

Morphological and Dermatoglyphic Peculiarities in a Family with Autosomal Dominant Inherited Syndactyly

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ABSTRACT A family with isolated, autosomal dominant syndactyly of the hands is presented. 40 persons from 5 generations are included in the study. Morphological and dermatoglyphic investigations were carried out on 10 probands, only 1 of whom showed solely the characteristic changes of the dermatoglyphics. Syndactyly of the fingers 3-5 occurred with reduced penetrance and variable expressivity. 8 persons exhibited bilateral osseous or cutaneous changes. Analysis of the pattern on fingertips revealed an increased number of whorls in probands in comparison to their relatives and the middle-european population (65.6 % :28.6 % :25.4%). A parallel course of ridges without pattern formation was observed on 5 fingers of 4 probands. The c-triradius was absent in 14 hands of 9 persons, fusions bc were found in 3 hands and fusions cd in 8 hands. In 3 cases the C-line was reduced. The number of palmar interdigital patterns was reduced in probands. The ridge structure was aberrant in the regions of syndactyly in 8 of 9 probands. A chromosome rearrangement was excluded as the cause of the syndactyly. An assignment to Syndactyly Ia, II and III was excluded by the molecular investigations. A morphologic correspondence to Type I seems obvious.

INTRODUCTION

Syndactyly is a specific type of extremity malformation, a developmental abnormality caused by the inhibition of the transversal differentiation of the extremity bud in the 6th to 7th week of pregnancy. Exogeneous syndactyly is caused by mechanical influences during embryogenesis.

Endogeneous syndactyly can either be a symptom of a syndrome, such as Apert- or Oculo-Dento-Digital-Syndrome, or of an isolated malformation. As the latter it has a frequency of 1:2000 in the population (de Smet et al. 1994).

Three types and one subtype of syndactyly which show the best correspondence to the family whom we investigated are described in detail.

1. Syndactyly Type I or Zygodactyly (MIM #185900)

It is the most frequent type. Temtamy and

McKusick describe investigations carried out on 169 males and 142 females and on 32 pedigrees (1978).

Morphology: Mainly the 3rd and 4th fingers and the 2nd and 3rd toes are involved; in some cases the 5th finger and the 4th toe can be affected, also. This type of syndrome shows high variability of symptoms and can include the nails or be restricted to the basic phalanges. The syndactyly can be cutaneous or osseous. It may be restricted to hands or feet. The feet are involved four times more frequently than the hands and about 50 % of the patients show a bilateral involvement (Lenz and Majewski 1981; Winter et al. 1993).

2. Type Ia-Syndactyly Type Lueken. Subgroup of Zygodactyly.

In 1938 Lueken presented 5 generations of a family with 29 female and 18 male probands.

Morphology: They showed variable syndactyly of the fingers 2-5. The second and third toes were mainly involved.

Genetics: Type I and Ia are inherited in an autosomal-dominant manner with variable expressivity and reduced penetrance. Men are carriers as often as females.

Bosse et al. (2000) reinvestigated Type Ia and localized the responsible gene on chromosome 2q34-q36.

3. Synpolydactyly Type II (MIM#18600)

The cases of 16 families were published. Thomsen (1928) investigated the largest family with 31 male and 11 female carriers in 7 generations.

Morphology: The 3rd and 4th fingers are often completely fused, including synostosis. Duplications of these fingers are frequently observed. The 5th finger is sometimes included; additionally, contractions and clinodactyly can occur. In 50 % of the cases the 4th and 5th toes show complete syndactyly. The 5th toe additionally may have partial and complete

polydactyly (Temtamy and McKusick 1978; Lenz and Majewski 1981; Winter et al. 1993).

Genetics: Autosomal-dominant inheritance and variable expressivity. Some families exhibited reduced penetrance. The phenotype is caused by a mutation of the HOXD-13 gene, localized in 2q31. A 27 bp duplication occurs in the region coding for polyalanine. The expressivity of the disorder is about 97 % (Akarsu et al. 1996; McKusick 1998).

4. Syndactyly of fingers 4 and 5, Type III (MIM#186100)

This type was observed in 4 families, the largest with 7 men and 7 women in 5 generations.

Morphology: The 4th and the 5th fingers are involved, the middle phalanx of the 5th finger is reduced or missing. In cases of complete syndactyly, the 4th finger shows contractions. The nails can be fused as well as the end-phalanx. The toes do not exhibit syndactyly (Temtamy and McKusick 1978; Lenz and Majewski 1981; de Smet 1994).

Genetics: The mutation follows an autosomal-dominant inheritance with complete penetrance in all but one family. The gene is localized in 6q22-q23, the region of the Oculo-Dento-Digital-Syndrome (Gladwin et al. 1997; Boyadjiev et al. 1999).

FAMILY INVESTIGATED

In this paper we present a family with an

autosomal-dominant syndactyly of the hands (Fig.1). Clinical, cytogenetic and molecular investigations were carried out. Special emphasis was placed on the analysis of the dermatoglyphics.

INVESTIGATION METHODS

Clinical Examinations: Hands and feet of the probands were investigated and photographs taken, X-ray-pictures and operation reports were included in the analysis of symptoms (Fig. 2).

8 of 10 persons were bilaterally affected (III:5; III:8; IV:11; IV:12; IV:17; V:6; V:8; V:10) and 2 only unilaterally (IV:7; IV:10) (including one proband (IV:10) with microsymbptoms who is not taken into consideration in the following description).

In 7 of 9 probands there are 3 fingers involved (III:5; IV:11; IV:12; IV:17; V:6; V:8; V:10) and 2 persons have two phalanges affected, namely the 3rd and 4th finger (III:8; IV:7). In 5 cases there were osseous fusions (III:5; IV:11; IV:12; IV:17; V:10) and in 4 cases there were cutaneous fusions (III:8; IV:7; V:6; V:8).

7 of 9 probands have a complete syndactyly (III:5; IV:11; IV:12; IV:17; V:6; V:10), one person has only fusions of the proximal phalanx (III:8) and another proband has the proximal and middle phalanx included (IV:7).

Dermatoglyphics: Prints from fingers and palms were taken by the graphite-cling- and film-method. The analyses were performed according to Cummins and Midlo (1961) and Schaumann

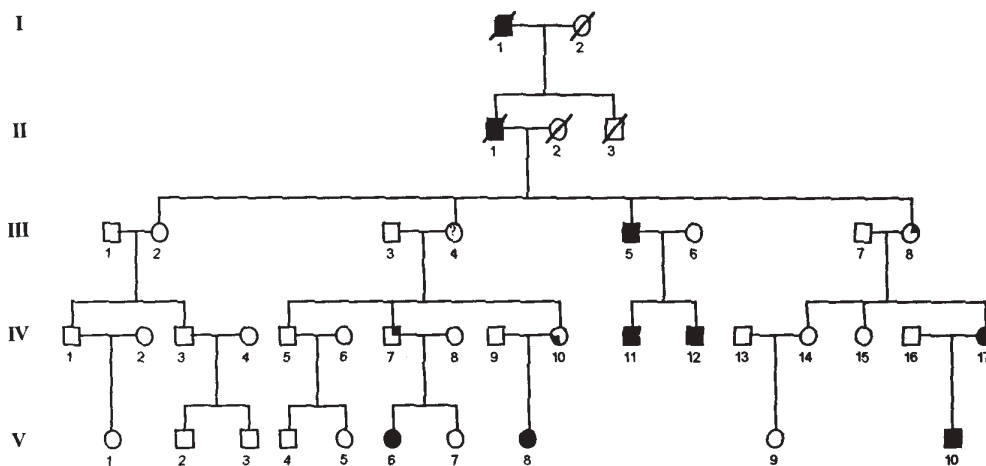


Fig. 1. Family with dominant inheritance of isolated syndactyly of the hands in 5 generations



Fig. 2a



Fig. 2b



Fig. 2c

Fig. 2. Proband IV:17: a) X-ray preoperative (1974)
b) preoperative (1974)
c) postoperative (2000)

and Alter (1976).

Chromosome Diagnostics: In one test person (IV/17) a chromosome analysis was performed to exclude a balanced rearrangement in carriers as a cause of syndactyly. A lymphocyte culture was set up and chromosomes were analysed after GTG-banding.

Moleculargenetic Investigations: Microsatellite investigations were performed for regions 2q34-q36, 2q31 and 6q22-q23 which show mutations in syndactyly type Ia to III. These investigations proved that there was no linkage between the trades examined here and the above mentioned chromosome regions.

RESULTS

Family investigation

It was possible to obtain data from 40 persons out of 5 generations, 12 of whom were affected (7 men and 5 women; Fig. 1). In all cases the syndactyly was restricted to the hands and showed a significant variability of symptoms that was sex-independent. There was no progression in the severity of the expression of clinical syndactyly from generation to generation. The inheritance of the syndactyly was thus autosomal-dominant with variable expressivity. There were no additional teratogenic agents involved in the pregnancies.

Personal investigations were performed on 10 carriers and 8 healthy first-degree relatives from 3 generations (pedigree, Fig. 1, generations III, IV, V).

Dermatoglyphics

In the investigated family the dermatoglyphics of 16 persons were analysed; 7 of these were non-affected relatives of the probands. Seven probands were severely affected; 5 of them (III:5, IV:11, IV:12, IV:17; V:6) were investigated postoperatively and one proband (V:8) preoperatively. Three further probands showed a very mild expression of the syndrome, making an operation unnecessary (III:8, IV:7, IV:10).

Patterns on the Fingertips

The patterns of 6 probands and 7 non-affected relatives were analysed.

Two probands (IV:12, V:8) did not have a pattern on the fourth finger of the left hand and

one did not have one on the fourth finger of the right hand. Proband IV:17 showed a pattern-free area on both 4th fingers. The abnormality is caused by the syndactyly.

The pattern-analysis on the fingertips showed a large number of whorls in the probands (65.6 %); the non-affected relatives and the average population have this pattern in 28.6 % and 25.4 %, respectively. The probands had a frequency of 21.1 % ulnar loops while their relatives showed 67.1 % and the general population recorded 69.7 % ulnar loops respectively.

Radial loops showed up more frequently in the probands (7.8 %) than in the relatives and the average of the population (Table 1).

The bimanual differences were not significant among the probands, their relatives and the general population.

A comparison of the Total Finger Ridge Count (TFRC) of the probands (average: females=172; males = 178) with that of their relatives (average: females = 149; males = 152) reveals that the index group had a higher TFRC than the relatives, due to the higher frequency of whorls.

Sex-specific differences occurred in both groups: men had a higher average value than women.

Formulation of Configurational Areas

Hypothenar, thenar and interdigital areas II to IV of 9 probands and 7 non-affected relatives were analysed: three of the probands show a loop-pattern on the hypothenar on one hand (III:5, III:8 and IV:12) while V:8 has an ulnar loop on both hands. The pattern-frequency in the hands of the probands was 28.0 %. In the relatives it was 21.0 % and in the general population 32.9 % (Cummins and Midlo 1961).

The thenar was always patternless in the

Table 1: Pattern frequency of the fingertips in the affected probands, their relatives and the average of the population (n= 5000 (Cummins und Midlo 1961))

	W	L ^u	L ^r
Probands	65.6 % (TL 6.0 %)	21.1 %	7.8 %
Relatives	28.6 % (TL 5.7 %)	67.1 %	4.3 %
Average population	25.4 % (TL 3.1 %)	69.7 %	5.7 %

(W = whorl; L^u = ulnar loop; L^r = radial loop, TL = twinloop)

proband group (0 %). One of the relatives (V:7) had a proximal loop and a vestige (7.0 %). By contrast, 17.0 % of the general population show a pattern on the thenar (Schade 1954).

The interdigital area II was patternless in all probands (0 %). One relative had distal loops on both hands (14.0 %). According to Schade, 6.0 % of the average population showed patterns (1954).

Two probands had digital loops in the interdigital area III on one hand (11.0 %). IV:7 and V:6 showed a vestige bilaterally, IV:11 unilaterally. 4 relatives had bilateral patterns in this region of the palm (7 distal loops and one vestige). The pattern-frequency was 11.0 % for probands, 50.0 % for relatives and 53.6 % for the general population (Cummins and Midlo 1961). Vestiges were not counted as patterns.

Only proband V:8 showed a pattern in the interdigital area IV; she had a distal loop on the right hand. The relatives showed 5 distal loops on both hands in addition to one vestige. The pattern-frequency of the probands was 5.5 % as compared to 71.4 % among the relatives and 55.8 % in the general population (Cummins and Midlo 1961).

We found that the probands had a lower pattern-frequency than their relatives, especially in the interdigital areas III and IV, the main regions of alterations caused by the syndactyly. The degree of severity of the syndactyly did not influence this distribution.

Analysis of the Digital Triradii

The formation and position of the triradii a-d were examined. Probands and relatives possessed a well-expressed triradius 'a' in central proximal position of the second finger on both hands. The second finger was not involved in the syndactyly in any of the probands. In 7 cases two of the triradii b, c and d were fused and they were shifted into the interdigital area. One fusion bc and 6 fusions cd were found. In three cases the digital triradius was displaced into the interdigital space. Despite a digital triradius d an interdigital triradius cd was found.

The average number of triradii in probands was 2.4 on the left hand and 2.7 on the right hand. All relatives showed the normal number of 4 triradii (a, b, c, d). One proband (III:8) and 3 relatives (III:7, IV:9, IV:14) showed additional triradii a', ab', bc' and cd'; they were caused by the patterns of the interdigital areas.

Position of the Axial Triradii and size of the atd-angle

In the probands it was possible to analyse the atd-angle in only 4 of 18 hands, as the triradius d was missing in all the others. The atd-angle of the probands was between 31° and 54°, which is the same range as in the average population. Additional triradii were found in 2 probands and 2 relatives, the maximum being 2 triradii in the axial part of the palm. The additional triradii appeared in combination with a pattern on the hypothenar and in proband V:7 on the thenar.

Identification of the Main Lines on the Palms

Due to the missing d-triradius, 72.0 % of the patients showed a loss of the D-line. None of the probands had a D-line on the left hand and, on the right hand it was missing in 5 of 9 persons. The C-lines were missing in 78.0 %, with both hands equally affected. The line was rudimentary in 3 cases.

The B-line was missing in 50.0 %. When present it was equally frequent on both hands.

The A-line was normal in all patients.

The relatives did not show any missing or rudimentary main-lines (Table 2).

Comparison of the Fingers Affected by the Syndactyly and the Development of the Main Lines of the Patients.

The findings showed that the alteration of the main lines did not occur only under those fingers which were involved in the syndactyly. They were also a phenotypic expression of the hereditary disease. Patient III:8 showed this phenomenon on the right hand and patient IV:7 on both hands. The dermatoglyphic changes thus were not exclusively a result of the fusions of fingers.

The end areas of the main lines were comparable only for the A-line. 78.0 % of the patients' lines terminate in the areas 4 and 5 as compared to 71.0 % of the relatives' lines. This is known to be the characteristic diagonal course of the middle-european population (Cummins and Midlo 1961).

Ridge Formation

The structure of the ridges showed alterations in the probands in the distal parts of the palmae.

Table 2: The ending areas of the main lines on the palms of the probands and their relatives (X = rudimentary main line)

Probands	D-line	C-line	B-line	A-line	D-line	C-line	B-line	A-line
	Left hand				Right hand			
III:5	-	-	-	2	-	-	-	5''
III:8	-	-	-	4	11	9	7	5''
IV:7	-	X	5''	4	11	-	-	5''
IV:10	-	X	5'	3	9	X	5'	4
IV:11	-	-	-	3	11	-	-	5'
IV:12	-	-	-	2	-	-	5''	5''
IV:17	-	-	5''	5''	-	-	5''	5''
V:6	-	-	5''	5'	-	-	5''	5'
V:8	-	-	-	5'	11	-	-	5''
Relative	Left hand				Right hand			
III:6	9	5'	5'	3	9	7	5'	4
III:7	7	9	5''	5'	11	11	7	11
IV:8	7	5''	5''	4	7	7	5''	5'
IV:9	11	9	7	5''	11	9	7	11
IV:14	7	9	5'	5''	11	9	7	5'
IV:15	9	9	5	L'	11	9	7	4
V:7	7	5''	5''	5'	7	7	5''	5'

The distance between them was partially increased in 6 patients (III:5, IV:7, IV:11, IV:12, V:6, V:10). Patient V:6 exhibited a meandering course of the ridges and probands IV:10 and V:6 had an increased number of minutiae. The diameter of the ridges varied in 2 cases (IV:11, IV:17). Two patients showed a disruption of the ridges (III:5, IV:12). None of these alterations was observed in the non-affected relatives.

The course of the palmar flexion creases was normal in the probands.

Chromosome Findings

The proband IV:17 showed a normal female karyotype (46,XX,GTG,400-450 bands/genome). Thus a balanced translocation or inversion was excluded as the cause of the syndactyly in the family.

Molecular Investigations

Investigations were performed by microsatellite-fragment analysis. There was no evidence of linkage for the marker on chromosome 2q34-q36 (Type Ia), 2q31 (Type II) and 6q22-q23 (Type III). Further investigations are intended.

DISCUSSION

In 1923 Cummins and Midlo pointed out that clinical investigations in patients with zygo-

dactyly remain incomplete or may lead to false conclusions if only cutaneous or osseous changes on fingers and toes of probands are considered as symptoms for carrier determination. Alterations of the dermatoglyphics must always be taken into consideration. Wolff-Quenot and Clavert (1983) investigated the dermatoglyphics in syndactyly patients and found various alterations. Watanabe et al. (1949) found a fusion or aplasia of digital triradii under the fused fingers as the main symptom of dermatoglyphic changes in their patients.

In some carriers of the mutation the only symptom was a reduction of an interdigital area and a shift of the digital triradius. In patients with syndactyly Type I Matton et al. (1982) found an increased reduction of the C-line.

In our study, the *c-triradius* was absent in 14 hands of 9 probands. In 3 hands there were fusions of bc and in 8 of cd. In 3 cases the C-line was reduced.

One carrier (IV/10) showed dermatoglyphic changes as the only symptom of the syndrome. Her child (V:8) had a complete syndactyly of fingers 3-5 on both hands.

According to Matton et al. the *pattern on fingertips* revealed an increase in whorls in carriers as compared to their relatives and the general population (1981). The same peculiarity was found in our family. The frequency of whorls was 65.6 % compared to 28.6 % in relatives and 25.4 % in the general population.

The *fingertip ridges* may show a parallel

course without formation of pattern (Matton et al. 1981). In the family investigated here we observed this abnormality on 5 fingers of 4 persons.

The analysis of the *palmar pattern* showed a reduced occurrence of loops and whorls in the interdigital areas II-IV in probands as compared to their relatives and the general population. Hypothenar and thenar patterns showed no differences for the 3 groups who were compared.

The *structure of the ridges* showed peculiarities in 8 of the 9 probands in the regions of the syndactyly. The distance of the ridges varied and was significantly increased in some cases. The ridges were interrupted, the number of minutiae was increased and the course of ridges appeared wavy. Comparable findings have not been published by other investigators.

Embryological investigations of Matton showed an increased bud formation in the 7th week of development in probands with syndactyly (1981). It is known that large buds lead to more complex dermatoglyphic patterns. The authors assumed a common mechanism for the bud formation of the fingers and the development of the syndactyly, but further investigations are necessary to obtain detailed insight into the differentiation mechanisms.

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