A large Turkish kindred with syndactyly type II (synpolydactyly). 2 Homozygous phenotype?

A Nurten Akarsu, Okan Akhan, Bekir Sitki Saylı, Uğur Saylı, Gülay Baskaya, Mansoor Sarfarazi

Department of Medical Biology and Genetics, University of Ankara, Faculty of Medicine, Sihhiye, Ankara, Turkey
A N Akarsu
B S Saylı

Department of Radiology, University of Hacettepe, Faculty of Medicine, Sihhiye, Ankara, Turkey
O Akhan

Orthopedics Clinic, Etimesgut Community Hospital, Ankara, Turkey
U Saylı

Barbaros Health Centre, Kayseri, Turkey
G Baskaya

Surgical Research Centre, Department of Surgery, University of Connecticut Health Centre, Farmington, Connecticut 06030-1110, USA
M Sarfarazi
A N Akarsu

Correspondence to:
Dr Sarfarazi.

Received 9 August 1994
Revised version accepted for publication 5 January 1995

Abstract
Syndactyly type II (synpolydactyly, SPD) is an autosomal dominant condition with typical abnormalities of the distal parts of both upper and lower limbs. We report here a previously undescribed phenotypic feature of people with severe hand and foot deformities who were born to two affected parents. This is the first example of SPD subjects manifesting a very distinctive phenotype, suggesting that they must be homozygous for this condition. The typical characteristic clinical features in these subjects are as follows: (1) short hands with wrinkled fatty skin and short feet; (2) complete soft tissue syndactyly involving all four limbs; (3) polydactyly of the preaxial, mesoaxial, and postaxial digits of the hands; (4) loss of the normal tubular shape of the carpal, metacarpal, and phalangeal bones, so as to give polygonal structures; (5) loss of the typical structure of the cuboid and all three cuneiform bones while the talus calcaneus and navicular bones remain intact; (6) large bony islands instead of metatarsals, most probably because of cuboid-metatarsal and cuneiform-metatarsal fusions; and (7) severe middle phalangeal hypoplasia/aplasia as well as fusion of some phalangeal structures that are associated with the loss of normal phalangeal pattern. We report seven subjects with this phenotype from three different branches of a very large SPD pedigree exhibiting the same phenotype with minimal variation. In mice, the Poly syndactyly (PS) mutation shows a pattern of synpolydactyly very similar to that of human SPD, suggesting that they may well be homologous mutations. A molecular genetic study is currently under way to determine the chromosomal location of the SPD locus in humans and to identify the corresponding homologous region in mice.

Materials and methods
The family structure and results of physical examinations are reported in the preceding paper and summarised on each individual pedigree. The people with more severe deformities were shown as solid symbols and abbreviated as “CS” below each subject in each pedigree.

The personal identification numbers (PID) of these people in the same pedigrees are given in table 1 for comparison. There is a total of seven subjects showing complete complex syndactyly, all of whom were examined in the field by at least one of us, and x ray films were obtained from five willing subjects.

Results
CLINICAL FINDINGS
Case 1 (SPD-1, PID 43)
This 30 year old female has short hands and feet with complete soft tissue syndactyly involving all four extremities (fig 1A,B). She was born to two affected parents with typical phenotypic expression of SPD (SPD-1, PID 17 and PID 18). The upper limbs are “paw-like” and have “cat’s paw” appearance. Both hands display complete soft tissue syndactyly involving all fingers, and the thumb and forefinger are extremely rudimentary. The remaining digits are within the mass of this soft tissue. The nails of the first two fingers are hypoplastic, but the others are hardly detectable within this mass. The left hand differed somewhat in that the third finger is identifiable and there is an enlarged nail, probably representing the fourth or more fingers. The “paw-like” appearance was further aggravated by a large amount of wrinkled and fatty skin over the dorsum and by camptodactyly of the digits (fig 1A). Palpation of the hands also gave the impression that some bones were missing under the skin. X rays of the hands showed patches of abnormal bone, beginning at the carpal level all the way to the third phalanx (fig 1C). In par-
Table 1. The corresponding personal identification numbers (PID) of homozygotes in the previously reported circular and individual pedigrees.3

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Family No in each pedigree</th>
<th>PID numbers in pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1, female</td>
<td>SPD-1</td>
<td>43 VI-4</td>
</tr>
<tr>
<td>Case 2, female</td>
<td>SPD-1</td>
<td>74 VII-4</td>
</tr>
<tr>
<td>Case 3, male</td>
<td>SPD-1</td>
<td>75 VII-5</td>
</tr>
<tr>
<td>Case 4, female</td>
<td>SPD-1</td>
<td>45 VI-5</td>
</tr>
<tr>
<td>Case 5, female</td>
<td>SPD-2</td>
<td>44 VI-34</td>
</tr>
<tr>
<td>Case 6, female</td>
<td>SPD-2</td>
<td>45 VI-35</td>
</tr>
<tr>
<td>Case 7, female</td>
<td>SPD-3</td>
<td>109 VII-14</td>
</tr>
</tbody>
</table>

In particular, the normal tubular shape of the metacarpals and phalanges was lost and was substituted by some cuboidal or polygonal bony structures. Similarly, although to a lesser extent, the carpal bones were transformed into cuboidal forms with partial fusion. Carpometacarpal lines were hardly identifiable. Up to six consecutive abnormal bones in two rows replaced the metacarpal bones (fig 1C). These structures may be tandem duplication of rudimentary and abnormal metacarpals.

There were eight bony structures on the right hand and seven on the left hand which replaced normal digits, so that both pre- and postaxial polydactyly were present. The bones in the thumb formation were extremely hypoplastic and deformed with an articulation defect. The second digits were similarly abnormal, in that either the middle phalanx was absent or the presence of the distal bone was the result of fusion of the middle and distal phalanges. Middle phalangeal hypoplasia/aplasia was noted in all fingers as well as brachymetaphalangism. In the postaxial region, there was one abnormal bone on the left and two on the right, possibly representing little fingers. In addition to these abnormalities, the middle and distal phalanges of the fourth and fifth fingers were synostotic on the left side. The feet were similarly short and exhibited complete soft tissue syndactyly. The big toe was normal on both sides, but their nails were extremely hypoplastic (fig 1B). The distance between the big toe and the subsequent complex of toes was enlarged. The second toe was hypoplastic and was attached to a complex in which other toes were not discernible individually.

X ray examination of the feet showed normal talus, calcaneus, and navicular bones, whereas all three cuneiform bones were indistinguishable from each other. The distance between the big toe and the subsequent complex of toes was enlarged. The second toe was hypoplastic and was attached to a complex in which other toes were not discernible individually.

Figure 1A–D  Hands and feet of case 1 (subject 43, SPD-1) with characteristic manifestation of the SPD homozygous phenotype.
able from the fused metatarsal bones (fig 1D).
The cuboid bone was completely lost and was
substituted by a large polygonal bony structure,
probably representing the cuboid as well as the
fourth and fifth metatarsal bones. These bony
islands did not allow the tarsal and metatarsal
bones to be distinguished. No extra digit was
present on either side. The distal phalanx of the
big toe was rudimentary. All of the phalangeal
structures lost their normal tubular appearance,
and the middle phalanges were extremely hypoplastic or even absent on both sides. On the
right, the proximal phalanges of the third and
fourth toes were fused with abnormal me-
tatarsal structures. There were similar findings
on the left, except for the presence of a me-
tatarsalphalangeal fusion.

There was no associated abnormality in this
person. Pedigree data in our previous work
indicated that the subject belonged to a sibship
of 10, of whom nine are affected. All of the
affected sibs showed typical features of SPD,
except one (PID 45) (tables 2 and 3). Both of
the parents were affected with typical SPD.
However, the mother showed an enlarged hal-
xus on the right foot, which may suggest pre-
axial polydactyly. The husband (PID 44) also
has typical features of synpolydactyly and two
offspring are affected with similar complex
complete syndactyly.

Case 2 (SPD-1, PID 74)
This 8 year old female has bilaterally short
hands with a typical “paw-like” appearance (fig
2A). On her right hand, the first and second
digits are distinguishable and there is complete
soft tissue syndactyly involving the remaining
digits. On her left hand, none of the digits
except the thumb were discernible separately
within the mass. Her nails are normal and there
is camptodactyly involving all digits bilaterally.
Palpation gave the impression that some bones may be missing under the skin, being masked by wrinkled and fatty skin over the dorsum. There was an increased distance between the mass and the index finger. X-ray examination showed normal radial and
A large Turkish kindred with syndactyly type II (sympolysyndactyly). 2 Homozygous phenotype?

ulnar bones on both sides. Abnormal development has apparently started from the carpal boundary (fig 2B). Briefly, the carpal bones have lost their normal shape and are substituted by bony islands. All of the carpo-metacarpal bones are replaced by polygonal or cuboid structures. Bony fusion was noted at the carpal level bilaterally. Six bony structures and triphalangeal thumbs constitute the fingers of both hands. Additionally, a small piece of extra bone is present next to both thumbs. There was bony fusion between the proximal, middle, and distal phalanges on the third and fourth digits of the right hand only.

In the foot, the halluces were found to be normal, whereas the other toes were within the mass of soft tissue (fig 2C). X ray examination showed normal talus, calcaneus, and navicular bones. There were large bony islands resulting from fusion of the cuneiform-metatarsal and cuboid-metatarsal bones (fig 2D). No extra toe was present, but all toes have lost their normal shape and the phalanges were hardly discernible. A triphalangeal hallux with its tibial deviation is the additional feature of this phenotype.

Other cases
The phenotypes of cases 3 (fig 3A–D), 4 (fig 4A,B), 5 (fig 5A–D), 6, and 7 are strikingly similar to those of the above mentioned cases and are summarised in tables 2 and 3.

PEDIGREE ANALYSIS
We have identified eight marriages between two affected people. One of these is a marriage between a homozygote and a heterozygote (SPD-1 PIDs 43 and 44) producing two homozygous offspring. In the other marriages both parents are heterozygotes. Eight marriages
Figure 6  Inheritance of the homozygous and heterozygous subjects in one branch of the SPD-2 pedigree. The segregation and phenotypic expression in the hands and feet in the homozygous subjects (persons 44 and 45) are shown for comparison with their heterozygous parents and sibs. The location of each subject in the circular pedigree is indicated below each subject.

produced a total of 30 offspring, 27 affected and three unaffected. Seven of the 27 affected subjects exhibited more severe features, suggesting homozygosity at the genetic level. Furthermore, despite the fact that they come from different branches of the same kindred, there are close phenotypic similarities among them. Seven of the above mentioned eight marriages were between two typical heterozygote SPD parents producing a grand total of 25 affected (expected n = 21) and three normal (expected n = 7) offspring. Only one marriage was noted between an SPD heterozygote and homozygote producing two affected (expected n = 2) and no normal (expected n = 0) offspring. The observed frequencies of a total of 27 affected and three normal offspring in these eight matings are well within the expected values of 23 affected and seven normal offspring ($\chi^2 = 2.98$, p = 0.084). Fig 6 exemplifies the “homozygous phenotype of SPD” as compared with typical SPD of heterozygous parents and sibs. A drawing of the observed characteristic features in the hands and feet of these homozygous cases is presented in fig 7 and 8 respectively.

Discussion

To the best of our knowledge, this work presents the first cases of people with severe hand and foot deformities who were born to two parents affected with SPD. The phenotypic expression is uniquely different from other patients affected with SPD (that is, heterozygotes) who are usually born to one affected and one normal parent. So, at the genotypic level, the subjects presented here must be homozygous for the SPD gene, representing yet another phenotypically detectable example of homozygotes for a rare autosomal disorder. The characteristic findings in these subjects

Figure 7  Drawings of the homozygote's hands representing changes in the normal tubular formation of the bones. See text for details.
are: (1) short hands with wrinkled fatty skin and short feet; (2) complete soft tissue syndactyly involving all four limbs; (3) polydactyly on preaxial, mesoaxial, and postaxial areas of the hands; (4) loss of normal tubular shape of carpal, metacarpal, and phalangeal bones leading to polygonal structures; (5) loss of typical structures of the cuboid and all three cuneiform bones, with the talus, calcaneus, and navicular bones remaining intact; (6) large bony islands of metatarsals, most probably arising from cuboid-metatarsal and cuneiform-metatarsal fusions; and (7) severe middle phalangeal hypoplasia/aplasia, together with fusion of some phalangeal structures that are associated with the loss of the normal phalangeal pattern. There is little variation between the left and right hands (if any) as shown by x rays indicating a "mirror effect". On x ray examination, this phenotype can be easily distinguished from the other types of complete syndactyly. Thus, this unusual phenotype must represent homozgyosity for the SPD gene.

In mice, syn/polydactyly results from a number of distinct mutations. In addition to these mutations, Johnson described another mutant gene which is designated poly syndactyly (Ps). The characteristic features of this mutation are the most similar to those described in our patient population, as originally suggested by Winter. However, homozygous mice die at or before birth. Embryological studies in the mouse showed that cell death of interdigital areas is almost totally absent in fore- and hind feet in Ps/Ps mutants, chondrification is poor, and up to six metatarsals can be seen. Thus, phenotypically, the Ps mutation could be the counterpart of the human SPD mutation in mice. No homology is known between the Ps locus and its counterpart in humans. However, the two flanking loci to the Ps locus on mouse chromosome 4 (Pgm-2 and C8b) do show homology with the region 1p36–p22 in humans, providing an excellent candidate region for polydactyly. However, a genetic linkage study of DNA markers selected from the entire short arm of chromosome 1 produced a negative lod score in the Derbent kindred. These preliminary linkage studies showed that either the mouse Ps mutation is not the counterpart of SPD in humans or the precise homologous region of the Ps locus in the mouse is not the corresponding region of 1p36–p22 in humans.

From an embryological point of view, the differentiation of specific cell types and structures suggest that limb buds have positional information which must relate to the proxi modinal, anteroposterior (preaxial-postaxial), and dorsoventral axes. In this particular phenotype, while the thumb and hallux are situated on the preaxial side of the limb and the fifth digit on the postaxial side, the formation of a correct number of digits and a correct pattern of formation is likely to be defective. The typical SPD phenotype (heterozygous) shows at least a normal pattern formation on positional information. Thus, it is classified as "increased number of digits on the mesoaxial line with normal pattern formation" according to the newly devised classification of Winter and Tickle. Speculatively, to have such a normal pattern of formation (that is, heterozygous SPD), it seems likely that at least one copy of a normal gene is essential. Positional mapping of the putative gene, mutation identification, and cloning of the eventual molecular defect will solve the synpolydactyl puzzle. Studies are currently under way in our laboratory to identify the chromosomal location of the SPD locus.

We would like to thank the Turkish Ministry of Health, Division of Basic Health Services for providing many facilities including x rays and transport to and from the village of Derbent. We would also like to thank Dr P Erdogdu from the Turkish Ministry of Health for her participation in ascertaining the SPD kindred. We are equally grateful to the proband and her family for travelling from remote areas in order to participate in this study. The authors also express their deepest appreciation to other affected people and their families for participating in the study. This work is supported by an intermural Faculty Research Program from the University of Connecticut Health Center. The work described here was originally presented for fulfillment of a PhD degree (A N Akarsu).