The Syndrome of Familial Defects of Heart and Upper Extremities
(Holt-Oram Syndrome)

By R. A. Massumi, M.D., and D. O. Nutter, M.D.

The ASSOCIATION of atrial septal defect and anomalies of the upper extremities specifically involving one or both thumbs was first reported by Holt and Oram in 1960.1 In that same year, McKusick2 referred to this association in one family and used the term “atriodigital dysplasia” as well as the “Holt-Oram syndrome.” Since that time one family has been reported by Zetterqvist,3 one family by Kuhn et al.,4 one family by Lewis et al.,5 and, most recently, two families by Holmes6 (table 1). The present report adds two families with typical findings and two sporadic cases probably representing the formes frustes of the syndrome. Actually, identical cases were reported in 1949 by Birch-Jensen in his comprehensive monograph on congenital deformities of the upper extremities7 under the heading of “Radial Defects” whose similarity to the skeletal anomalies under discussion are pointed out below.

The present report is considered of interest because (1) many more family studies are needed before the full spectra of cardiac and skeletal anomalies are delineated; (2) the pattern of bony anomalies will be shown to be specific and to correspond to the so-called radial defect of the orthopedists; (3) a possible chromosome abnormality will be demonstrated. It is hoped that more physicians and particularly orthopedists who care for most of these patients will become acquainted with the syndrome and be stimulated to investigate the afflicted families through a combined cardiologic-orthopedic approach.

The pedigrees of families I and II are illustrated in figure 4.

Family I

Case 1

H.W., an asymptomatic 19-year-old Negro boy, had a heart murmur detected in the second month of life. Cardiac catheterization performed at the age of 14 documented the diagnosis of secundum atrial septal defect. Attempted surgical correction of this defect was abandoned when cardiac arrest occurred shortly after the start of the operation. During a recent hospital admission for evaluation of a coin lesion in the chest he was found to be free from cardiovascular symptoms or signs of failure. Examination of the heart demonstrated palpable right ventricular and pulmonary artery lifts, a grade-III, basal, systolic ejection murmur, and fixed splitting of the second heart sound. First-degree heart block and the pattern of incomplete right bundle-branch block were noted on the electrocardiogram. The chest films are illustrated in figure 1.

His body habitus was short and stocky with a height of 167 cm., a weight of 65 Kg., arm span of 143 cm., crown-to-pubis length of 81 cm., and pubis-to-heel length of 86 cm. The left arm was shorter than the right by 5 cm. (fig. 2A). A moderate degree of pectus excavatum, a conically shaped, narrow-inlet chest, and a narrow shoulder girdle were observed. Bilaterally, there was limitation of motion of the elbows with loss of the carrying angle and radial bowing of the forearms. These defects were more striking on the left in which functional impairment was significant. Striking also were the manus vara hand deformities with absence of the left thumb and a nonfunctioning, gracile right thumb producing a fingerlike first digit which lay in the plane of the other fingers (fig. 2A). Roentgenologically, the fingerlike right thumb possessed three phalanges and its metacarpal segment was short and thin. There was hypoplasia of the right greater multangular and navicular bones. On the left, the entire radial portion including the thumb, its metacarpal, and the radial carpal bones (namely, the greater multangular and navicular) were missing (fig. 1). The radius and ulna on the left were thin and
Table 1

Summary of Previously Reported and Present Cases of Familial Cardiac-Upper Extremity Defect (Holt-Oram Syndrome)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Family members &amp; age</th>
<th>Cardiac defect</th>
<th>ECG</th>
<th>Cardiac catheterization</th>
<th>Thumbs</th>
<th>Skeletal defects</th>
<th>Misc.</th>
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<tr>
<td></td>
<td>Uncle 52</td>
<td>IASD‖</td>
<td>RBBB-RVH Arrhyth.</td>
<td>—</td>
<td>Fing. like 3 phal. Absent Abn. Abn.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McKusick 1961 (2)</td>
<td>Mother</td>
<td>IASD‖</td>
<td>—</td>
<td>—</td>
<td>Fing. like 3 phal. Fing. like 3 phal. Abn. —</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daughter</td>
<td>IASD‖</td>
<td>—</td>
<td>Performed</td>
<td>Fing. like 3 phal. Absent Abn. —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zetterqvist 1963 (3)</td>
<td>Mother 34</td>
<td>IASD‖</td>
<td>RBBB Arrhyth.</td>
<td>L-R shunt, 3/1</td>
<td>Absent Fing. like 3 phal.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Son 12</td>
<td>IASD‖</td>
<td>RBBB Arrhyth.</td>
<td>L-R shunt, 2/1</td>
<td>Fing. like 2 phal. Fing. like 2 phal. Abn. —</td>
<td>High palate Abn. shoulders</td>
<td></td>
</tr>
<tr>
<td>Kuhn 1963 (4)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Lewis 1964 (5)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Son 5 mos.</td>
<td>IVSD</td>
<td>Normal</td>
<td>L-R shunt, 1.2/1</td>
<td>Fing. like 2 phal. Fing. like 2 phal. Abn. Abn.</td>
<td>Abn. shoulders</td>
<td></td>
</tr>
<tr>
<td>Family II</td>
<td>Father</td>
<td>IASD</td>
<td>RBBB</td>
<td>Fing. like 3 phal.</td>
<td>Fing. like 2 phal.</td>
<td>Pigeon breast</td>
<td>Dorsal kyphosis</td>
</tr>
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<tr>
<td>Daughter 8</td>
<td>IVSD</td>
<td>?</td>
<td>L-R shunt, 1.1/1 R-L shunt Pulm. hypert.</td>
<td>Fing. like 3 phal.</td>
<td>Absent</td>
<td>Abn.</td>
<td>Abn.</td>
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<td>Half-sister 30</td>
<td>Case 2</td>
<td>IASD</td>
<td>RBBB</td>
<td>Arrhythm.</td>
<td>L-R shunt</td>
<td>Long</td>
<td>Long</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Pec. excav.</td>
<td>Short 5th digit</td>
<td></td>
<td></td>
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<tr>
<td>Mother 47</td>
<td>Case 4</td>
<td>IASD</td>
<td>RBBB</td>
<td>Arrhythm.</td>
<td>L-R shunt, 1.8/1 Pulm. hypert.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

| Family II | Mother | 23 | Case 1 | IASD || RBBB | L-R shunt, 2/1 | Fing. like 3 phal. | Absent | Abn. | Short rad. Radioulnar synostosis | Uneq. arm length | Short trunk | Sprengel's def. | — |
|-----------|--------|-----|--------|------|------|----------|-------------------|--------|------|-------------------------------|--------------------|--------------|------------------|------|
| Daughter 2 | Case 2 | ASD, VSD | PVS, PBS | RVH | L-R shunt, 3.8/1 | — | — | — | — | — | — | — |

*Five other affected family members not reported.
†A family with ten cases (7 males, 3 females) covering three generations is reported. The cardiac defect in the majority was considered to be "primary" pulmonary hypertension; however, diagnostic studies were incomplete and inconclusive. The skeletal defects were chiefly radial and varied greatly including two examples of phocomelia.
‡Preliminary report of a family with 18 affected subjects in three generations. The skeletal defects varied in degree, but were usually radial in type. The cardiovascular defects covered a wide spectrum.
§Three other affected members (family I) not reported.
¶Diagnosis documented by autopsy.
||Diagnosis documented by surgery.
IASD, secundum interatrial septal defect; IVSD, interventricular septal defect; PDA, patent ductus arteriosus; PVS, pulmonary valve stenosis; PBS, pulmonary branch stenosis; RAD, right axis deviation; RVH, right ventricular hypertrophy; RBBB, right bundle-branch blocks; Atr. Abn., atrial abnormality; Fing. like, fingerlike; pec. excav., pectus excavatum.
synostotic in the upper portion. The left humerus was considerably shorter and thinner than the right and its head was hypoplastic. There was prominence of the medial epicondyles on both sides (fig. 2B). The scapulae exhibited ill-defined dysplasias suggestive of a Sprengel deformity.

Case 2

A.B., a 30-year-old Negro housewife and half-sister to H.W., had a heart murmur discovered at 8 years of age. The presence of a secundum atrial septal defect was confirmed by cardiac catheterization when she was 23 years old. Examination demonstrated a prominent pulmonary impulse, a grade-III, basal, systolic ejection murmur, and wide, almost fixed splitting of the second heart sound. First-degree heart block, right axis deviation, and incomplete right bundle-branch block were noted on the electrocardiogram. Chest films showed modest cardiomegaly with dilatation of the main pulmonary artery and an increased pulmonary arterial flow.

She was 159 cm. tall, weighed 51 Kg., had an arm span of 160 cm., crown-to-pubis length of 72.5, and pubis-to-heel length of 85 cm. The visible anomalies were limited to a moderate pectus excavatum, hyperextensible wrist joints, long thumbs, and short fifth fingers. Also present was a significant limitation of motion of the elbow joints and abnormal carrying angles. Radiographs of the upper extremities showing prominent humeral epicondyles are depicted in figure 3.

Case 3

R.W., the 8-year-old brother of H.W., was found to have the Wolff-Parkinson-White (WPW) syndrome but was otherwise free from cardiac or skeletal anomalies.

Case 4

E.W., a 47-year-old Negro housewife and mother of patients 1 to 3, noted weakness and effort dyspnea during the past year. Her previous cardiopulmonary history was negative and her pregnancies were uncomplicated. She was moderately obese (weight 83 kg.) and had no discernible musculoskeletal anomalies. Cardiac examination revealed a palpable right ventricular lift, a grade-II ejection murmur over the pulmonary artery, and fixed splitting of the second heart sound. Incomplete right bundle-branch block and first-degree heart block were present on the electrocardiogram, and chest films showed moderate cardiomegaly with large pulmonary arteries and increased pulmonary arterial flow. Cardiac catheterization in October 1964 documented the presence of secundum atrial septal defect associated with mild pulmonary hypertension (PA pressure, 45/25).

Congenital upper extremity anomalies identical with those found in the propositus (H.W.) are reported in a maternal great-uncle (case 5), a maternal great-aunt (case 6), and a maternal great-grandfather (case 7), none of whom had been known to have heart disease. There is no other history of congenital defects, mental retardation, or heritable diseases in this family.

Comment. In this family the syndrome appears in its complete form in the propositus and in a variety of incomplete presentations in six other
members spanning four generations (fig. 4). The incomplete forms were manifested by isolated atrial septal defect in one case, the WPW syndrome in one case, and presumably isolated radial defects in three others. In the latter cases, atrial septal defects may have been overlooked. The skeletal anomalies in case 3 were subtle and would have escaped detection in a routine, otherwise unconditioned, clinical examination. The occurrence of cardioradial defects in the children issuing from case 4 and two unaffected husbands offers support for the dominant mode of inheritance proposed in this syndrome.

Family II

Case 1

A.J., a 22-year-old Negro housewife, was admitted to this hospital with pulmonary tuberculosis in 1960 at the age of 17 years. Effort dyspnea and easy fatigue had been noted from the age of 10 years but a heart murmur was not detected until this admission. The ejection systolic murmur, the fixed splitting of the second heart sound, and the electrocardiographic evidence of incomplete right bundle-branch block led to a suspicion of secundum interatrial septal defect, and its presence was documented by cardiac

Figure 2

A, left. Photograph of arms in the same case as figure 1 demonstrating on the left side, shortness of the entire arm, absent thumb and hypoplasia of the hand, radial bowing of the forearm, and loss of carrying angle of the elbow. Note pectus excavatum, narrow shoulder girdle, flattening of the deltotoid area, and the scar of previous attempted thoracotomy. Note also the gracile, nonopposed right thumb. B, right. Roentgenograms of the humeri and upper thirds of forearms depicting hypoplasia of the left humerus, prominent medial epicondyles, and synostosis of the radius and ulna on both sides.
Roentgenograms of the forearms and hands in case 2, family I, showing lax wrist joints, long thumbs, and prominent medial humeral epicondyles as the only anomalies.

catheterization. The defect was successfully repaired by open-heart surgery when she was 19 years old.*

She was 157 cm. tall, weighed 44% Kg., had an arm span of 137 cm., crown-to-pubis length of 75 cm., and pubis-to-heel length of 80 cm. She possessed skeletal anomalies virtually identical with those of H.W. (in family I), including a narrow shoulder girdle, shortening and abnormal carrying angle of the arms, limitation of supination-pronation bilaterally, radial bowing and manus vara deformity, and absence of the left thumb (fig. 5). Here, too, the left arm was shorter than the right with more impressive deformity and impairment of function. Radiologically, the left thumb, its metacarpal and the two radial bones of the carpal assembly were absent (fig. 6). The lesser multangular, capitate and hamate appeared fused as did the lunate and triangular. The right thumb was tripahlangelal and slender and the corresponding metacarpal was thin. The two radial carpal bones were small on the right side. The left radius was short and slender and joined with the ulna in its upper portion. The medial epicondyles of both humeri were prominent. The left humerus was short and slender and its head was hypoplastiek and subluxated. The glenoid surfaces of both scapulae were small in area, and dysplasia of the superjacent portion of the bone caused a hollow deformity.

Case 2

L.J. was the 2-year-old daughter of patient 1. A heart murmur was discovered shortly after birth, and recurrent respiratory infections followed by congestive heart failure occurred at the age of 9 months. Examination revealed a prominent right ventricular lift, a systolic thrill and a harsh systolic, grade-IV systolic ejection murmur present over the pulmonary artery with wide and fixed splitting of the second sound. The electrocardiogram was compatible with right ventricular hypertrophy, and chest films showed cardiomegaly. Cardiac catheterization at this time demonstrated a secundum atrial septal defect, small ventricular septal defect, moderate valvular pulmonic stenosis (systolic gradient, 47 mm. Hg), and peripheral pulmonary branch stenosis. No musculoskeletal defects have been thus far recognized.

The mother of the propositus had tuberculosis and died 2 months after the birth of her daughter; her father is reputed to have heart disease but has not been examined. There is no history of heart disease, congenital anomalies, or mental retardation in other members of the family.

Comment. In this family, the complete form of the syndrome identical in all its manifestations with those of H.W. (family I) was observed in the propositus and the form manifested by multiple cardiac anomalies in her child. Information relative to the child’s father and his relatives is not available.

Sporadic Cases

S.G., a 4-year-old white boy, was born with anomalies of the thumb but appeared to be free from congenital heart disease. Family history included normal parents, two spontaneous abortions, and a neonatal death of a term infant with hand anomalies described as “loose thumb” on one hand and four fingers on the other.

It is possible that this family manifests the same syndrome and that the neonatal death was caused by severe congenital heart disease.

C.E., a 21-year-old mentally retarded Negro girl, was found, on a routine survey for congenital heart disease in a local institution for mental retardation, to have hand deformities identical with those of the propositi of families I and II. Unfortunately, the family history was unobtainable. Careful clinical, electrocardiographic, and x-ray

*We are grateful to Dr. Paul Adkins of The George Washington University Hospital for performing the operation.
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Numbers in parentheses = age in years

- d = dead

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cardiac Anomaly Only</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Skeletal Anomaly Only</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cardiac and Skeletal Anomalies</td>
<td></td>
</tr>
</tbody>
</table>

FAMILY I

Case 1 (19)  
Case 2 (8)  
Case 3 (30)  
Case 4 (47)  
Case 5 (70)  
Case 6 (82)  
Case 7 (65d)

FAMILY II

Case 1 (21)  
Case 2 (2)

Figure 4

Pedigrees of family I (top) and family II (bottom) showing the affected members. The code on top of illustrations describes the significance of the symbols used. The asterisk in case 2, family I, indicates presence of WPW syndrome as the only positive finding.
haustive in its treatment of skeletal defects, gives little, if any, information regarding the associated cardiac defects.\textsuperscript{13, 14} Only the papers describing the syndrome under discussion seem to provide a reasonably detailed description of both groups of anomalies. The work of Birch-Jensen\textsuperscript{7} is an exception to the rule and particularly relevant to this study. According to this author defects of the upper extremities fall in several distinct groups, of which defects of the radial structures (thumb, first metacarpal, the carpal bones on the radial side and radius) constitute one of the most frequent and most important categories. Defects of the

Discussion

The association of bony anomalies and congenital cardiac defects have been reported by a number of authors.\textsuperscript{8–12} Most skeletal anomalies have been localized in the upper extremities and include polydactyly, syndactyly, and other undescribed deformities. The cardiac defects have encompassed chiefly atrial and ventricular septal defects, but also other miscellaneous defects. Whether these reports contain examples of the Holt-Oram syndrome cannot be judged primarily because of the inadequate descriptions of the bony anomalies. Similarly, the orthopedic literature, while ex-

Figure 5

Photograph of the arms in case 1, family II, showing anomalies identical with those described in case 1, family I (see fig. 2 A).

examination of the cardiovascular system failed to disclose any congenital defects.

Figure 6

Top. Roentgenogram of upper arms and shoulders in the same case as figure 5 depicting a short, hypoplastic, subluxated left humerus and gross dysplasia of the area of the scapulae superjacent to the glenoid fossae. Bottom. Diffuse anomalies in both hands of case I, family II, identical with those described in case 1, family I (see fig. 1).
ulnar structures, on the contrary, are relatively rare and of lesser severity. Characteristic features of radial defects include absence of the thumb on one side and hyperphalangeal thumb on the other side, manus vara, short radius and radio-ulnar synostosis. Asymmetry of the upper extremity defects and absence of lower extremity anomalies are considered features of this type of defect. It is of note that the description of radial defect given by Birch-Jensen and also by previous German orthopedists$^{15,16}$ fits very closely with the defects reported here in our cases. Moreover, a high degree of association of the radial defects with congenital heart disease in sharp contrast to the low incidence in ulnar defects and other types of upper extremity skeletal anomalies has been noted by Birch-Jensen. Excluding the very large number of early deaths presumably cardiac in nature, Birch-Jensen found congenital heart disease 12 times in 73 cases of radial defects studied by him personally and nine times in 85 cases reported by others prior to 1949. Contrasted with these high figures is the incidence of only one congenital cardiac defect in 19 cases of ulnar defect. Equally low was the incidence of congenital heart disease in other defects of the upper extremities. Even though details of cardiac anomalies associated with the radial defects are not given, careful study of his published accounts and of photographs in his case 102 (p. 193), case 132

Figure 7

Karyotype in case 1, family I, demonstrating a constriction above the centomere of autosomal pair 16. An identical anomaly was found in case 1, family II.
A and B. Left and right hand, respectively, in case 1, family I. Note the presence of only one digital triradius on each side (open arrows) and absence of palmar main ridge. The left hand possessing only four fingers and otherwise severely malfunctioning shows grossly abnormal palmar ridges with no pattern whatever. The right hand with the rudimentary thumb and functionally less impaired than the left displays a well-developed loop pattern (solid arrow). Note hollowness of the thenar areas and absence of carpal triradii on both sides. C. Normal palm reproduced for comparison. Note the carpal triradius $t$ and digital triradii $a$, $b$, $d$. D. Palmar pattern in case 3, family I, demonstrating features identical with those of the normal palm in C. This patient had atrial septal defect with normal hands.
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(p. 197), and cases 136, 138, 139 (p. 198) leaves little doubt as to the identity of these five cases with the Holt-Oram syndrome.

Other pertinent data given in this monograph are those related to the hereditary nature of the defect and the high incidence in members of the same family suggesting a dominant genetic transmission. Lange’s report17 of a woman with absent thumbs who bore three similarly affected children from three different unaffected men emphasizes the dominant inheritance and the high degree of penetrance of the radial defect. That the same pattern of inheritance exists in the Holt-Oram syndrome can be inferred from the present study and from the Lewis report.5

Specific studies related to the pattern of transmission in this syndrome are presently in progress at Dr. McKusick’s Laboratory at The Johns Hopkins Hospital. Blood samples from the cases presented herein have been submitted to that laboratory for linkage studies and the results will be incorporated into their material. Other studies pertaining to inheritance have been carried out in the present material.

Chromosome Studies

Genetic defects play a minor etiologic role in most cases of congenital heart disease although a discrete number of conditions caused by single gene or chromosome defects have been determined.18 Previous karyotype studies in the Holt-Oram syndrome have been normal3, 5, 6. In the present study, the karyotypes (blood cells) were obtained in cases 1 and 4 of family I, and cases 1 and 2 of family II (and also from the father of another family with the typical syndrome but not included in this report).* They revealed a minor but identical aberration in autosomal pair 16 of the two propositi, with the complete syndrome, and the father of the unreported family. It consisted of a secondary constriction in the short arm of this chromosome setting off a bar-like satellite (fig. 7). This abnormality has been observed in approximately 60 per cent of the preparations from the affected cases. In Dr. Jacobson’s experience with over 500 karyotypes from various congenitally malformed children this abnormality in chromosome 16 has been noted in less than 5 per cent of the preparations. This finding, though preliminary, may represent a chromosomal aberration which, if borne out in future studies, may add to the understanding of the genetic transmission in this interesting syndrome.

Dermatoglyphics

The study of digital and palmar ridge patterns has been found to be of significance in genetic observations19 and abnormal palm patterns have been found to occur with some frequency in cases of congenital heart disease.20

We have studied dermatoglyphics of the digits, palms, and soles in all the cases of the Holt-Oram syndrome and the available unaffected siblings. The digital and solar patterns have been found to correspond to the normal standards established by Scotland Yard in all cases taken individually or as a group. The palmar patterns have been grossly abnormal only in cases with overt deformities of the hand and the magnitude of dermal ridge abnormality has been proportional to the skeletal defect (fig. 8). Cases of congenital heart disease with minimal or absent skeletal defects (cases 3, 4, family I) and those with no skeletal defects have exhibited palmar patterns that are within the wide limits of the normal. The inescapable conclusion is that the abnormality of the palmar ridges is secondary to skeletal deformities and the attendant muscular defects and not primary or genetically determined.

Summary

Two families with familial defects of the heart and upper extremities and two sporadic cases of skeletal anomalies of the same type are reported.

In the most complete and prototypal form the syndrome consists of a secundum atrial septal defect of moderate size and the so-called radial defect of the upper extremities. However, less complete forms exhibiting cardiac

*Through the kind collaboration of Dr. Cecil B. Jacobson of the Laboratory of Human Genetics of the Department of Anatomy, George Washington University School of Medicine.
anomalies alone, skeletal defects alone, or a combination of certain features of both, have been observed. Forms frustes undoubtedly occur.

The mode of inheritance seems to be autosomal dominant and of a high degree of penetrance.

Chromosome studies have suggested an abnormality in the pair 16.

Study of palm and sole prints have shown the abnormalities to be secondary to musculoskeletal defects and not likely to be genetically determined.

The syndrome is probably much more common than is realized. Identification of cases leading to the affected families depends upon awareness of pediatricians and orthopedists of its existence and inclusion of a careful examination of the upper extremities in all instances of atrial septal defect.

References
The Syndrome of Familial Defects of Heart and Upper Extremities (Holt-Oram Syndrome)
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