Holt-Oram Syndrome: Clinical and Genetic Study of a Large Family

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INTRODUCTION

MENDELIAN INHERITANCE of congenital heart malformations is not a common phenomenon. However, a striking example of such a genetic trait is the syndrome of atrial septal defect, cardiac arrhythmia, and malformations of the hands first described by Holt and Oram (1960). McKusick (1961) observed a case of mother-daughter transmission of the same condition, and a further case in mother and son was reported by Zetterqvist in 1963. Additional families have been studied by Kuhn, Schaaf, and Wagner (1963); Pruzanski (1964); Lewis, Bruce, and Motulsky (1964); and Holmes (two pedigrees, 1965). All of the published pedigrees are consistent with an autosomal dominant mode of transmission, and considerable variability of the cardiac and skeletal malformations has been shown to occur even in the same family.

This paper describes the ninth and largest reported pedigree of Holt-Oram syndrome. Information hitherto lacking on penetrance, expressivity, and the range of variation of the cardiac and skeletal lesions is provided by the large number of affected persons studied in detail. Of particular interest in this syndrome is the abnormal pattern of palmar friction ridges. Palmar dermatoglyphics of affected members of this family were studied by means of a newly devised quantitative index which may throw light on the disturbance of development of the hand in this condition and may further clarify the relationship of friction ridge patterns to underlying growth centers. In addition, segregation ratios in this kindred suggest the possibility of abnormal segregation.

The Kindred (Family F)

The pedigree (Fig. 1) was constructed through interviews with reliable members of the family. Information gathered independently from several informants allowed verification of family relationships and served to substantiate previously existing pedigree data. At risk are 13 sibships (49 persons) in four

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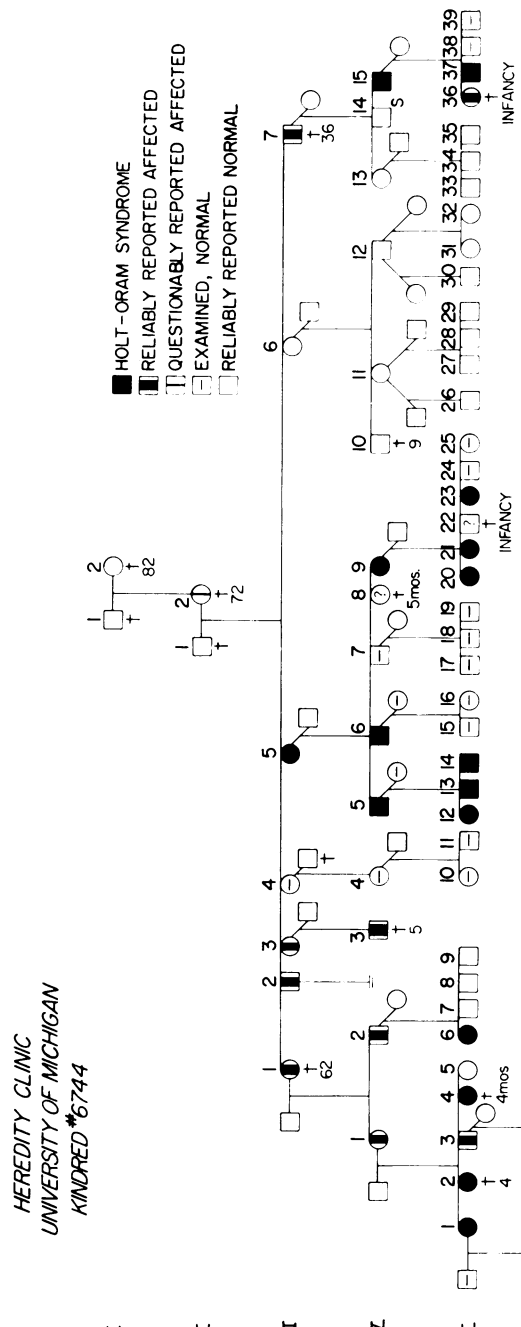

FIG. 1. Pedigree of family F.

successive generations. Fifty-six per cent (33/59) of the living members of the last four generations have been examined by us. Nineteen of the 22 living affected individuals have undergone clinical examination, chest X ray, and electrocardiography. Cardiac catheterization has been performed in 13 of these 19. In addition, chromosome studies were performed in eight cases—seven affected and one normal person.

CLINICAL OBSERVATIONS

Clinical Summaries of Typically Affected Individuals

VI-5, younger sister of the proposita, was first examined at the University of Michigan Hospital at age three months in 1956 because of cyanosis and poor weight gain. Cardiac catheterization and angiocardiography revealed a large ventricular septal defect with left to right shunt and pulmonary hypertension. The left superior vena cava anomalously entered the right atrium. A banding operation to produce a supravalvular constriction of the pulmonary artery was carried out in 1957, with some clinical improvement. In 1959, the ventricular septal defect was closed and the band released. A second cardiac catheterization performed in 1960 revealed the presence of a small patent ductus arteriosus.

Although no gross bony abnormalities were noted on initial examination, the patient was re-examined after the syndrome was recognized in other affected family members. The characteristic distal displacement and hypoplasia of the thenar eminence bilaterally, with a tendency for the thumb to be carried in the same plane as the fingers, were found. X-ray examination of the upper extremities showed all tubular bones to be more narrow than normal but without gross abnormalities. There was questionable slight overgrowth of each radius. Palm print patterns showed a distally displaced axial triradius.

V-13, a distant cousin of the proposita, was studied at the University of Michigan Hospital in April, 1965, at the age of 14 years. Neither he nor his parents had suspected any abnormality. He was a husky boy who played on the school football team and had a good scholastic record. Examination revealed a robust adolescent male with no gross deformities. However, the clavicles were somewhat short, and the arms showed a slight thickening about the elbows (Fig. 2). The hands showed slenderness of the thenar eminence bilaterally with a slight diminution of opposability of the thumb (Fig. 3). Palm prints showed an abnormal pattern of the friction ridges, with absence of the axial triradius. The apical rate was 56; a blowing grade II systolic murmur was heard along the left sternal border. Chest X ray confirmed the clinical impression of mild cardiomegaly. Cardiac catheterization revealed a small defect in the muscular portion of the ventricular septum, near the apex of the heart. An electrocardiogram showed variable P-R interval and an occasional ventricular extrasystole. The findings were strikingly similar to those of his younger brother, V-14, who is also shown in Fig. 2.

Clinical Findings in Family F

Of 13 affected family members who underwent cardiac catheterization, nine showed conclusive or strongly suggestive evidence of anatomic malformation

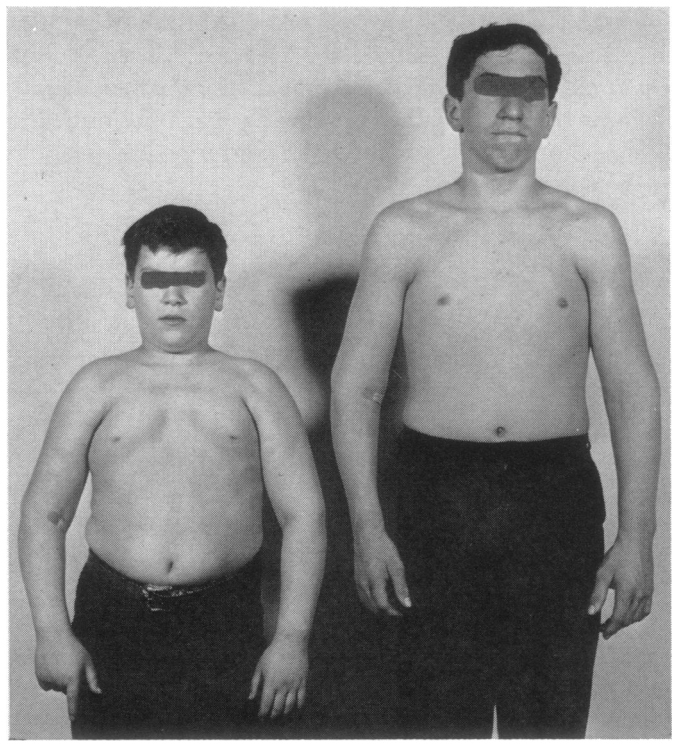

FIG. 2. Affected brothers, P. F. (V-14) and M. F. (V-13). Note characteristic appearance of shoulders and relatively slight hand involvement.

of the heart or great vessels (Table 1). In two others, in whom strong clinical evidence of septal defects was found, technical difficulties prevented demonstration of the lesions at cardiac catheterization. In the remaining two persons thus studied, the only demonstrable lesion was abnormally heavy trabeculation in the right ventricle.

Of the nine persons in whom an anatomic lesion was conclusively demonstrated or strongly suggested, a septal defect was diagnosed in eight. The ninth showed findings of persistent left superior vena cava. Of the eight in whom septal defect was diagnosed, only one was thought to have isolated atrial septal defect. One had findings of both atrial and ventricular lesions, and six had ventricular septal defect without atrial septal defect. Two of the six had large ventricular septal defects with associated malformations of the great vessels and secondary pulmonary hypertension. In general, however, the size of the septal defect was found to be small in relation to the clinical findings, particularly the degree of cardiomegaly, and except for the two cases with large septal defects, the disturbance of cardiovascular dynamics was slight.

Electrocardiographic studies were available for ten affected females. Seven of these exhibited a bizarre derangement of atrioventricular conduction, with bradycardia of 50–60/minute. One (VI-2) had no demonstrable arrhythmia nor bradycardia despite a significant heart murmur. In most cases, the arrhythmia was intermittent. All of the six males for whom electrocardiographic

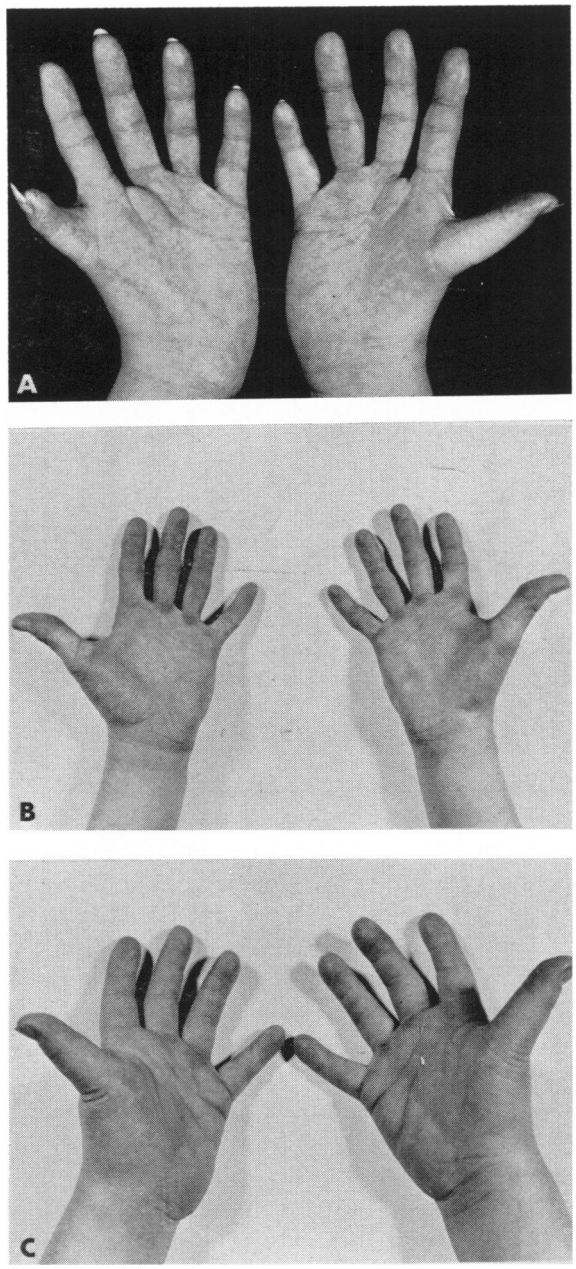

FIG. 3. Hand involvement in offspring of IV-5. (A) Hands of A. F. (V-12) showing severe deformity. (B) M. F. (V-13) showing minimal involvement. (C) P. F. (V-14) showing mild involvement.

tracings were available had prolonged P-R interval, but none had persistent atrioventricular dissociation. However, ventricular rates of 50–60/minute were noted in three of the six.

Skeletal involvement varied from subtle change in the configuration of the

TABLE 1. THE CARDIAC LESION: FINDINGS ON CARDIAC CATHETERIZATION

	V.S.D.	A.S.D.	Other	Pulmonary hyper-tension
Males				
1. IV-5	+*	+	—	—
2. V-13	+	—	—	—
3. V-14	+	—	—	—
4. IV-6	+ (large)	—	Persistent left superior vena cava	+
5. IV-15‡	+*	—	—	—
Females				
1. V-12	—	—	Persistent left superior vena cava§	—
2. IV-9	—	—	— §	—
3. V-20	+	—	—	—
4. V-21†	—	—	—	—
5. V-23†	—	—	—	—
6. V-1	—	+*	—	—
7. VI-3	—	—	— §	—
8. VI-2	+ (large)	—	Patent ductus Anomalous left coronary	+

*Findings inconclusive.

†Physical examination suggested ventricular and atrial septal defects which could not be demonstrated on this occasion.

‡Performed by Dr. E. H. Drake at Henry Ford Hospital (1939). Data courtesy of Dr. Drake.

§Abnormally heavy trabeculation in right ventricle.

hands, upper extremities, and shoulders to severe malformation and hypoplasia of the entire upper appendicular skeleton. The minimal detectable degree of hand involvement consisted in flattening and distal displacement of the thenar eminence, giving a graceful, slender appearance to the hand. There was associated diminution of opposability of the thumb, more severe in those cases in which the thumb resembled a triphalangeal digit. The range of hand involvement is indicated by Fig. 3, showing the hands of all three members of one sibship.

The variety of the skeletal lesions is indicated by Fig. 2, showing two affected brothers in one sibship, and by Fig. 4, showing three affected and two normal children in another. In fully expressed cases, the general appearance was striking; the clavicles were short and the shoulders narrow, causing the arms to hang away from the body. The elbows could not be brought against the chest wall, and the arms could not be raised above shoulder level.

Close clinical and X-ray examination revealed some degree of malformation and/or hypoplasia of the bones of the shoulder girdle and upper extremities in every affected person except one (V-37)—even those with minimal hand involvement. Shallowness and hypoplasia of the glenoid fossa were frequently observed on X-ray examination. One member of the kindred (V-6) was able to dislocate her shoulders at will. Pectus excavatum was an occasional finding. In no individual were the lower extremities affected.

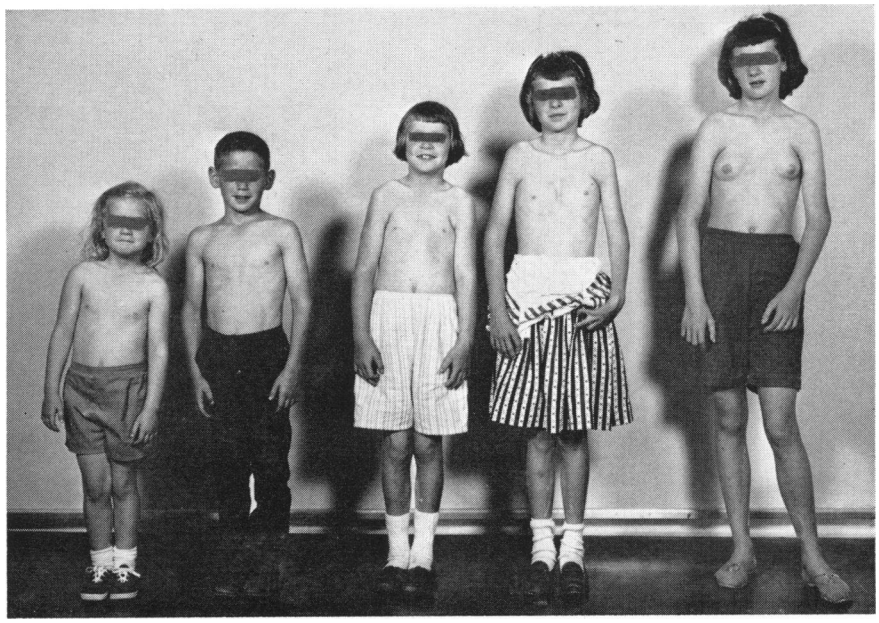

FIG. 4. Offspring of IV-9. Left to right: R. M. (V-25), G. M. (V-24), De. M. (V-23), Di. M. (V-21), and F. M. M. (V-20). (V-22 died of diarrhea at six months of age.) The two youngest children are unaffected. Note the hypoplasia of the shoulder girdle in the three affected girls. The two oldest girls exhibit hypoplasia of the entire left upper extremity and scapula. Di. M. (V-21) also exhibits pectus excavatum.

The majority of cases showed a strong tendency toward symmetry of skeletal involvement. In severe cases, one side (usually the left side) was often more severely affected than the other. However, no case of unilateral involvement was observed.

Patterns of Expression

Severity of involvement was quantitated on a scale ranging from 0 to 10 for the cardiac and skeletal lesions and from 0 to 4 for the conduction abnormality. In evaluating the degree of cardiovascular involvement, a score of 1 was assigned to each of the following findings: significant heart murmur, mild cardiomegaly, small septal defect, anatomic heart defect other than septal defect, pulmonary hypertension, and dyspnea or limited activity in adult life. Cardiovascular findings indicative of more severe involvement, such as pronounced cardiomegaly, large septal defect or presence of two septal defects, cardiac symptoms in childhood, or death from cardiac causes in childhood, were assigned a value of 2 for scoring purposes. In assessing the conduction defect, bradycardia (60/minute or less) and prolonged P-R interval were each assigned a value of 1, while complete atrioventricular dissociation was assigned a value of 2. The skeletal findings assigned a value of 1 included deformity (distal displacement) of the thenar eminence, nonopposable thumb(s), digitized (triphalangeal) thumb(s), syndactyly, mild shoulder deformity, hypoplastic scapula, shallow glenoid fossa, and pectus excavatum. A value of 2 was assigned to significant shortening of the long bones of the arm.

TABLE 2. CLINICAL EVALUATION OF AFFECTED PERSONS
For explanation of scoring, see text.

	Median Scores*		
	Cardiac	ECG	Skeletal
Females	4 (14)	3 (11)	5 (12)
Males	3 (6)	1.5 (6)	2 (6)

*Numbers of observations are given in parentheses.

Maximum involvement would receive, under this scoring system, a score of 24. The median score for affected members of Family F was 10. However, males and females, scored in this way, exhibited significantly differing characteristic patterns of clinical involvement, as shown in Table 2. The differences between males and females in scores for conduction system and skeletal system involvement were significant ($P = 0.002$) when tested by the rank sum test.

The male pattern of involvement characteristically included a small defect at atrial or ventricular level, mild to moderate skeletal defect, and mild conduction defect (prolonged P-R interval). Severe involvement of the hands did not occur in males. Females tended to exhibit more severe skeletal involvement, particularly of the hands, and more pronounced conduction defect (complete atrioventricular dissociation). Cardiac malformation was, in general, equal in both sexes. No clear evidence of a tendency toward transmission of distinct clinical patterns was noted.

Correlation in Severity of Skeletal and Cardiac Involvement

In Fig. 5, each affected person is represented by a point located according to his cardiac and skeletal scores (horizontal and vertical axes, respectively). This presentation yields a graphic representation of expressivity and correlation in severity of cardiac and skeletal involvement. Both scores could be estimated for 18 persons. None showed failure of expression of the skeletal lesions, and none was free of cardiac involvement. Three of the catheterized females were thought not to have a septal defect. One of these had a persistent left superior vena cava demonstrated at cardiac catheterization; in the other two, the only anatomic abnormality detected was abnormally heavy trabeculation in the right ventricle. In one affected girl (not yet studied by catheterization) serial observations strongly suggested spontaneous closure of a septal defect.

A wide range of expression, from minimal to very severe, was observed for both the skeletal and cardiac lesions. However, as can be seen from Fig. 5, males exhibited a smaller range (as well as a lesser average amount) of skeletal involvement than females. The grouping of the points in Fig. 5 suggests a weak positive correlation in severity of cardiac and skeletal lesions. Spearman's rank correlation coefficient r_s for the entire sample (18 points) was 0.97; for females only (12 points), $r_s = 0.94$. Although this association is statistically significant, the inherent inaccuracy of the scoring method used, taken in conjunction with the large number of ties (identical ranks) and the small total number of observations, suggests that this finding should be regarded as very tentative.

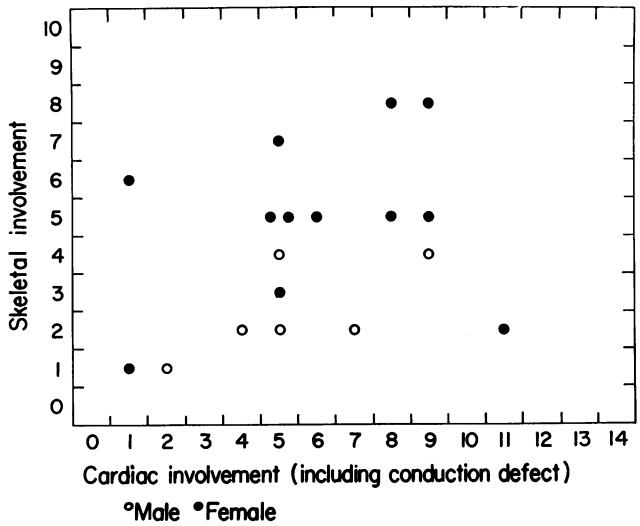

FIG. 5. Correlation in severity of skeletal and cardiac involvement in affected members of family F. For explanation see text.

Reproductive Performance

Seven affected females produced an average of 4.4 children each in contrast to an average of 2.6 offspring for five normal females in the kindred. Six affected males produced an average of 3.0 offspring apiece, while four normal males in the kindred produced an average of 1.8 children apiece. Since some of the parents are still within the reproductive period, these figures do not measure completed reproductive performance. However, they indicate that the condition is not associated with any striking reduction of fecundity.

General growth and development of affected individuals was normal, except for two with large septal defects and two who died of cardiac causes in childhood. Skeletal age was normal in the children studied. The adult males were stocky and muscular and performed heavy labor in factory and farm work. The adult females carried out their homemaking duties with no demonstrable limitations of activity, although two, III-5 and IV-9, reported shortness of breath on heavy exertion. There was no evidence of shortened life expectancy among those who survived early childhood. General intelligence of affected persons was apparently normal or better than average. Only one member of the entire kindred, V-33, was mentally retarded; he was in a branch of the family that does not manifest the syndrome.

Chromosome Studies

Cytogenetic studies were performed on the chromosomes of cultured peripheral leukocytes following a modification of the method of Moorhead *et al.* (1960). Eight family members (seven affected and one normal) were studied. At least 15 well spread metaphase plates per individual were analyzed in detail. In each case, the karyotype was normal both numerically and morphologically. There were no discrepancies in phenotypic and chromosomal sex.

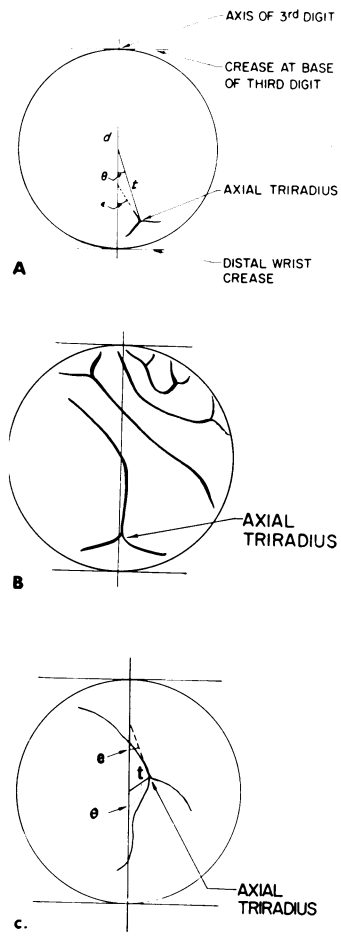

FIG. 6. Palmar dermatoglyphics in Holt-Oram syndrome. (A) Surface of right palm mapped on a circle. *d:* diameter of circle; *t:* distance from center of circle to triradius; θ: angle formed by line joining triradius to center of circle and vertical diameter of circle; *e:* angle of declination of principal axis of triradius. (B) A normal right palm. (C) Right palm in Holt-Oram syndrome (V-20) showing abnormal position and orientation of axial triradius.

Dermatoglyphics

Palmar friction ridge patterns in affected members of Family F were normal except in the area of the thenar eminence. In order to study the dermatoglyphic abnormality in a quantitative way, the right palm was mapped on a circle whose center was midway from the base of the third digit and the distal wrist crease, on a line perpendicular to the distal wrist crease and passing through the center of the base of the third digit. (This line approximates the long axis of the hand.)

The abnormality in the thenar area was then expressed in terms of the position and orientation of the axial triradius. The position of the axial triradius was measured in terms of polar coördinates (angle θ, distance t/d) with reference to the center of the circle defined above. The orientation of the axial

TABLE 3. MEAN VALUES (PLUS OR MINUS ONE STANDARD ERROR OF THE MEAN) FOR POSITION AND ORIENTATION OF AXIAL TRIRADIUS ON RIGHT PALM IN 12 AFFECTED MEMBERS OF FAMILY F AND IN 50 NORMAL INDIVIDUALS

For explanation of symbols see Fig. 6.

	Affected*	Normal
θ	94 ± 17	15 ± 2
t/d	0.19 ± 0.03	0.35 ± 0.02
e	26 ± 4	5.0 ± 2.7

*Includes three affected individuals with normal values. Two affected persons who lacked an axial triradius on the right palm were excluded.

triradius was measured as the angle e formed by extending its principal radius to its point of intersection with the long axis of the hand (Fig. 6A). Mean position and orientation of the axial triradius in 12 affected members of family F and in a control series of 50 unrelated 13–16 year old high school students are given in Table 3. In six unaffected members of Family F who were examined, all palm print measurements were normal. These variables were found to be closely correlated with each other both in the normal series and in affected members of Family F. Even higher correlations were obtained when the two samples were combined, thereby increasing the range of values (see Discussion).

These measurements (position and orientation of the axial triradius) discriminate affected persons with significant hand malformation from normal persons very well. All palm print measurements on nine of the 12 affected persons who were examined fell more than two standard deviations away from the mean values for normal persons. However, three affected members of Family F with minimal hand involvement which was clearly visible clinically had normal palm print patterns. Palm print measurements are therefore no substitute for careful clinical observations. This finding is compatible with the notion that friction ridge patterns are a secondary reflection of underlying patterns of development of growth centers in the fetal hand and are not independently determined genetically.

GENETIC CONSIDERATIONS

Mode of Transmission

The syndrome in this kindred clearly fulfills the requirements of an autosomal dominant trait with complete or nearly complete penetrance. In no case was an affected child born to an apparently unaffected parent. The occurrence of father-to-son transmission of the trait on four occasions (IV-5 to V-13 and V-14, III-7 to IV-15, and IV-15 to V-37) rules out a sex-linked pattern of inheritance.

Segregation Analysis and Sex Ratios

Although autosomal dominant inheritance is clearly indicated, there is a suggestion of disturbance in the segregation ratios. The over-all segregation ratio of 27 affected (proposita subtracted) to 19 normal offspring at risk does

TABLE 4. PERSONS AT RISK IN FAMILY F.

Parental status	Affected			Not affected			Indeterminate*		
	M	F	Total	M	F	Total	M	F	Total
Affected father	4	3	7	8	3	11	0	0	0
Affected mother	7	14	21	3	5	8	1	1	2
Total	11	17	28	11	8	19	1	1	2

*Died in infancy; no data.

not differ significantly from 1:1. However, when this ratio is broken down by sex of affected parent, it is seen that affected mothers produced 20 affected to eight normal offspring, a result significant at the 0.04 level of probability (probability based on the cumulative binomial distribution). However, the total numbers involved are very small, and, if the two indeterminate persons at risk (see Table 4) are counted as normal, the ratio is not statistically different from expectation. For this reason the figures should be regarded as suggestive only.

The over-all sex ratio of 26 females to 23 males among offspring at risk does not deviate significantly from expectation. Although affected mothers produced more female than male offspring (20 females to 11 males), this distribution is not statistically different from 1:1.

DISCUSSION

The association of cardiac and skeletal anomalies in various clinical entities, including some of the chromosomal aberrations, has been reviewed by Holmes (1965). The Holt-Oram syndrome differs from other such conditions in that the cardiac and skeletal anomalies constitute a specific entity which is transmitted as a dominant trait. This dominant pattern of inheritance, together with evidence suggestive of disturbed segregation in Family F, prompted a search for cytogenetic evidence of a chromosomal abnormality. The negative findings must be viewed in the light of the inherent difficulties of detecting small chromosomal aberrations with present cytogenetic techniques.

Abnormal Segregation

Significant departures from classic Mendelian ratios at birth can be caused by many factors, including differential intrauterine mortality, gametic selection, and abnormal segregation (nonrandom distribution of chromosomes to gametes during meiosis). Examples of abnormal segregation in man are rare. Perhaps the best known possibility is Alport's syndrome of hereditary renal disease and deafness (Graham, 1959; Shaw and Glover, 1961; Cohen, Cassady, and Hanna, 1961). Other reported pedigrees of Holt-Oram syndrome, reported in sufficient detail to be analyzed, are too small for individual segregation analysis. Taken together, however, they show no significant departures from expected sex and segregation ratios.

Dermatoglyphics

Dermatoglyphic patterns are sensitive indicators of disturbed developmental processes of the structures underlying the friction skin (Cummins, 1926). They

are made up of many parallel friction ridges covering the palmar (and plantar) surfaces. These ridges develop during the tenth to thirteenth weeks of fetal life and conform to the relief of the palmar surface present at that time (Cummins and Midlo, 1943). The parallel ridges probably take the shortest course possible in covering the irregular surface of the fetal palm (Penrose, 1965).

Normal differentiation of the first digit involves a proximal migration of the carpal-metacarpal joint and a rotation of this joint to a more ventral position to allow opposition. There are also modifications of the carpal bones (expecially the greater multangular) which facilitate the function of the thumb. Affected members of Family F manifest incomplete accomplishment of this differentiation.

In affected members of Family F, the position of the axial triradius is correlated with the amount of rotation of the principal axis of the triradius. This may indicate that both its position and its orientation are influenced by an underlying focus which in the Holt-Oram syndrome is abnormally located, presumably as a result of incomplete differentiation of the first digit into a functional thumb. The three cases reported by Holmes (1965) also had a "distally located triradius," and the published figure seems to show a change in position and orientation very similar to that found in Family F.

SUMMARY

An extensive pedigree of Holt-Oram syndrome is reported. Detailed clinical examination of 19 of 22 living affected members has shown wide variability in expression of the cardinal features of the syndrome, with a clear-cut sex difference. The abnormal palmar dermatoglyphics have been related to an underlying disturbance of development of the first carpal ray by means of a quantitative index based on position and rotation of the axial triradius.

In this pedigree as in other reported pedigrees of Holt-Oram syndrome, the condition is transmitted as an autosomal dominant with essentially complete penetrance; but, in contrast to other reported families, this kindred shows an excess of affected offspring of affected mothers, suggesting abnormal segregation (meiotic drive). No abnormality of chromosome morphology was detected.

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