited fully penetrant skeletal disorder.<sup>1</sup> The name of the syndrome is derived from the first letter of the surname of the family in which it was originally described. Major anomalies include carpal synostoses, malformation of first and second fingers with frequent syndactyly between these digits, hypoplasia and dysgenesis of metatarsal bones with invariable synostosis of the proximal portions of the fourth and fifth metatarsals, variable degrees of duplication of distal portions of preaxial toes, extensive webbing between adjacent toes, prominence of the sternum with variable pectus excavatum and spina bifida occulta of L3 or S1. Affected individuals also have minor craniofacial anomalies and moderate impairment of performance on psychometric tests.<sup>3</sup>

Two families have been reported to date. The condition was first described by Grosse<sup>1</sup> in eight members of a four generation American family of European origin. Camera<sup>4</sup> presented an Italian family with two affected relatives and a very similar phenotype, suggesting the diagnosis of F syndrome. Recently, Dundar et al<sup>2</sup> reported a six generation Turkish family with an acropectoral-like condition showing some phenotypic overlap with F syndrome. Affected individuals have soft tissue syndactyly of all fingers and toes and, to a variable degree, pre-axial polydactyly of hands and feet. The condition was mapped to chromosome region 7q36.

Here we report that the F syndrome family originally described by Grosse et al<sup>1</sup> maps to chromosome region 2q36 and is thus distinct from the acropectoral syndrome published by Dundar et al.<sup>2</sup>

## SUBJECTS

At the time of the original study in 1968,<sup>1</sup> the F family consisted of four generations of affected and unaffected persons. A fifth generation born since then includes an

## Key points

- Acropectorovertebral dysgenesis, also called F syndrome, is a unique skeletal malformation syndrome, originally described in a four generation American family of European origin.<sup>1</sup> The dominantly inherited disorder is characterised by carpal and tarsal synostoses, syndactyly between the first and the second fingers, hypodactyly and polydactyly of feet, and abnormalities of the sternum and spine.
- We have mapped F syndrome in the original family and were able to localise the gene for F syndrome to a 6.5 cM region on chromosome 2q36 with a maximum lod score of 4.21 for marker *D2S2250*. The region contains a number of genes expressed during limb development such as *IHH*, *WNT6a*, *WNT10a*, *PAX3*, and *STK36*. Genomic sequencing of these genes showed no mutation.
- This region harbours two further limb malformation phenotypes, namely syndactyly type I and the mouse mutant doublefoot (*Dbf*), of which both show overlapping features with F syndrome.
- Our results indicate that F syndrome is clinically and genetically distinct from a previously published acropectoral syndrome located on 7q36<sup>2</sup>.

affected female and two affected males. A total of nine affected and 18 unaffected family members aged 14–79 provided blood samples for DNA analysis, representing four living generations of the five affected. Of these, 18 individuals were used for linkage; the pedigree is shown in fig 2. The phenotype of each individual was assessed and characterised on the basis of the previous report,<sup>1</sup> a clinical examination at the time of blood drawing, and by medical record review of all charts available on any person in the family. The results are summarised in table 1. Characteristic examples of the F syndrome limb phenotype are shown in fig 1.

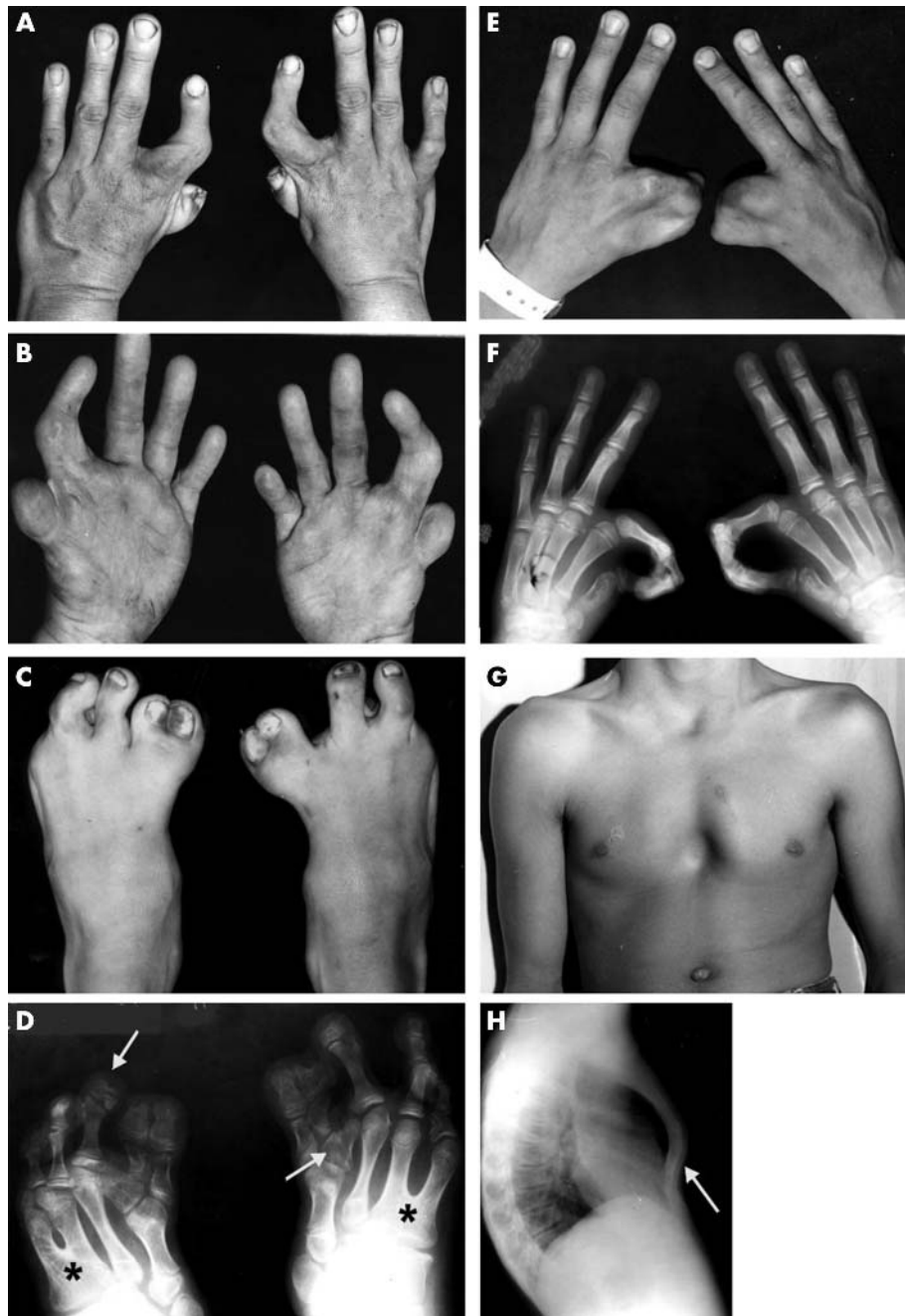
## METHODS

Genomic DNA was extracted from peripheral blood lymphocytes by standard techniques. A panel of 395 microsatellite markers from the Généthon final linkage map<sup>5</sup> with an

**Table 1** Phenotypic characteristics of F syndrome

Phenotype	affected individual
Brachycephaly	2/10
Macrocephaly	3/10
Facies sign abnormal	3/10
Low/abnormal hairline	4/10
Dental hypoplasia/dysplasia	7/10
Wide alveolar ridge	6/10
High, narrow palate	7/10
Kyphosis	3/10
Spina bifida occulta	5/10
Pectus excavatum	5/10
Syndactyly involving thumb	9/10
Carpal fusion	10/10
Broad, bifid 1 <sup>st</sup> toe	10/10
Tarsal fusion	10/10
Short, acromelic limbs	1/10

**Abbreviations:** *Dbf*, mouse mutant doublefoot; PPD, preaxial polydactyly; SD1, syndactyly type 1; *SHH*, sonic hedgehog gene; *Ssq*, mouse mutant *Sasquatch*; TPT, triphalangeal thumb-polydactyly syndrome



**Figure 1** Phenotype of F syndrome. (A) and (B) show the hand phenotype of a relatively mildly affected individual. Note the severe shortening of the thumb and partial syndactyly with the second digit. (C) shows the foot phenotype with fusion of the first and second toes. (D) is an X ray of (C), demonstrating a single first metatarsal and duplication of the first toe phalanges. The duplicated toe has, however, three phalanges (arrow, patient's right foot) indicating that this is likely to be the second toe fused to the first. There is also duplication of distal phalanges in the other toes (arrow, left foot). In addition, there is fusion of metatarsals 3 and 4 at their proximal ends (\*). (E) shows an affected hand with complete syndactyly between the first and second digits with the corresponding radiograph given in (F). (G) and (H) show a sternal deformity (arrow).

average distance of 11 cM was used to perform a genome wide linkage analysis. PCR reactions were performed using the manufacturers' protocols. Semi-automated genotyping was performed by a MegaBACE-1000 analysis system. Data were analysed by Genetic Profiler Software 1.5.

For fine mapping, a novel microsatellite marker *MO1HT1A* located 704 kb q telomere from marker *D2S434* and 477 kb centromere from marker *D2S2250* using forward primer TTACAAGgACAAGAAAAgAAg and reverse primer gggTgACAggTgCgACTC was established. A two point lod score calculation was performed with LINKAGE v5.2 program

package<sup>6</sup> using an autosomal dominant model with 100% penetrance and a gene frequency for F syndrome at 0.00001. Multipoint lod score calculation was performed using Vitesse<sup>7</sup> with the aid of Alan Young's GAS2.0 interface. The most probable haplotypes were constructed with Simwalk2 v2.82.<sup>8</sup>

Candidate genes (*IHH*, *WNT6a*, *WNT10a*, *PAX3*, and *STK36*) were tested by amplifying all known exons of each gene (Ensemble database) using primers that were placed within the introns. PCR products were sequenced from both ends and compared to the wild-type sequence.

**Table 2** Two point lod scores generated in the kindred at various recombination fractions ( $\theta=0-0.4$ ) for markers of the 2q36 region

Marker	cM*	0	0.001	0.01	0.05	0.1	0.15	0.2	0.3	0.4
D2S2382	213.49	—∞	1.208	2.149	2.579	2.528	2.332	2.063	1.383	0.579
D2S164	—	2.408	2.403	2.360	2.164	1.910	1.646	1.370	0.794	0.243
D2S434	215.78	—∞	-0.225	0.733	1.239	1.287	1.199	1.047	0.643	0.217
M02HT1A	—	3.311	3.306	3.255	3.022	2.717	2.394	2.053	1.312	0.518
D2S2250	216.31	4.214	4.207	4.145	3.858	3.482	3.086	2.666	1.751	0.756
D2S163	218.45	0.505	0.505	0.501	0.492	0.485	0.474	0.452	0.368	0.220
D2S377	220.59	1.505	1.503	1.479	1.373	1.236	1.095	0.950	0.649	0.334
PAX3.PCR1	—	—∞	0.907	1.852	2.302	2.278	2.115	1.884	1.295	0.585
D2S2228	224.33	—∞	-1.967	-0.018	1.148	1.448	1.484	1.402	1.034	0.498
D2S2308	227.00	—∞	-0.119	0.842	1.367	1.446	1.392	1.273	0.908	0.422
D2S2354	227.54	—∞	-0.132	0.833	1.371	1.458	1.407	1.287	0.916	0.422
D2S401	229.14	—∞	-0.505	0.464	1.023	1.143	1.127	1.046	0.752	0.339

\*Marker positions in cM refer to the Marshfield map.<sup>9</sup>

## RESULTS

We performed a genome wide linkage search in 16 individuals, nine affected and seven unaffected relatives. The first evidence for linkage to chromosome 2q36 was indicated by the marker *D2S377* with a lod score of  $Z_{\max}=1.505$  at  $\theta=0$  (table 2). Further fine mapping with an additional 10 markers confirmed the locus and documented critical recombination events between markers *D2S434* and *D2S2250* and markers *D2S377* and *PAX3.PCR1*. Marker *D2S2250* showed the highest two point lod score value of  $Z_{\max}=4.214$  at  $\theta=0$  (table 2). Genome wide multipoint analysis reached the same value indicating that full information from all the meioses had already been obtained using marker *D2S2250* alone (not shown).

Haplotype analysis showed clear evidence that the mutant allele cosegregated in all the affected individuals and was absent from unaffected individuals (fig 2A). Individuals II.2 and IV.3 were identified as obligate recombinants determining the critical interval. To further narrow the 8.5 cM interval between markers *D2S434* and *D2S2228*, novel microsatellite markers were developed based on the NCBI genomic sequence assembly data (build32; April 2003). Marker *PAX3.PCR1* is located upstream of the *PAX3* gene, some 530 kb towards the centromere from *D2S360* (GDB:187424<sup>10</sup>; fig 3). Since this marker was still subject to recombination in individual II.2, the critical interval could be further reduced distally by about 1.53 cM. Unfortunately, the new marker *M02HT1A* identified in the interval between markers *D2S434* and *D2S2250* was uninformative for the relevant meiosis in individual III.7 (fig 2). Thus, the current critical interval is confined by the markers *D2S434* and *PAX3.PCR1* and spans a physical distance of approximately 4.6 Mb. This corresponds to a genetic distance of approximately 6.5 cM. For the Italian family, originally described by Camera and colleagues,<sup>4</sup> haplotype analysis at chromosome 2q36 was consistent with linkage to this region (fig 2B).

Searching for candidate genes using the NCBI MapViewer showed several interesting candidate genes, such as *PAX3*, *WNT6*, *WNT10A*, and *IHH*. We identified a 469C>G transition (based on accession number AB059570) resulting in substitution of proline to arginine (P155A) in exon 3 of the *WNT6* gene. However, this change was also present in person III.1 who is unaffected (fig 2). This change does not correspond to a known SNP. The residue was not found to be conserved between mouse and human. Thus, sequencing of the exons and flanking splice sites of all these genes failed to detect mutations in the two F syndrome families, the original F syndrome family and the Italian family.<sup>4</sup>

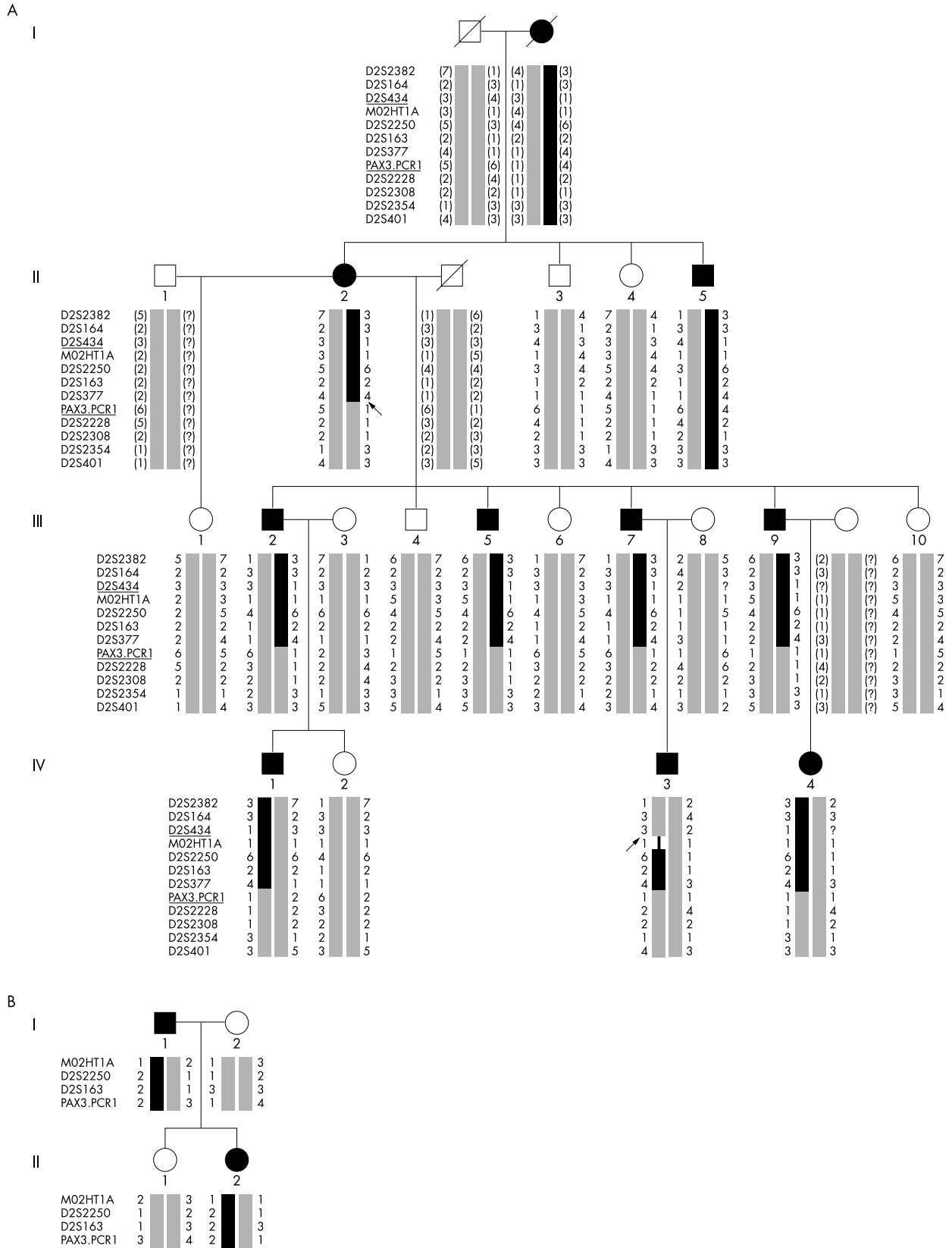
## DISCUSSION

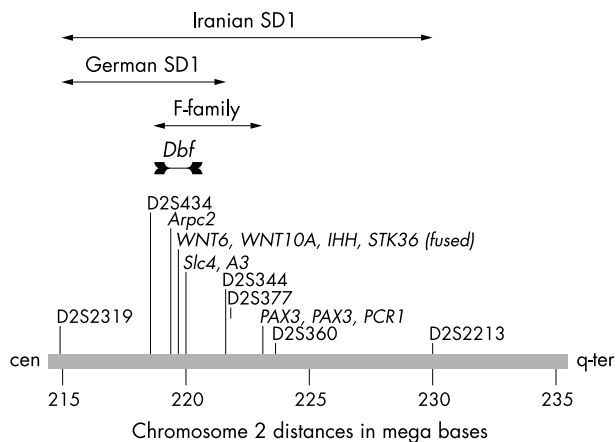
F syndrome comprises carpal and tarsal synostoses, dysgenesis of the first and second finger with frequent syndactyly between them, fusion of first and second toes, syndactyly of toes and fusion of metatarsals, malformation of the sternum, and spina bifida occulta (fig 1, table 1). The presence of syndactyly of fingers and toes suggests that the causative gene is involved in early limb patterning at a stage when the number of digits is determined or when digits are separated from each other. Several pathways such as the hedgehog, fibroblast growth factor and bone morphogenetic protein pathways, are involved in these complex processes and an increasing number of phenotypes is being identified with defects in these regulatory pathways.<sup>14</sup> It may be assumed that the identification of the F syndrome gene or mutation may give new insights into the pathogenesis of limb development and malformation syndromes with syndactyly or polydactyly.

We performed a genome wide linkage analysis of the F syndrome and were able to localise the underlying gene at chromosome 2q36 within a physical fragment of approximately 4.6 Mb correlating to a genetic distance of approximately 6.5 cM (fig 2A). *PAX3* is located at the very telomeric end of the critical segment. Different mutations in *PAX3* cause Waardenburg syndrome type 3 and craniofacial-deafness-hand syndrome.<sup>15,16</sup> Because affected individuals in Waardenburg syndrome type 3 have skeletal upper-limb hypoplasia,<sup>16,17</sup> we considered *PAX3* a candidate gene for F syndrome. However, sequencing of *PAX3* showed no mutation in our patients. *WNT6* and *WNT10A* were considered interesting candidate genes. They are clustered in a head-to-head manner within an interval of less than 7 kb inside the critical segment.<sup>18</sup> *Wnt6* is expressed in the developing murine limb.<sup>19</sup> Similar results were obtained by Hayes et al<sup>13</sup> who demonstrated expression of both *Wnt6a* and *Wnt10a* in the progress zone of the developing limb buds. However, no mutations in *WNT6* and *WNT10A* could be demonstrated.

*IHH* appeared to be a further candidate gene located within the F syndrome critical region. *Ihh* is known to mediate condensation, growth, and differentiation of cartilage.<sup>20</sup> Mutations in *IHH* cause brachydactyly type A1<sup>21</sup> and acrocapitofemoral dysplasia,<sup>22</sup> two conditions involving the growth and differentiation of limb skeletal elements. The *fused* gene (*FU*, or *STK36*) encodes a serine/threonine kinase positively acting in the hedgehog pathway. Given the previous finding that many polydactyly conditions are caused by mutations in genes involved in the hedgehog pathway, we considered *fused* as a further candidate for F syndrome. However, no mutations were identified in *IHH* or *STK36*.<sup>23</sup>

Other conditions with limb malformations and syndactyly/polydactyly are linked to this region of 2q36. Syndactyly type





**Figure 3** Physical map of the linkage region on chromosome 2. Marker and gene positions are plotted in megabases according to the NCBI genomic sequence (build33; April-2003). Mapping intervals of the F family,<sup>1</sup> German syndactyly type 1 family<sup>11</sup> and Iranian syndactyly type 1 family<sup>12</sup> are shown as horizontal double arrows. Mapping interval of the mouse mutant doublefoot (*Dbf*)<sup>3</sup> is indicated as inverted double arrows. The genes *Arpc2* and *Slc4A3* represent approximate flanking locations from the region of conserved synteny on mouse chromosome 1. cen, centromeric orientation; q-ter, q-terminal orientation.

1 (SD1) also referred as “type Lueken syndactyly” was mapped to a region overlapping with the F syndrome defining a 9.4 cM region between markers *D2S2319* and *D2S344*,<sup>11</sup> (fig 3). The locus for SD1 could be confirmed in a second six generation Iranian family.<sup>12</sup> Syndactyly type 1 is characterised by variable syndactyly between the second and third toes, extending to complete syndactyly between the second and the fifth finger and the first to fifth toes. The involvement of the second finger appears to be a rather rare event in syndactyly type 1, raising the possibility that this family may be unique, and has therefore been classified as syndactyly type Lueken.<sup>24</sup> In contrast to the F syndrome phenotype, polydactyly and involvement of the thumbs is not observed. In particular, the characteristic syndactyly of the first and second fingers and the fusions of carpal and tarsal bones are not part of syndactyly type 1. However, both conditions affect the patterning of early digit formation and in particular the separation of digits, a process known to involve extensive apoptosis partly controlled through the bone morphogenetic protein pathway. Hence, it is conceivable that the F syndrome and syndactyly may be caused by different mutations in the same gene.

The mouse mutant doublefoot (*Dbf*) was mapped to a 0.4 cM region on mouse chromosome 1.<sup>13, 25</sup> This region is syntenic to human 2q36 and contains the F syndrome critical interval including the genes *Ihh*, *Wnt6*, *Wnt10a*, and *fused* (fig 3). *Dbf* is characterised by preaxial (anterior) duplication of digits resulting in one to four additional digits and syndactyly. Ectopic expression of *Ihh* throughout the distal limb bud mesenchyme appears to be a main causative event<sup>26</sup> resulting in two hedgehog signals, one posterior by regular *Shh* expression and one anterior by ectopic *Ihh* expression. No mutation has been detected for *Dbf* to date but regulatory mutations affecting *Ihh* have been proposed. The phenotypic overlap between F syndrome, SD1 and *Dbf* raises the question of whether *IHH* misexpression could be involved in the pathogenesis of the human condition as well. *IHH* is causally involved in another condition already mentioned above, brachydactyly type A1. This condition is characterised by hypoplasia or aplasia of the middle phalanges, a phenotype not present in F syndrome or syndactyly type 1.

Dundar described a novel syndrome in a large Turkish family that maps to 7q36.<sup>2</sup> The authors describe overlap with F syndrome and concluded that the two conditions are related but distinct. Both conditions show syndactyly and involvement of the sternum but neither the characteristic syndactyly of fingers 1 and 2 nor the tarsal or metatarsal synostoses were observed in the Turkish family. Our present results clearly show that F syndrome and the previously published acropectoral syndrome<sup>2</sup> can be considered to be clinically and genetically separate conditions. Interestingly, the conditions described by Dundar et al map in close vicinity to the *sonic hedgehog* (*SHH*) gene which shows a high degree of homology to *IHH*. Like the locus at 2q36, the locus at 7q36 harbours several limb malformation syndromes such as preaxial polydactyly (PPD) types 2 and 3, triphalangeal thumb-polydactyly syndrome (TPT), and Haas type syndactyly (syndactyly type IV).<sup>27</sup>

Recently this form of TPT/PPD has been shown to be caused by mutations in a *Shh* long range cis-regulatory element, located within intron 5 of the adjacent *C7orf2* gene.<sup>23</sup> In addition, the syntenic region in the mouse is disrupted in the mouse mutant *Sasquatch* (*Ssq*) exhibiting preaxial polydactyly.<sup>23</sup> Acheiropodia is a recessive condition, characterised by a phenotype resembling the murine *Shh* null phenotype with hemimelia of both upper limbs and a distal third of both lower limbs. Acheiropodia is caused by homozygous deletion of exon 3 of *C7orf2* and parts of the flanking introns.<sup>28</sup> The mutation has also been interpreted as loss of a cisregulatory putative *Shh* regulatory element, located in an *C7orf2* intron, approximately 1 Mb away from *Shh*.<sup>23</sup> If the clustering of limb phenotypes around the *IHH* locus has pathogenetic similarities to those conditions clustered around the *SHH* a regulatory mutation leading to disruption of the fine tuned expression of *IHH* may also be considered as a possible cause for F syndrome.

**ACKNOWLEDGEMENTS**

We would like to thank all the individuals who participated in this study.

**Authors’ affiliations**

- H Thiele, S van’t Padje, G C Schwabe, S Mundlos, P Nürnberg**, Institute for Medical Genetics, Charité University Hospital, Humboldt-University, Berlin, Germany
- H Thiele, H C Hennies, P Nürnberg**, Gene Mapping Centre, Max Delbrueck Centre for Molecular Medicine, Berlin-Buch, Germany
- G C Schwabe, S Mundlos**, Max Planck Institute for Molecular Genetics, Ihnestr. 73, 14195, Berlin, Germany
- C McCann**, Providence Alaska Medical Genetics Center, Anchorage, USA
- G Camera**, Servizio di Genetica e Dismorfologia, Ospedali Galliera, Genoa, Italy
- R Laxova**, Clinical Genetics Center, University of Wisconsin-Madison, USA
- J Opitz**, Pediatrics (Medical Genetics), Human Genetics, Obstetrics & Gynecology, Pathology, University of Utah, Salt Lake City, Utah, USA

This work was supported by a grant from the Deutsche Forschungsgemeinschaft to S.M. and by grant 01 GR 0104 to P.N.

Correspondence to: Stefan Mundlos, Institute for Medical Genetics, Charité University Hospital, Augustenburger Platz 1, D-13353 Berlin, Germany; stefan.mundlos@charite.de

Received 23 September 2003  
 Revised version received 6 November 2003  
 Accepted 14 November 2003

**REFERENCES**

1 Grosse FR, Herrmann J, Opitz JM. The F-form of acropectorovertbral dysplasia: the F-syndrome. *Birth Defects Orig Artic Ser* 1969;3:48–63.

- 2 **Dundar M**, Gordon TM, Ozyazgan I, Oguzkaya F, Ozkul Y, Cooke A, Wilkinson AG, Holloway S, Goodman FR, Tolmie JL. A novel acropectoral syndrome maps to chromosome 7q36. *J Med Genet* 2001;**38**:304–9.
- 3 **Trites LT**, Matthews CG. Psychologic test findings in the F-form of acro-pectoro-vertebral dysplasia: the F-syndrome. *Birth Defects Orig Artic Ser* 1969;**3**:64–5.
- 4 **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.
- 5 **Dib C**, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J. A comprehensive genetic map of the human genome based on 5264 microsatellites. *Nature* 1996;**380**:152–4.
- 6 **Lathrop GM**, Lalouel JM. Easy calculations of lod scores and genetic risks on small computers. *Am J Hum Genet* 1984;**36**(2):460–5.
- 7 **O'Connell JR**, Weeks DE. The VITESSE algorithm for rapid exact multilocus linkage analysis via genotype set-recoding and fuzzy inheritance. *Nat Genet* 1995;**11**:402–8.
- 8 **Sobel E**, Lange K. Descent graphs in pedigree analysis: applications to haplotyping, location scores, and marker sharing statistics. *Am J Hum Genet* 1996;**58**:1323–37.
- 9 **Broman KW**, Murray JC, Sheffield VC, White RL, Weber JL. Comprehensive human genetic maps: individual and sex-specific variation in recombination. *Am J Hum Genet* 1998;**63**:861–9.
- 10 **Wilcox ER**, Rivolta MN, Ploplis B, Potter SB, Fex J. The PAX3 gene is mapped to human chromosome 2 together with a highly informative CA dinucleotide repeat. *Hum Mol Genet* 1992;**1**:215.
- 11 **Bosse K**, Betz RC, Lee YA, Wienker TF, Reis A, Kleen H, Propping P, Cichon S, Noethen MM. Localization of a gene for syndactyly type 1 to chromosome 2q34–q36. *Am J Hum Genet* 2000;**67**:492–7.
- 12 **Ghadami M**, Majidzadeh AK, Haerian BS, Damavandi E, Yamada K, Pasallar P, Najafi MT, Nishimura G, Tomita HA, Yoshiura KI, Niikawa N. Confirmation of genetic homogeneity of syndactyly type 1 in an Iranian family. *Am J Med Genet* 2001;**104**:147–51.
- 13 **Hayes C**, Rump A, Cadman MR, Harrison M, Evans EP, Lyon MF, Morriss-Kay GM, Rosenthal A, Brown SD. A high-resolution genetic, physical, and comparative gene map of the doublefoot (*Dbf*) region of mouse chromosome 1 and the region of conserved synteny on human chromosome 2q35. *Genomics* 2001;**78**:197–205.
- 14 **Kornak U**, Mundlos S. Genetic disorders of the skeleton: a developmental approach. *Am J Hum Genet* 2003;**73**(3):447–74.
- 15 **Asher JH Jr**, Sommer A, Morell R, Friedman TB. Missense mutation in the paired domain of PAX3 causes craniofacial-deafness-hand syndrome. *Hum Mutat* 1996;**7**:30–5.
- 16 **Hoth CF**, Milunsky A, Lipsky N, Sheffer R, Clarren SK, Baldwin CT. Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *Am J Hum Genet* 1993;**52**:455–62.
- 17 **Tassabehji M**, Newton VE, Liu XZ, Brady A, Donnai D, Krajewska-Walasek M, Murday V, Norman A, Obersztyn E, Reardon W. The mutational spectrum in Waardenburg syndrome. *Hum Mol Genet* 1995;**4**:2131–7.
- 18 **Kirikoshi H**, Sekihara H, Kato M. WNT10A and WNT6, clustered in human chromosome 2q35 region with head-to-tail manner, are strongly coexpressed in SW480 cells. *Biochem Biophys Res Commun* 2001;**283**:798–805.
- 19 **Parr BA**, Shea MJ, Vassileva G, McMahon AP. Mouse Wnt genes exhibit discrete domains of expression in the early embryonic CNS and limb buds. *Development* 1993;**119**:247–61.
- 20 **Vorkamp A**, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ. Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. *Science* 1996;**273**:613–22.
- 21 **Gao B**, Guo J, She C, Shu A, Yang M, Tan Z, Yang X, Guo S, Feng G, He L. Mutations in IHH, encoding Indian hedgehog, cause brachydactyly type A-1. *Nat Genet* 2001;**28**:386–8.
- 22 **Helleman J**, Coucke PJ, Giedion A, De Paepe A, Kramer P, Beemer F, Mortier GR. Homozygous mutations in IHH cause acrocapitofemoral dysplasia, an autosomal recessive disorder with cone-shaped epiphyses in hands and hips. *Am J Hum Genet* 2003;**72**:1040–6.
- 23 **Hill RE**, Heaney SJ, Lettice LA. Sonic hedgehog: restricted expression and limb dysmorphologies. *J Anat* 2003;**202**(1):13–20.
- 24 **Lenz W**, Majewski F. Fehlbildungen der Gliedmaßen. In: Schinz HR, ed. *Lehrbuch der Röntgendiagnostik*. Thieme. Stuttgart: Verlag, 1981:935–1032.
- 25 **Crick AP**, Babbs C, Brown JM, Morriss-Kay GM. Developmental mechanisms underlying polydactyly in the mouse mutant Doublefoot. *J Anat* 2003;**202**:21–6.
- 26 **Yang Y**, Guillot P, Boyd Y, Lyon MF, McMahon AP. Evidence that preaxial polydactyly in the Doublefoot mutant is due to ectopic Indian Hedgehog signaling. *Development* 1998;**125**:3123–32.
- 27 **Kantaputra PN**, Chalidapong P. Are triphalangeal thumb-polysyndactyly syndrome (TPTPS) and tibial hemimelia-polysyndactyly-triphalangeal 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.
- 28 **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**(1):38–45.