

Oto-Palato-Digital Syndrome: Comparison of Clinical and Radiographic Manifestations in Males and Females

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INTRODUCTION

The oto-palato-digital syndrome is a generalized skeletal dysplasia resulting in short stature, characteristic facies, and unusual deformities of the hands and feet. In addition, cleft palate and other congenital malformations are present [1-3]. Some patients have conductive deafness due to dysplastic auditory ossicles. Clinical features in female carriers of the trait have usually been minimal, and the question of X-linked recessive inheritance has been raised. However, in the kindred of Weinstein and Cohen [2], the mother of two affected boys also exhibited certain features of the syndrome; and more recently, Aase reported clinical stigmata (including submucous cleft palate) in the mother of two affected boys [4]. Clinically affected females have also been reported by Jäger and Refior [5] and observed by R. I. MacPherson (personal communication, 1971) and Gorlin [6]. On the basis of this evidence, therefore, the trait could be either X-linked, with intermediate expression in the females, or an autosomal dominant with sex limitation of expression.

Because of the importance for genetic counseling of being able to detect the female carrier of this genetic trait, the kindred of Weinstein and Cohen has recently been reexamined with special attention to females who could be carriers. The presence of the trait has been established in six females in four consecutive generations (fig. 1). This report concerns the clinical and roentgenographic fea-

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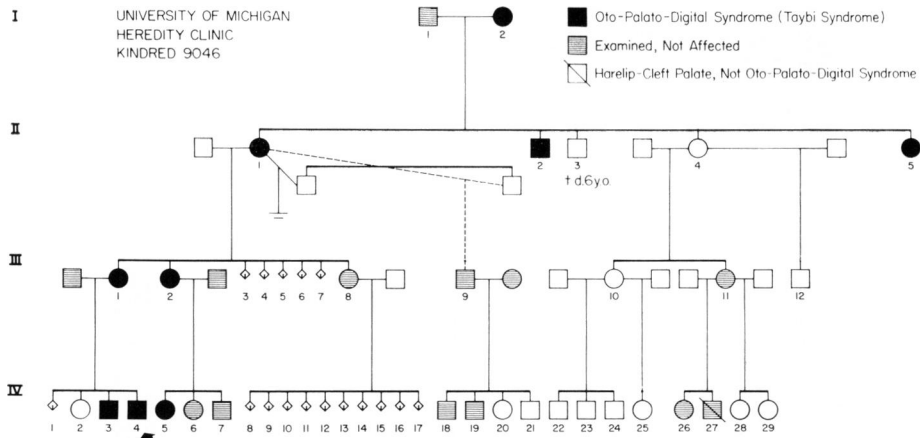


FIG. 1.—Pedigree of Family *N* (Hereditary Clinic no. 9046)

tures of the trait as it occurs in females, with comparisons where appropriate with corresponding features in affected males [7].

SUBJECTS AND METHODS

For the purposes of this study, the entire kindred of Weinstein and Cohen was re-examined. All previously examined members—both affected and unaffected—were re-examined. In addition, several previously unexamined family members were sought out and examined, resulting in detection of five new cases of the trait, all females. Each available family member received a detailed physical examination and radiologic bone survey. X-rays and photos of family members I-1, I-2, and II-5, residing in Oklahoma, were supplied through the cooperation of Dr. David F. Watson. Dermatoglyphic studies were also performed on the three affected males, four of the six affected females, and several unaffected family members.

RESULTS

A. Clinical Features of Affected Males

The three affected males in this kindred exhibited most of the classical clinical features of the syndrome, including unusual facies, cleft palate, and deformities of hands and feet. Two of the three were below the third percentile for stature. Patient IV-4 had a hypoplastic left kidney, and patient IV-3 had an inclusion cyst of the penile meatus at birth. However, none of the three patients had significant deafness. Patient IV-4 had bilaterally symmetrical conductive hearing loss thought to be due to repeated otitis media, but this was of mild degree, and his comprehension of normal conversational speech was excellent.

Facial features (figs. 2*b*, 2*c*, 2*e*, 2*f*) included overhanging brow, prominent supraorbital ridges, prominent occiput, lowset slanted ears, broad nasal root, low vertical nasal bridge, hypertelorism, antimongoloid slant of palpebral fissures (two out of three), mandibular angle greater than normal, small mouth with down-

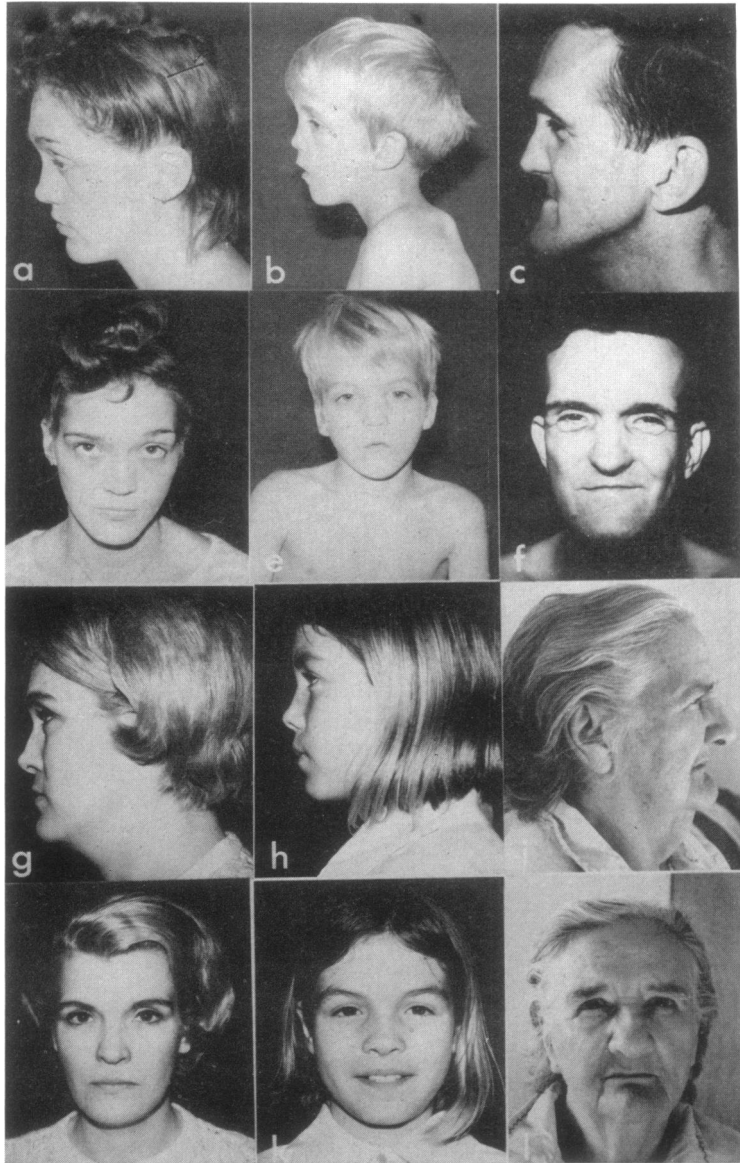


FIG. 2.—Facial features of two affected males (*b*, *e*, kindred member IV-3; *c*, *f*, kindred member II-2) and four affected females. Note characteristic appearance produced by depressed, vertical nasal bridge in kindred members III-1 (*a*, *d*), III-2 (*g*, *j*), and IV-5 (*h*, *k*). In kindred member I-2 (*i*, *l*), clues to carrier state are given by supraorbital fullness, broad fronto-nasal area, hypertelorism, and configuration of upper lid.

turned corners, maxillary and malar flattening, and severe dental caries. The cleft palate was midline and, in the case of IV-4, was extremely wide.

Hands and feet exhibited clinodactyly, short broad distal phalanx of the thumb

and hallux, bulbous tips of toes, and short fifth fingers and toes. The great toe was also very short.

B. Clinical Findings in Affected Females (Table 1)

TABLE 1
CLINICAL FEATURES OF AFFECTED FEMALES

FEATURE	FEMALE					
	IV-5	III-1	III-2	II-1	II-5	I-2
Face and head:						
Median frontal eminence	+	+	+	+/-	+/-	+/-
Overhanging brow	+	+	+	+/-	+/-	+/-
Prominent occiput	-	+/-	-	-	-	-
Prominent supraorbital ridges-						
supraorbital fullness	+/-	+	+	+/-	+/-	-
Lowest ears	-	+	-	-	+/-	+/-
Broad frontonasal area	+	+	+	+/-	+/-	+
Low (flat) vertical nasal bridge ...	+	+	+	-	-	-
Antimongoloid slant	-	-	-	-	-	-
Laterally drooping upper lid	+	+	+	+	+	+
Hypertelorism	+	+	+/-	+	+	+
Flattened maxillary area	+	+	+	+	+	+/-
Flattened malar area	+	+	+	+	+	-
Severe caries or edentulous state ...	-	+	-	+	+	+
Cleft palate	-	-	-	-	-	-
Hands:						
Clinodactyly 2-3	+	-	+	-	+/-	+
Clinodactyly 5	+	-	+	+	+	+
Short fifth	+	-	+	-	-	+
Stub thumb (short distal)	-	+	-	-	-	-
Feet:						
Broad flat foot	+	+	+	+	-	-
Short great toe	+	+	+	+/-	-	-
Bulbous tip of great toe	+/-	+	+	-	+	+/-
Bulbous tip of other toes	-	-	+	-	+/-	-
Space between first and second toes	+/-	-	+/-	+	+	+/-
Space between third and fourth toes	+	+	+	+	-	-
Relatively long second and						
third toes	+	+	+	+/-	+	-
Clinodactyly	+	+/-	+/-	-	+	-

NOTE.— + = present; - = absent; +/- = questionable.

The facial features included mild hypertelorism with broad nasal root, median frontal prominence (overhanging brow), prominent supraorbital ridges, depressed bridge of nose, flattened maxillary and malar areas, and slightly lowset ears. In three of the six cases, the combined features resulted in a sufficiently characteristic appearance to be easily recognizable (figs. 2*a*, 2*d*, 2*g*, 2*h*, 2*j*, 2*k*). This was due primarily to the depressed nasal bridge which, together with the overhanging brow, produced a vertical, flattened profile and an appearance similar to that of affected males, though of lesser degree. However, in the other three cases the nasal

bridge was not flattened and the characteristic appearance was partially lost (figs. 2i, 2l). Only a careful summation of individual facial features, each usually present only in mild degree, produced evidence enough to justify a suspicion of the presence of the trait. The canthal index was beyond the upper limits of normal in four of the six females [8] (table 2).

TABLE 2
CANTHAL INDICES

Affected		Not Affected	
Males			
1. II-2	46*	1. II-1	35
2. IV-3	47*	2. IV-27	37
3. IV-4	45*		
Females			
1. IV-5	47*	1. III-8	37
2. III-1	40*	2. IV-2	39
3. III-2	38		
4. II-1	40*		
5. II-5	40*		
6. I-2	38		

* Value is beyond the upper limits of normal for age and sex.

Significant antimongoloid tilt of the palpebral fissures was not observed in females. However, an illusion of antimongoloid tilt was present in all six and was traced to the configuration of the upper eyelid, which arches sharply upward in its medial one-third, and then follows a long, downward curve to the outer canthus. (This eyelid configuration is probably not in itself abnormal.) An unusual fullness in the area below the lateral third of the eyebrow, due to the prominent supra-orbital ridging, further accentuates the downward sweep of the upper eyelid. This feature is even more pronounced in affected males (fig. 2). In two of the three males a slight notching was noted at the junction of the medial one-third and lateral two-thirds of the upper eyelid.

Hands generally provided only slight clues to the presence of the trait; these consisted of slight ulnar deviation of the second and/or third digits and short, slightly incurved fifth fingers. A short, broad thumb was present in one case.

Clinical examination of the feet was somewhat more rewarding (figs. 3a, 3b). The foot was usually broad and flat with some degree of shortening of the great toe and a bulbous tip of the great toe. The space between the first and second toes was slightly increased in some cases, and there was a detectable gap between the third and fourth toes. There was some clinodactyly of the toes with a tendency toward bulbous tips.

On the average, all these clinical features were much less pronounced in females

than in males, although individual findings were occasionally quite marked. None of the six females exhibited unusual shortness of stature, deafness, cleft palate, or significant mental retardation.

C. Radiologic Changes in the Oto-Palato-Digital Syndrome

The radiological findings in this syndrome involve many areas of the body. Generally speaking, the findings are much milder in females than males, and they are significantly different depending on whether the patient is an adult or a child.

The clinically characteristic cranial configuration of involved individuals is also apparent on the radiographs of the skull. In the lateral view, the frontal and occipital regions are prominent, much more so in the males than the females. There is often associated thickening of the frontal and occipital bones with hypoplasia of the frontal sinuses (fig. 3*k*). Males have hypoplastic mastoids and vertical clivus while these findings were present in only one female. The sinuses generally are hypoplastic, and sinusitis is frequently present in both sexes. The angle of the mandible was greater than normal in males.

Spine findings are much more common in males than females but do occur in both sexes. These include failure of fusion of the posterior aspects of the spine and spondylolysis. A curious, unexplained widening of the interpedicular distance in the upper lumbar region was present in both young males but was not apparent in either the adult females or the adult male (fig. 3*i*). No myelograms are available to explain this phenomenon. The adult male also had failure of fusion of the dorsal aspects of the upper cervical vertebrae, and one adult female had evidence of laminar fusion of the cervical spine.

The radiologic hand findings are most remarkable in young males (fig. 3*g*). They include a capitate which is transverse in position, a comma-shaped trapezium with a corresponding indentation of the base of the second metacarpal, and an occasional extra carpal ossification center in the distal row on the ulnar side. These are also evident but not described in other published cases. In our one young female these changes were not present, and they did not occur in our adult members. The female adults occasionally had evidence of trapezium-scapoid fusion (fig. 3*h*). Minimal radial clinodactyly of the fifth finger is common in both males and females.

The thumb was short in males (fig. 3*g*) but was unremarkable in most females. The thumb anomaly was characterized by a short, broad distal phalanx, which during childhood had a prominent cone epiphysis with central fusion.

The feet show significant radiologic stigmata in both males and females. Again the findings are more severe in the male than in the female, and young males show the most dramatic changes, with a short great toe and abnormally short distal phalanx, often with an unusual or cone-shaped epiphysis (fig. 3*c*). Fusions involving the cuneiforms are common in both males and females (figs. 3*d*, 3*e*, 3*f*). The cuneiforms may be fused to adjacent metatarsals or tarsals. Some type of tarsal fusion, or joint narrowing between the tarsals, implying a fibrous fusion, was common in both sexes; the fusions were generally less marked in females. In the

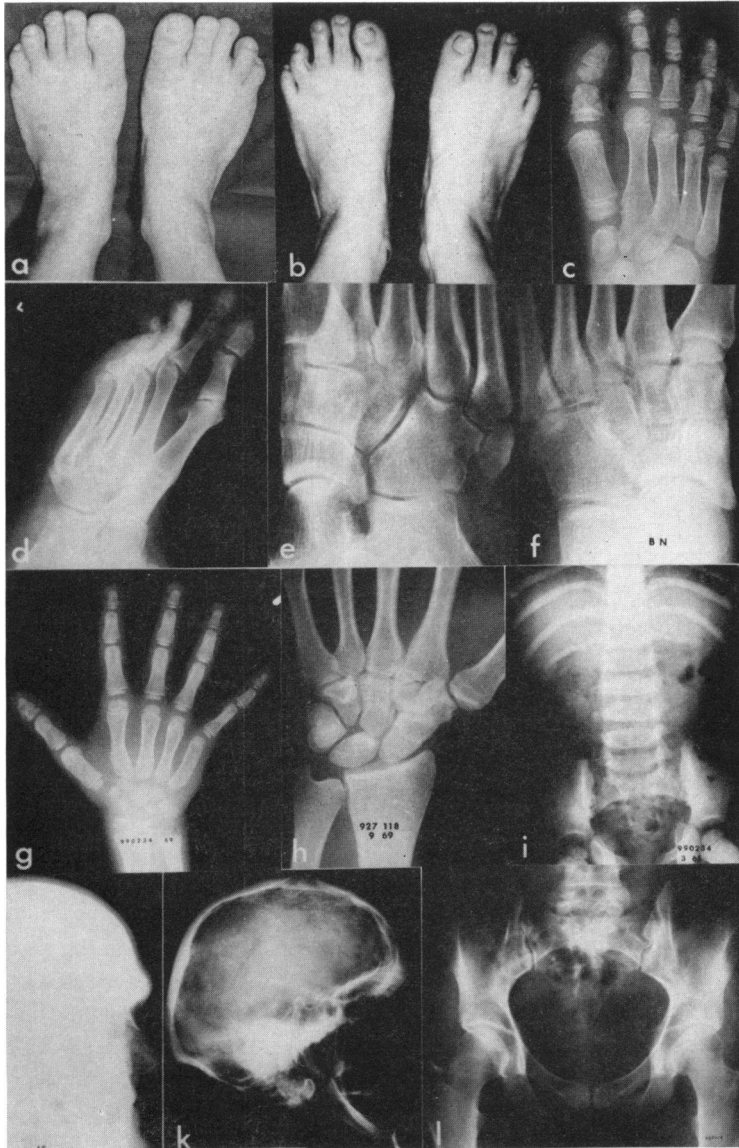


FIG. 3.—*a-b*, Clinical appearance of the feet in affected females; *c-l*, radiologic findings in affected males and females. In *a* (kindred member III-1) and *b* (III-2) note broad forefoot, short first toe, and irregular, widely spaced toes with bulbous tips. *c* (IV-3), Typical radiologic foot findings in a male child. Short proximal and distal phalanges of great toe; double ossification center of navicular; fusion of middle and lateral cuneiforms to their respective metatarsals. *d* (II-2), Adult male, multiple tarsal fusions; fusion of medial cuneiform, navicular, and calcaneus, fusions of medial and lateral cuneiforms to metatarsals and narrowing of the joint between cuboid and metatarsal. *e*, Adult female (II-5). Accessory ossicle along the fifth metatarsal. Evidence of fibrous unions between calcaneus and navicular and partial fusion of medial cuneiform and navicular. *f*, Adult female (III-2). Extensive tarsal fusion involving medial cuneiform and navicular. *g*, Male child (IV-4). Transverse capitate, comma-shaped

adult male (fig. 3*d*), extensive fusion was present between the cuboid and the fourth metatarsal, and extensive fusions between all of the tarsals were also present. The fifth metatarsal was unusually prominent in both sexes, although it was more apparent in adults than children. It either projected well over the cuboid or had a separate ossification center forming a rather large accessory bone in this area (fig. 3*e*). Both young males had two ossification centers for the navicular.

The pelvis in this syndrome has an unusual configuration with somewhat small iliac wings and, in the young boys, flattened acetabular angles (fig. 3*i*). Again, these are more dramatic in the male than the female, but these changes were present in two of the females where pelvis films were available (fig. 3*l*).

No elbow abnormalities were noted in our patients, although they have been described by Langer [7].

D. Hand Bone Profiles

Hand bone profiles, prepared according to the method of Garn [9], revealed striking patterns in the affected males (fig. 4). Pronounced reduction (relative and absolute) of the distal phalanx of the thumb, with slight compensatory relative lengthening of the proximal phalanx of the thumb, is clearly apparent. The middle phalanges tend to be relatively long. Overall hand size is quite variable from person to person without any apparent trend toward large or small hand size. These patterns were quite characteristic and may possibly be pathognomonic, although we have not yet had an opportunity to compare them with pattern profiles in a variety of other conditions involving the hand.

By contrast, the hand bone patterns of affected females were near normal and could not reliably be distinguished from those of unaffected females or unaffected males (fig. 4) by eye alone. There was no visible reduction of the distal phalanx of the thumb in affected females. However, the *ratio* of the length of the first metacarpal to the first distal phalangeal bone was more than 2 SD units above the normal ratio of the lengths of these two bones in all three affected males tested and in four of the six affected females. This ratio (Met I/Distal I) may therefore have some diagnostic usefulness in doubtful cases, although it is certainly not pathognomonic.

E. Dermatoglyphics

The hands of affected males exhibited abnormal palmar creases but no simian (single transverse) crease. Two of the three affected males exhibited complex,

trapezoid. Short thumb with short distal phalanx and prominent pseudoepiphysis. The double ossification center of the lunate is of doubtful significance. *h*, Adult female (III-1). Trapezium-scapoid fusion. The capitate is unremarkable. *i*, Lumbar spine (IV-4). Widening of interpeduncular distances in lower lumbar region; failure of fusion of arches posteriorly. *j*, *k*, Adult male (II-2). *k*, Lateral view of skull shows prominent supraorbital ridge, vertical clivus, poor sinus pneumatization, flattened facial skeleton, and increased mandibular angle. *j*, Demonstrates soft tissue relationships to cranial skeleton. *l*, Adult female, pelvis. The iliac wings are small.

TABLE 3

COMPARISON OF RADIOGRAPHIC FINDINGS IN MALES AND FEMALES

FEATURE	MALES					FEMALES				
	IV-3	IV-4	II-2	IV-5	III-1	III-2	II-1	II-5	I-2	
Hands:										
Clinodactyly or brachymesophalangia V	++	++	++	++	--	++	+-	++	++	
Broad first distal phalanx	++	++	++	--	++	++	--	++	++	
Trapezium-scapoid fusion	++	++	++	--	++	++	--	--	--	
Small carpals	++	++	--	++	--	--	--	--	--	
Transverse capitata	++	++	--	--	--	--	--	--	--	
Extra carpal ossification	++	++	--	--	--	--	--	--	--	
Some hand abnormality	++	++	++	++	++	++	++	++	++	
Feet:										
First toe shorter than second	++	++	++	++	++	++	++	--	--	
Short first distal phalanx	++	++	++	--	++	++	++	--	--	
Short first proximal phalanx	++	++	--	--	++	++	--	--	--	
Prominent fifth MT base	++	++	--	++	++	++	++	++	++	
Extra ossification center, base MTS	--	--	--	++	--	--	++	++	++	
Fusions or joint narrowing:										
MT1-medial cuneiform	--	--	++	--	--	--	--	++	--	
MT2-middle cuneiform	++	++	++	--	++	--	--	++	--	
MT3-lateral cuneiform	++	++	++	--	++	--	--	++	--	
MT-cuboid	--	--	++	--	--	--	--	++	--	
Involving cuneiform	--	--	++	--	--	++	--	++	--	
Other tarsal	--	--	++	--	++	--	++	++	--	
Summary of fusions or joint narrowing. ...	++	++	++	--	++	++	++	++	--	
Some foot abnormality	++	++	++	++	++	++	++	++	++	
Pelvis:										
Small iliac wings or flat angles	+	+	+	0	+	0	+	0	0	
Skull:										
Vertical clivus	+	+	+	--	--	+	--	0	0	
Poor mastoid pneumatization	+	+	+	--	--	0	--	0	0	
Prominent frontal	+	+	+	--	--	+	+	0	0	
Prominent occipital	+	+	+	--	--	+	+	0	0	
Sinusitis or sinus hypoplasia	+	0	0	0	+	+	+	0	0	
Spine:										
Delay or failure of fusion	+	+	+	+	+	--	0	0	0	
Lumbar spondylolysis	--	--	+	0	+	--	0	0	0	

NOTE: + = present; -- = absent; 0 = not examined; MT = metatarsal.

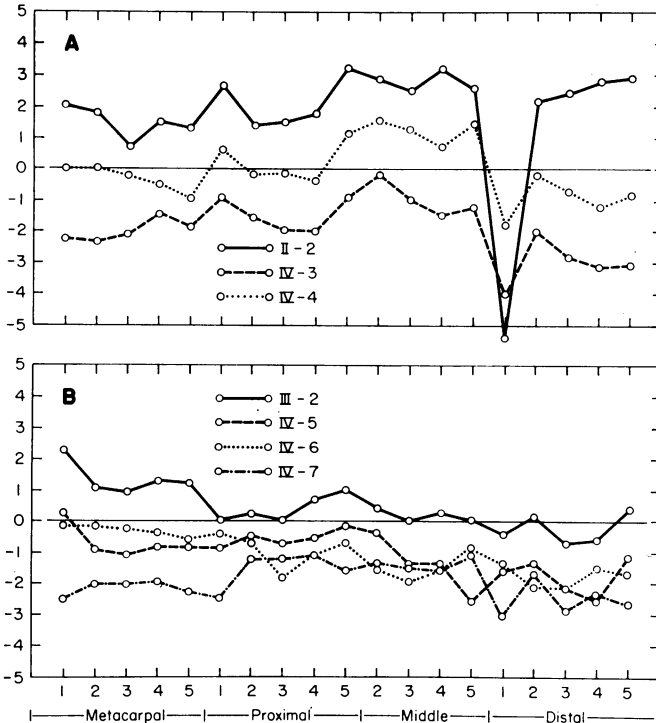


FIG. 4.—Metacarpal-phalangeal pattern profiles in sibships with the oto-palato-digital syndrome. Lengths of the 19 tubular bones of the hand are expressed in standard deviation units, relative to the norm for age, sex, and race. As shown in *A*, affected males have very similar metacarpal-phalangeal profile patterns with pronounced shortening of the distal phalanx of the thumb, consistently 2-7 sd below the average for the remaining segments. Shown in *B*, affected females (III-2 and IV-5) do not show distinctive patterns of metacarpal-phalangeal reduction as compared with unaffected females and males, respectively (IV-6 and IV-7).

whorl-like patterns on one thumb. However, no consistent pattern attributable to the syndrome could be discerned in either males or females.

F. Genetic Segregation Data

Five sibships at risk in four consecutive generations contained a total of 15 liveborn offspring, of whom eight (three of six males and five of nine females) were affected. These figures do not depart significantly from Mendelian expectations for a single dominant gene. No male-to-male transmission has yet occurred in the kindred. However, there has been no opportunity for such transmission since two of the three affected males are juveniles and the third is a confirmed bachelor.

G. Unaffected Family Members

Special attention was directed to family member III-8, who by 1970 had had 10 consecutive miscarriages with no normal pregnancies. The record of one such

miscarriage (which occurred in 1960) was obtainable; it indicated possible maldevelopment of one foot but gave no description of the head of the embryo. The mother was examined carefully and found to be clinically normal. In particular, there were no clinical stigmata of the oto-palato-digital syndrome. Her canthal index was normal.

A total of 11 unaffected family members and their spouses were examined. Of these, rampant caries and/or clinodactyly were noted in five. The diagnostic usefulness of these features is therefore probably quite limited. One individual (IV-27) had cleft lip and palate, but neither he nor his mother exhibited any feature of the oto-palato-digital syndrome.

DISCUSSION

Three of the affected females here reported (I-2, II-1, and III-1) are pedigree-proved carriers of the gene (fig. 1). One of these females (III-1) was easily detectable, while the other two had minimal clinical involvement. The three remaining cases (II-5, III-2, and IV-5) were diagnosed on clinical grounds alone. Of these, two were easily detectable clinically, while the third (II-5) had minimal clinical stigmata but fusions of tarsal and metatarsal bones. Thus, the combined clinical and pedigree data would appear to provide convincing evidence of the presence of the gene for the trait in all six cases. Significantly, the canthal index was beyond the limits of normal in four of the six.

The expression of the gene in females is mild and variable. The diagnosis cannot be determined with certainty in every case. X-rays of the feet are helpful if they show multiple tarsal and metatarsal fusions, but absence of such findings does not conclusively exclude the diagnosis. The most useful clinical features would appear to be those that contribute to the characteristic facial appearance, in particular the short, vertical nasal bridge, the hypertelorlic appearance of the eyes, and the supraorbital fullness with downward-tilted lateral portion of the upper eyelid. The canthal index was beyond normal limits in four of the six females in this kindred and may therefore be diagnostically useful. Although hands and feet may show some changes similar to those of affected males, it should be stressed that clinodactyly, shortened fifth digits, a slightly shortened great toe, and gaps between the toes frequently occur as isolated findings in the general population and are not pathognomonic of this trait. On the other hand, fusions of the cuneiform bones almost never occur as an isolated anatomical variant although they do occur in some other congenital malformation syndromes [10]. The abnormality involving the base of the fifth metatarsal is not commonly seen in other disorders.

X-rays of the hands and feet are probably the most useful of the special diagnostic procedures. Dermatoglyphics may only reveal changes in thumbprints of doubtful specificity. Measurements of hand bone dimensions produce striking patterns in affected males. Elevation of the ratio (Met I/Distal I) may be helpful in detection of affected females. Similar pattern profiles of feet would probably be of some value, but normal standards are currently lacking.

In this kindred, neither males nor females exhibited clinically apparent hearing

loss. The deafness occurring in previously reported cases of oto-palato-digital syndrome has been attributed to dysplastic auditory ossicles [11]. However, recurrent otitis media with resulting hearing impairment is an extremely common accompaniment of cleft palate of whatever type. The absence of deafness in the three affected males of this kindred suggests that (1) the deafness previously reported in oto-palato-digital syndrome may be due to recurrent otitis media; or (2) the degree of involvement of auditory ossicles in the dysplastic process may vary from individual to individual or from kindred to kindred.

SUMMARY

Study of three affected males and six affected females in four consecutive generations of a single kindred with oto-palato-digital syndrome revealed that females carrying the gene exhibit some clinical features similar to, but usually much milder and more variable than those of affected males. The diagnosis can usually be established in females by close attention to facial features (including canthal index) and appearance of the extremities, especially the feet. Various types of fusion anomalies involving carpal, tarsal, and metatarsal bones are seen radiologically in females as well as in males. Carrier females in this kindred did not exhibit cleft palate, vertical clivus, protuberant occiput (one exception), deafness, or unusually short stature. One of the three affected males had very mild hearing loss; the other two had normal hearing. No characteristic dermatoglyphic patterns were observed in either males or females. Segregation data were consistent with transmission as an X-linked Mendelian trait with intermediate expression in female heterozygotes or as an autosomal dominant trait with sex difference in expression.

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