TYPE A_2 BRACHYDACTILY

Report of a New Family

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A new family with the A_2 type brachydactily is described. It is the first one observed in Italy and the sixth of the world literature. Brachymesophalangy of index fingers and/or second toes is the typical osseous malformation which was present in 14 individuals from 4 generations. The defect is transmitted by an autosomal dominant gene with high penetrance and variable expressivity.

Brachydactily is a well-known genetic malformation. It can be the sole or predominant anomaly, or be part of a more complex syndrome. Since 1903, when Farabee for the first time interpreted as a Mendelian dominant a particular form of brachydactily, many data have been collected on this subject. Exhaustive reviews and classifications have been done by Bell (1951), Temtamy and McKusick (1969), McKusick (1971). According to these authors, at least nine types of major brachydactilies exist as an isolated malformation (Table). Type A_2 brachydactily (brachymesophalangy, Mohr-Wriedt type) is exceedingly rare, only five families having been reported so far.

This paper deals with a new family, the first studied in Italy.

CASE REPORTS

The kindred described (T. family) is of Northern Italian ancestry. The great-grandfather of the propositus (I,2 in the pedigree, Fig. 1) married twice with unrelated, healthy women. He is the oldest member of the family we could have notice of. The propositus (IV,1) has been seen for the first time at birth. His hands showed a rather peculiar radial deviation of the distal phalanges of both index fingers (Fig. 2). Otherwise, he was perfectly normal and, in particular, so were his toes. When he was seen again at age 7, the deviation of his index fingers was still evident. A similar malformation appeared in his second toes. His brother (IV,2), born two years later, had a tibial deviation of the second toes and curved fifth toes, while his hands were normal. The same picture was evident at age five.

Only recently, were we able to observe the other members of the family, some of whom, concerned about their malformation, did not consent to have roentgenographs taken. Subject III,6 has bilateral tibial deviation of second toes. The same toe malformation is present in two sibs (III,8 and III,10), while a sister (III,9), besides the anomalies of toes, has radial deviation of distal phalanges of both index fingers. Of the other members affected, only one (II,6) has radial deviation of index fingers with normal toes, the remaining seven showing the combined defect of index fingers and second toes (I,2; II,2; II,5; II,7; II,9; III,1; III,4). Subject I,1, not directly examined, was referred has having the malformation.

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Table. *Main types of major brachydactilies according to literature reports*

Denomination	Type of malformation	Affected digits	Associated malformations	Heredity
A_1 (Farabee 1903)	shortening of middle phalanges, shortening of proximal phalanges of thumbs and big toes	all	short stature	autosomal dominant
A_2 (Mohr and Wriedt 1919)	shortening of middle phalanges	index fingers, second toes	none	»
A_3 (Bauer 1907)	shortening of middle phalanges	fifth fingers	none	»
A_4 (Temtamy 1966)	shortening of middle phalanges	second, (fourth), fifth digits	talipse calcaneo-valgus, club foot (occasionally)	»
A_5 (Bass 1968)	absent middle phalanges	second, fifth digits	nail dysplasia	»
B (McKinder 1857)	shortening of middle phalanges, rudimentary or absent terminal phalanges symphalangism syndactily	all	none	»
C (Haws 1963)	short middle phalanges, brachymetapody, hyperphalangy, symphalangism	mainly second, third fingers	none	»
D (Thomsen 1928)	short and broad terminal phalanges	thumbs, big toes	none	»
E	short metacarpal and metatarsal	wide variability in number	short stature, round facies	»

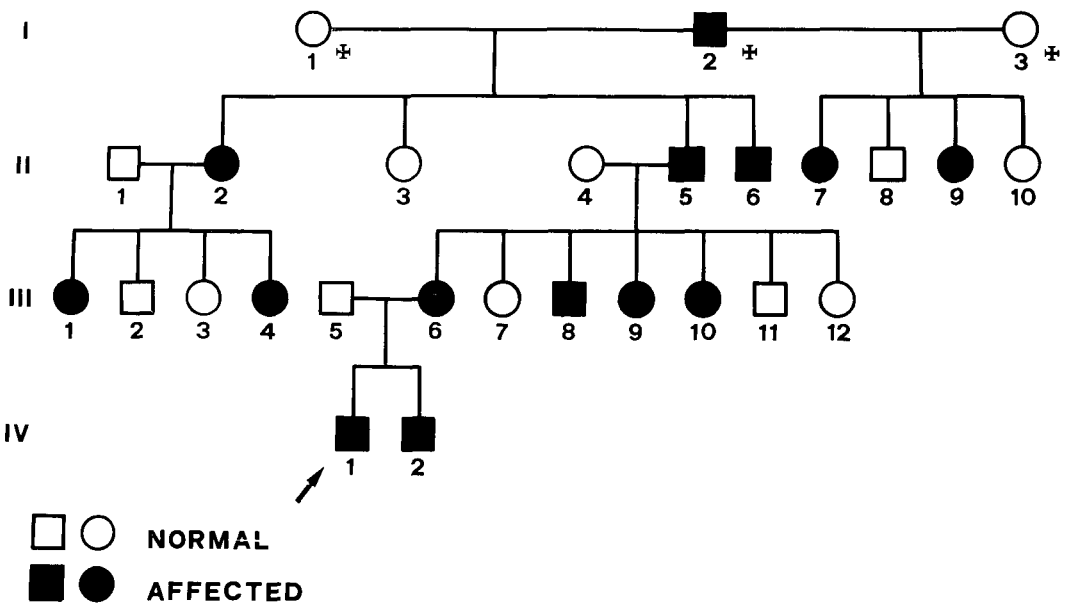

Fig. 1. Pedigree of the T. family showing autosomal dominance of the brachydactily gene.

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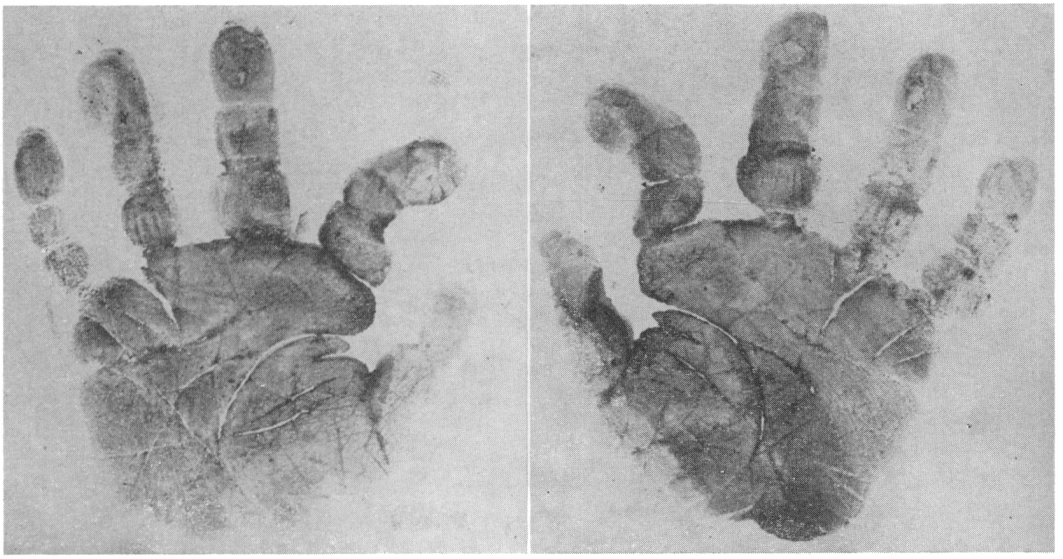

Fig. 2. Palm print of propositus (IV,1) at birth. The radial deviation of both index fingers is clearly visible.

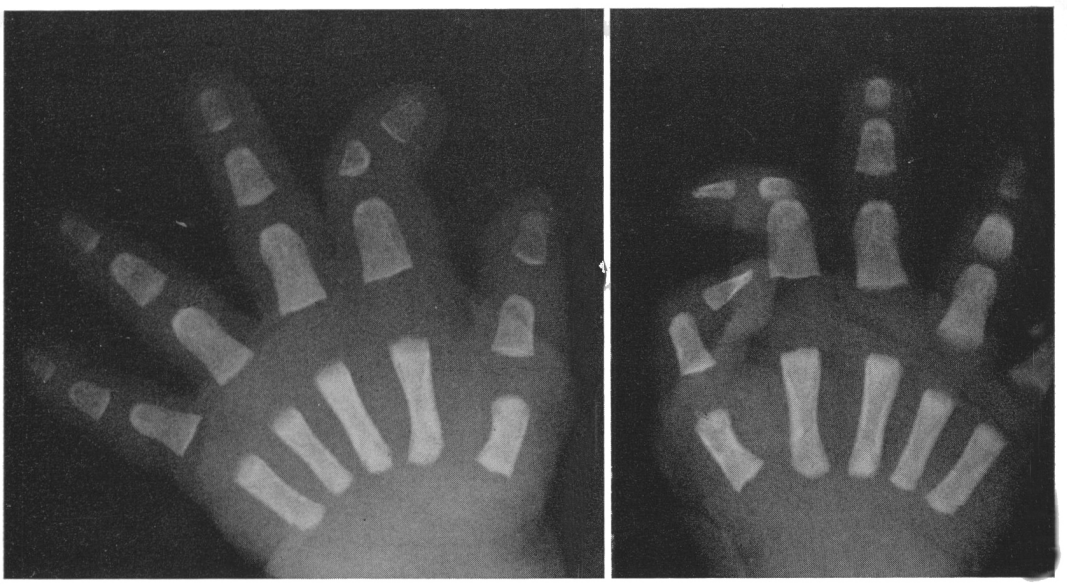

Fig. 3. Roentgenograms of the hands of propositus at birth showing the typical dysplasia of middle phalanges of index fingers.

Radiographic Findings

The typical osseous malformations of some members of the kindred are illustrated in the following pictures. Roentgenographs of the propositus' hands taken at birth show (Fig. 3) a delta shaped middle phalanx of his left index finger and a shorter and thinner middle phalanx of the right index finger. This causes the terminal phalanges to deviate radially. The same malformation is still present, rather unmodified, at seven years of

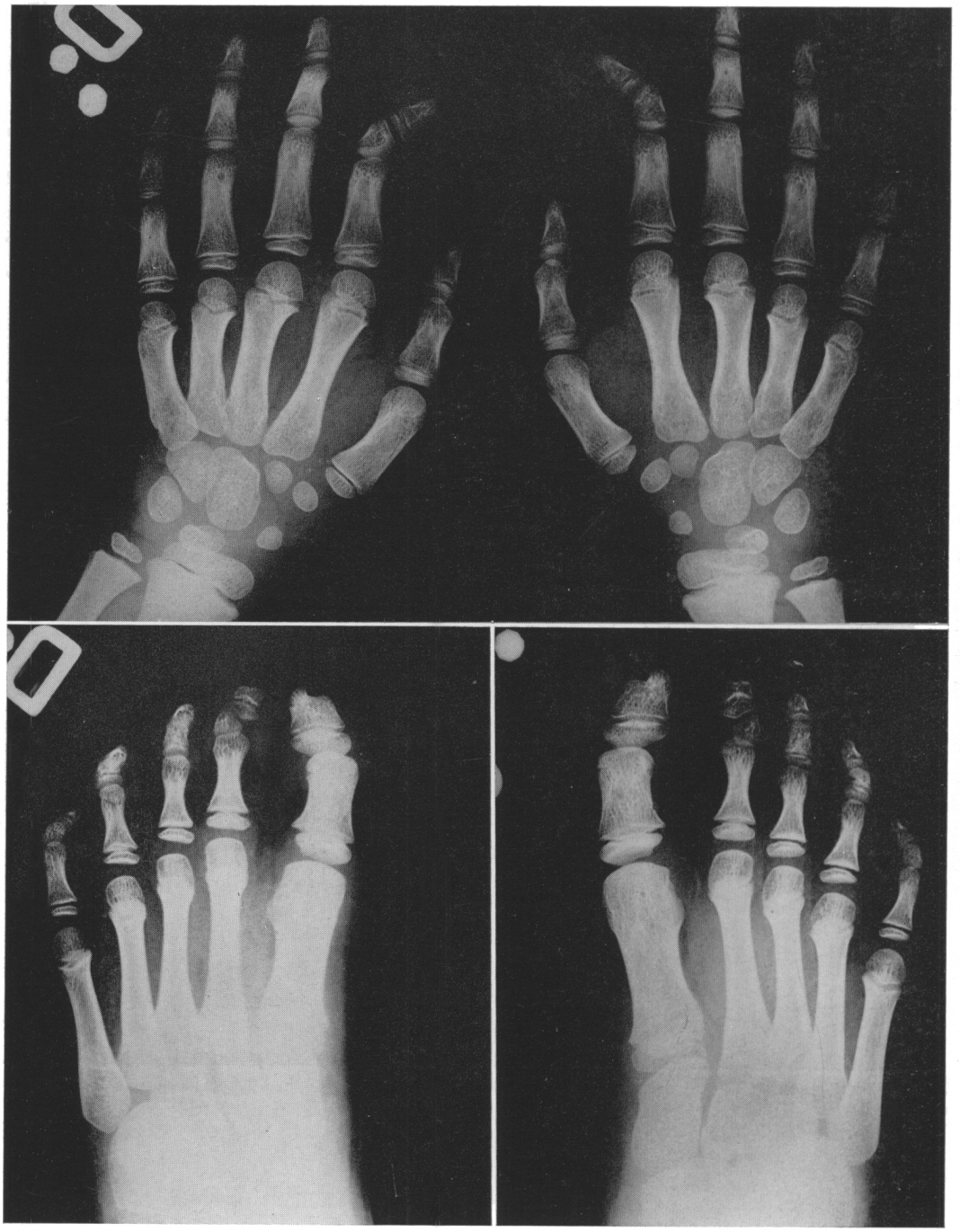

Fig. 4. Roentgenograms of hands and feet of propositus at 7 years. The same osseous anomalies are evident.

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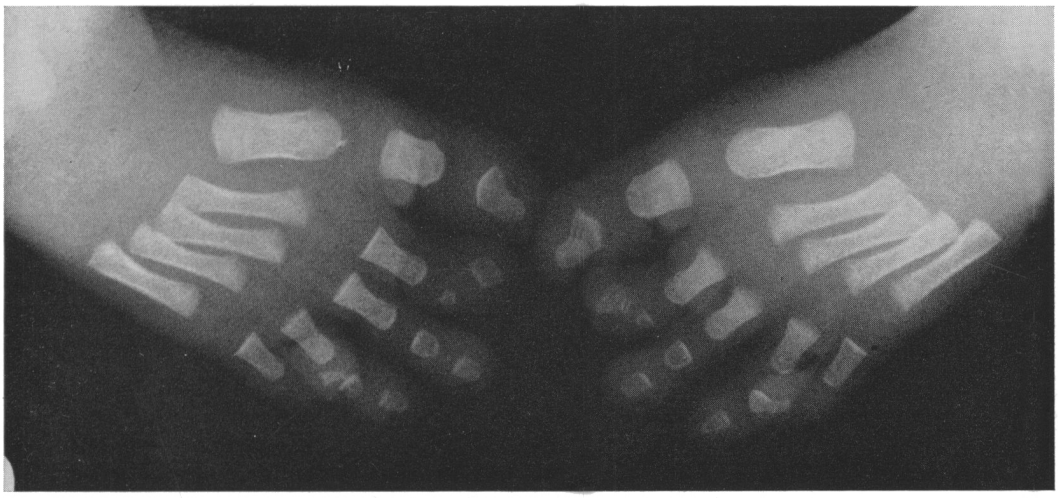

Fig. 5. Roentgenograms of the feet of the propositus' brother (IV,2) at birth, showing small medial phalanges of second toes.

age (Fig. 4). Roentgenograms of the feet also show bilateral hypoplastic and structurally abnormal middle phalanges of second toes, although the tibial deviation of the distal phalanges is not yet visible. Quite similar hypoplastic medial phalanges of second toes are present in the propositus' brother. Clinodactily of fifth toes is an associated malformation. His hands are normal (Figs. 5 and 6). The propositus' mother (III,5) has only affected feet. X-rays show severely shortened and dysplastic middle phalanges of second toes (Fig. 7*a*). Figures 7*b* and *c* show roentgenograms of hands of subjects III,6 and II,5 with a variable degree of phalangeal dysplasia. No other osseous malformations were found in the subjects investigated.

DISCUSSION

In the family studied, out of 22 members at risk, 14 in four generations were affected. Of these, 9 showed malformed hands and feet (index fingers and second toes), 4 had only malformed feet, and the last one malformed hands only. In none of the observed subjects, have other skeletal abnormalities been found.

The radial or tibial deviation of the distal phalanges of the affected digits results from either hypoplasia or dysplasia of the middle phalanges, that assume a triangular or rhomboidal shape, being therefore shorter than normal. This kind of malformation (brachymesophalangy) is common to all A type brachydactilies (Temtamy and McKusick 1969). According to Pol (1921), the histogenesis of the middle phalanges occurs later than other skeletal segments. On the contrary, their differentiation is almost contemporary to that of the other elements of the autopod, directly following the differentiation of the skeleton of the limbs. This could account for their peculiar lability. Moreover, the toes, which are rather commonly affected, represent in man a structure in regression (Duhamel 1966).

The genetics of the defect can be inferred, in our family, from the following considerations. The defect itself has a " vertical " pattern of transmission; the sex ratio of the affected members approaches 1 : 1 (6 males vs. 8 females); affected children have been born either to an affected man (I,2) or to affected women (I,1 and I,3); the segregation ratio in the offsprings

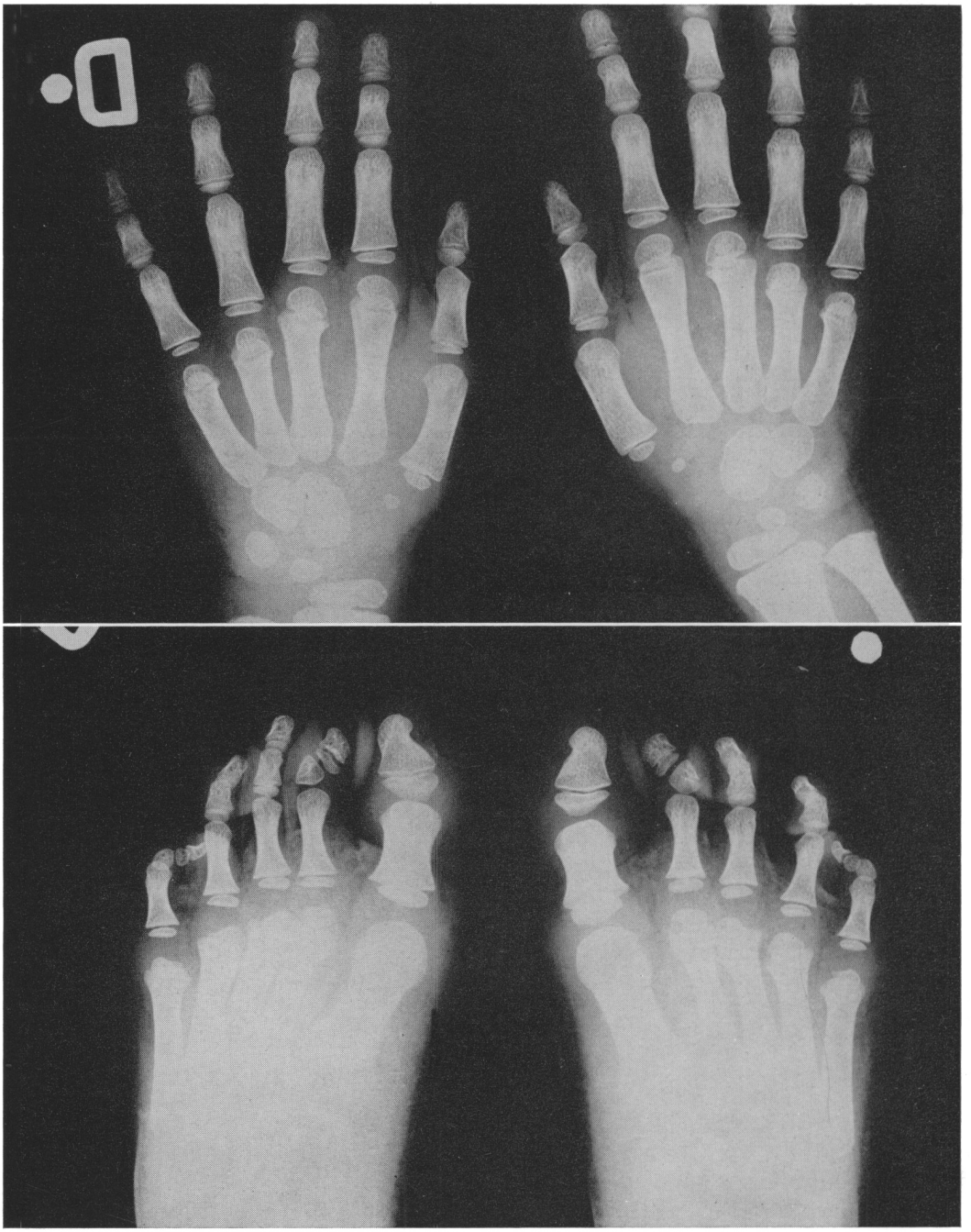

Fig. 6. Roentgenograms of hands and feet of the same subject (IV,2) at age 5. The malformation is present only in the phalanges of second toes.

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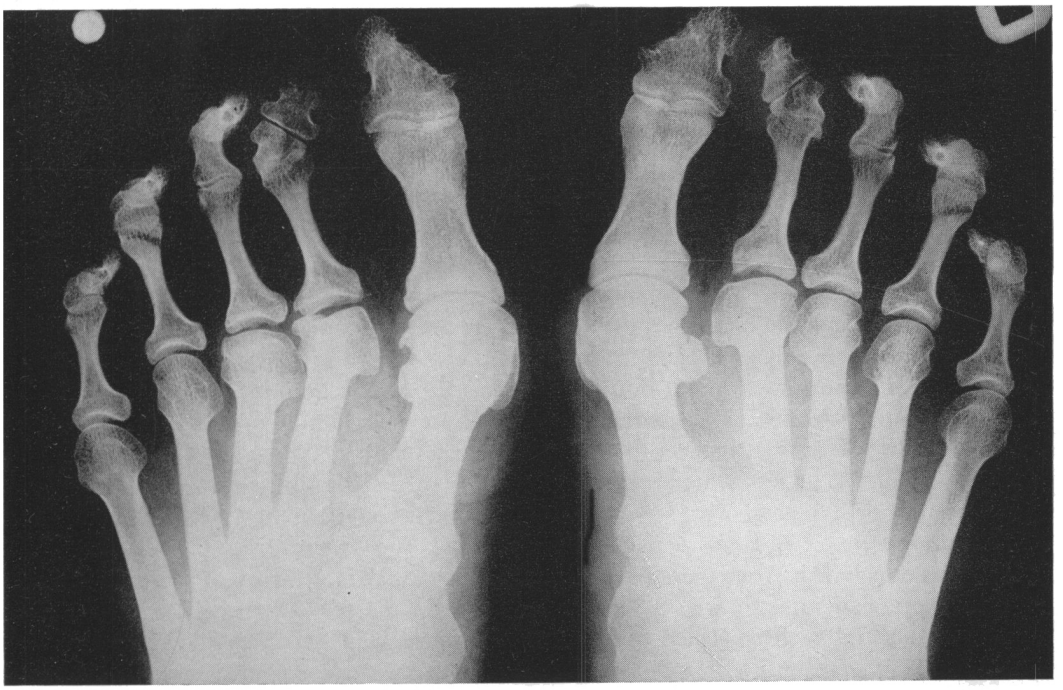

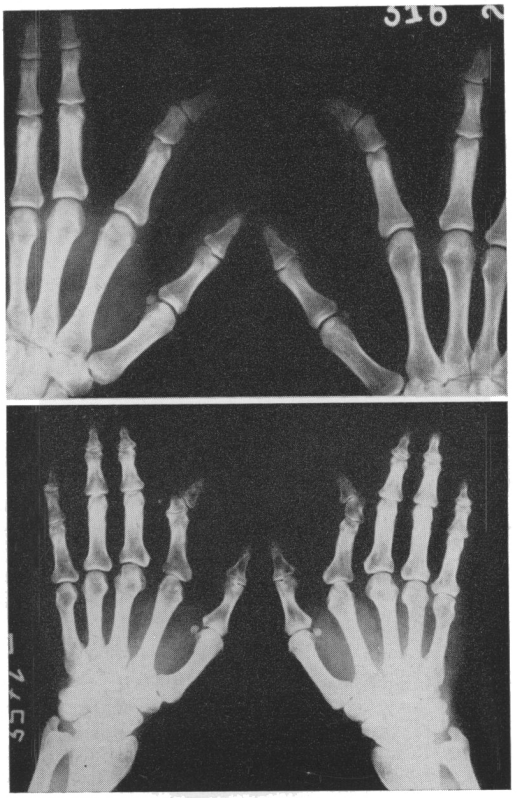

Fig. 7. Roentgenograms of feet of subject III,6 (*a*) and of hands of subjects III,9 (*b*) and II,5 (*c*) showing a different degree of severity in the expression of the dysplasia of middle phalanges of second digits.

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of affected individuals approaches 1 : 1 (13 affected vs. 8 normal). It can therefore be concluded that brachymesophalangy is transmitted through an autosomal, dominant gene, with high penetrance and variable expressivity (Temtamy and McKusick 1969).

The A_2 brachydactily gene is extremely rare. To our knowledge only five kindreds have been described so far. The first one was studied in 1903 by Ziegner, the others by Mohr and Wriedt (1919), Hanhart (1940), Freire-Maia and Pacheco (1966, reexamined by Freire-Maia et al. in 1976) and Temtamy (1966). The last one is the only Negro kindred.

The characteristic osseous malformations observed in the affected members of these families (hypodysplasia of middle phalanges of index fingers and/or second toes) do not differ in any way, as it seems, from those present in our cases.

We consider it important to point out the presence of possible homozygotes among the subjects investigated. Mohr and Wriedt described one in their family. Another was observed by Temtamy. This subject had more complex osseous malformations, such as marked shortening of the index fingers which were syndactylous to the thumbs, deformity of third and clinodactyly of fifth fingers. Two sibs were stillborn with severe, but not well-defined skeletal deformities.

It could be concluded, from these cases, that homozygosity is a factor of increased clinical severity, expressing sometimes as a lethal character. In the very extensive family described by Freire-Maia and Pacheco (1966), segregation of the abnormal gene was in favour of affected females. There were in fact 45 nonaffected vs. 51 affected males, and 38 nonaffected vs. 61 affected females. Extragenic influences could account for the difference.

As to the variability of the trait, it is rather wide, according to the different authors. There seems to be a marked tendency to intrafamilial resemblance and interfamilial variability. In the present kindred, affected individuals have mostly malformed hands and feet. Only one patient has normal toes and deviated index fingers. In Temtamy's kindred, on the contrary, affected feet were more common than affected hands. Unknown factors, modifying the expressivity of an identical gene can be responsible for the noted differences.

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RIASSUNTO

Brachidattilia Tipo A_2 - Una Nuova Famiglia

Viene descritta una nuova famiglia con brachidattilia di tipo A_2. Si tratta della prima descritta in Italia e della sesta in tutto il mondo. La brachimesofalangia del secondo dito delle mani e/o dei piedi, che è la malformazione ossea tipica, era presente in 14 soggetti su quattro generazioni. Il difetto è trasmesso da un gene autosomico dominante con elevata penetranza ed espressività variabile.

RÉSUMÉ

Brachydactylie de Type A_2 - Une Nouvelle Famille

Une nouvelle famille avec brachydactylie de type A_2 est décrite. Il s'agit de la première décrite en Italie et de la sixième dans la littérature mondiale. La malformation osseuse typique, une brachymésophalangie du deuxième doigt et/ou du deuxième orteil, était présente chez 14 sujets sur quatre générations. Le défaut est transmis par un gène autosomique dominant avec une pénétrance élevée et une expressivité variable.

ZUSAMMENFASSUNG

Brachydaktilie A_2: eine neue Familie

Beschreibung einer neuen Familie mit Brachydaktilie A_2: es handelt sich um den ersten Fall dieser Art in Italien und den sechsten in der ganzen Welt. Die Untersuchungen, die sich über 4 Generationen erstreckten, ergaben insgesamt 14 Individuen, die die typische Knochenmissbildung, nämlich Brachymesophalangie am 2. Finger oder/und an der 2. Zehe aufwiesen. Die Missbildung wird durch ein autosomes Gen mit hoher Penetranz bedingt und nimmt ganz verschiedene Ausdrucksformen an.

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