Holt–Oram syndrome: a clinical genetic study

RA Newbury-Ecob, R Leanage, JA Raeburn, ID Young

Abstract
A clinical and genetic study of the Holt–Oram syndrome (HOS) has been carried out in the United Kingdom involving 55 cases designated Holt–Oram syndrome, together with their parents and sibs. Data from the clinical assessment of both familial and isolated cases were used to define the HOS phenotype and to outline the spectrum of abnormalities, especially factors affecting severity. Skeletal defects affected the upper limbs exclusively and were bilateral and asymmetrical. They ranged from minor signs such as clinodactyly, limited supination, and sloping shoulders to severe reduction deformities of the upper arm (4-5%). The radial ray was predominantly affected and the left side was more severely affected than the right. All affected cases showed evidence of upper limb involvement. Cardiac defects were seen in 95% of familial cases and included both atrial septal defect (ASD, 34%) and ventricular septal defect (VSD, 25%); 39% had only ECG changes. Cardiac involvement ranged from asymptomatic conduction disturbances to multiple structural defects requiring surgery in infancy. Sudden death could be caused by heart block. Inheritance was autosomal dominant with 100% penetrance and no evidence of reduced fitness. Increasing severity occurred in succeeding generations consistent with anticipation.

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Key words: Holt–Oram syndrome; heterogeneity; maternal effect; anticipation.

Several heart-hand syndromes have been identified of which the Holt–Oram (HOS) is the best known. The first formal report by Holt and Oram in 1961 was based on a four generation family in which the main skeletal lesion was a triphalangeal thumb; the heart defect was a secundum atrial septal defect (ASD). There was also an unusual cardiac arrhythmia and evidence of hypoplastic peripheral vessels. Of nine subjects, four were confirmed as affected and five (not examined) were affected by history. ASD was suspected in four but only confirmed in one case. Electrocardiography (ECG) showed a variety of abnormalities including a long PR interval, sinus bradycardia, nodal escape, and atrial fibrillation. Three family members had a triphalangeal thumb. The thumb was absent in one subject and another had radial aplasia. One case had only a minor anomaly of the clavicle. Subsequent reports have included various combinations of upper limb abnormality and heart defect. The need to clarify the spectrum of abnormalities and to delineate the HOS phenotype led us to review the clinical features in our patients, and distinguish the clinical features most helpful for counselling purposes.

This study was carried out in conjunction with a genetic linkage study which has shown genetic heterogeneity in the Holt–Oram syndrome, with one gene (HOS1) being localised to chromosome 12 in five out of seven families. No phenotypic differences could be detected between the linked and unlinked families.

Patients and methods
The study was carried out between March 1991 and September 1993. Cases were ascertained by contacting clinical geneticists and paediatric cardiologists and through the support group REACH, for children with upper limb deficiency. Patients and first degree relatives were visited at home by RNE. A detailed family history was taken as well as all relevant medical and surgical details. Patients were examined carefully for any skeletal abnormalities or dysmorphic features. Measurements were taken of the upper arm, lower arm, palm, thumb, and middle finger. Where possible portable electrocardiography was performed. Information was sought from x rays, electrocardiograms (ECG), and cardiac ultrasound examinations previously undertaken.

In order to assess the severity of abnormalities, clinical examination data were recorded using a scoring system based on that devised by Gall et al and modified by Gladstone and Sybert (table 1). Measurements were compared with age matched standards. Statistical analysis was carried out using Mann–Whitney/Kruskall Wallis and Spearman Rank Correlation.

ASCERTAINMENT
Sixty six affected subjects from 28 families were referred to the study. Twelve families had three or more affected members. There were 33 males and 33 females; their ages ranged from

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Table 1 Severity score system

<table>
<thead>
<tr>
<th>Skeletal abnormalities</th>
<th>Cardiac abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No abnormality on physical or radiological examination</td>
<td>0 Asymptomatic with no physical findings</td>
</tr>
<tr>
<td>1 Minor abnormalities including reduced thumb eminence, clinodactyly, or hypoplasia of the thumb</td>
<td>1 Asymptomatic murmur or conductance defect</td>
</tr>
<tr>
<td>2 Triphalangeal or aplastic thumbs, Radial-ulnar hypoplasia</td>
<td>2 Structural heart abnormality not requiring surgery</td>
</tr>
<tr>
<td>3 Arms and forearms present but bone(s) missing</td>
<td>3 Structural heart abnormality requiring surgery</td>
</tr>
<tr>
<td>4 Phocomelia</td>
<td>4 Lethal malformation</td>
</tr>
</tbody>
</table>

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4 months to 70 years. Thirteen cases had no family history of HOS and are referred to in this study as isolated. Fifteen patients were not available for examination; these included five affected subjects who had died whose details were obtained from family history (5) and from case notes (2), PM details (2), and photographs (4). Twelve examined patients had not had ECG and echocardiography. Six relatives, thought previously to be unaffected, were found to be affected during the study examination. In total, 57 patients were examined. Details of the cases are given in table 2. Cases were included only if the heart and radial ray defects previously described in HOS were present in at least one affected family member. Two patients from one family who had upper limb abnormalities but no evidence of cardiac abnormality within the family were excluded from the study.

Clinical features

UPPER LIMB ABNORMALITIES (TABLE 3)

Familial cases

In all cases upper limb abnormalities were present and were clinically detectable. The radial ray was predominantly affected, with ulnar involvement only when the radius was also involved and with a lesser degree of severity. Transverse reduction defects were not seen.

Minor abnormalities, including hypoplasia of the thenar eminence, limited supination of the forearm, and narrow sloping shoulders, occurred without other evidence of skeletal involvement. Severe reduction abnormalities were found in two familial cases (4-5%). Fig 1 shows typical hand abnormalities in HOS.

Thumb

The thumb was the most commonly affected structure (84%). In contrast to the largest previous study, no patients had involvement of the thumb only. Even mild thumb hypoplasia was accompanied by hypoplasia of the thenar eminence (70%), limited supination of the forearm (61%), or narrowing of the shoulders. Triphalangeal thumb was only found in eight patients (18%); 19 (43%) had absence of one or both thumbs. Other frequent thumb abnormalities included a hypoplastic or rudimentary thumb (17, 39%) or a long thumb owing to elongation of the proximal phalanx (6, 14%). Five patients (11%) had syndactyly of the first and second digits and seven patients (16%) had no detectable abnormality of the thumb.
Fingers
Hand measurements showed reduced finger length in 19 cases (43%), including four in whom no thumb abnormality was present. Hypoplasia of individual fingers (16%) most commonly involved the index and middle fingers. Three patients had absence of one or more fingers. This occurred only where the thumb was also absent. Clinodactyly of the fifth finger was a common finding (64%).

Lower arm
In the lower arm, radial hypoplasia was seen in 18 cases (41%) and was invariably accompanied by a lesser degree of ulnar hypoplasia. No patients had involvement of the ulna only. Ten (23%) had complete radial aplasia. The commonest functional abnormality was limited supination of the forearm seen in 27 cases (61%). This was not always associated with radiological evidence of radioulnar synostosis but was sometimes associated with limited extension of the elbow.

Upper arm
Upper arm involvement leading to rhizomelic shortening was detected in almost half of all cases (45%), including four cases with no obvious radial hypoplasia. Phocomelia was seen in two familial cases (4.5%) (fig 2).

Shoulder
Proximal reduction defects were not present without distal defects, with the exception of shoulder abnormalities which were especially common (77%), giving a characteristic appearance of narrow, sloping shoulders, this being because of the combination of short hypoplastic clavicles, hypoplasia of the head of the humerus, and decreased musculature. Alternatively, prominence of the lateral third of the clavicle and acromioclavicular joint gave a bony prominence to the shoulder (fig 3).

Reduced shoulder movement, particularly abduction, was found. Hypoplasia of the overlying shoulder girdle musculature, especially the pectoralis major and the deltoids, was common.

Asymmetry. Abnormalities of the upper limb were always bilateral and often asymmetrical (69-5%). Where this was the case the left side was affected more than the right in 90-6% of cases and the right more than the left in 9-4%.

Fig 1B shows typical hands with absence of the left thumb and a right sided triphalangeal thumb. In fig 2 a severely affected child has phocomelia of the left arm but less severe radial aplasia on the right.

Isolated cases
The spectrum of abnormalities differed in the small group of isolated cases (table 3). In particular, four patients had predominantly ulnar aplasia with involvement of the ulnar ray of the hand. One child had a unilateral transverse reduction anomaly of the second to fifth fingers with hypoplasia of the thumb and radial and ulnar hypoplasia, an anomaly not seen in any familial cases. Five patients had exclusively unilateral defects. In general, abnormalities in isolated cases were more severe. For example, 73% of the isolated cases had aplasia of the thumb as opposed to 43% of familial cases, a greater proportion had radial and ulnar involvement, and two (18%) had bilateral phocomelia. In total, seven of the isolated cases were atypical for Holt–Oram syndrome as compared with the abnormalities seen in the familial cases. Full details of these are given in table 4.
Holt-Oram syndrome: a clinical genetic study

Table 4 Details of seven atypical cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Cardiac abnormality</th>
<th>Predominant skeletal abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>2</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>3</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>4</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>5</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>6</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
<tr>
<td>7</td>
<td>Isolated</td>
<td>Unilateral radial aplasia</td>
</tr>
</tbody>
</table>

Table 5 Cardiac abnormalities in 55 cases of HOS

<table>
<thead>
<tr>
<th>Defect</th>
<th>No of affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total familial</td>
<td>Total isolated</td>
</tr>
<tr>
<td>Structural</td>
<td></td>
</tr>
<tr>
<td>Secundum atrial septal defect</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Premun atrial septal defect</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Sinus venous atrial septal</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Dextrocardia</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>1 (9)</td>
</tr>
<tr>
<td>ECG abnormality only</td>
<td>17 (39)</td>
</tr>
<tr>
<td>Normal heart</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

CARDIAC ABNORMALITIES (TABLE 5)

Familial cases

Full cardiac details were available for 55 patients and 95% had evidence of cardiac involvement. Only two patients had normal clinical examination, ECG, and echocardiography. Of the familial cases, 25 (57%) had a structural heart lesion, 22 (50%) had a septal defect, 15 (34%) an ASD, and 11 (25%) VSD, including four patients with both. One patient had a complete atrioventricular septal defect and complete heart block. Three cases had mitral valve prolapse (MVP): two from the same family had MVP and first degree heart block and one patient had MVP, an ASD, and complete heart block (CHB). In total, three patients had complete heart block, two with septal defects and one without. Seventeen (39%) had no structural defect but had an abnormal ECG with evidence of conduction defect (table 6). The commonest ECG abnormality was first degree heart block (PR interval >0-2 sec) which was seen in 71%. Right and left bundle branch block, left axis deviation, and bradycardia were also seen. The majority (85%) had an asymptomatic cardiac lesion. Sixteen (38%) patients required cardiac surgery for correction of their cardiac defect; of these 11 required surgery in childhood and five were operated on in adult life. Ten had an asymptomatic structural lesion (VSD or MVP). All three patients with complete heart block became symptomatic and required insertion of a pacemaker.

Detailed family histories showed that one affected relative had died postoperatively following closure of an ASD. Three patients from one family had died suddenly of undiagnosed heart abnormality. Necropsy on one, a child aged 6 months, showed a large undiagnosed ASD. No postmortem information was available on the other two cases who died suddenly.

Isolated cases

By definition all isolated cases had a structural cardiac lesion. Five patients had an ASD, two with ASD alone, two with ASD and a VSD, and one with ASD and pulmonary stenosis (PS). Two further patients had a VSD, one of whom also had aortic stenosis (AS), and two cases had tetralogy of Fallot. There was one case with a sinus venous ASD, one with patent ductus arteriosus (PDA), and one case of dextrocardia with otherwise normal cardiac anatomy.

ASSOCIATED ABNORMALITIES

MODE OF INHERITANCE

The pedigrees were consistent with autosomal dominant inheritance with many examples of male to male transmission and no statistically significant difference between the numbers of affected males and females. Twenty two affected parents had a total of 36 affected and 36 unaffected offspring.

No parental age effect was observed. This was assessed by comparing the mean parental age of sporadic cases with the mean general population parental ages. The mean paternal and maternal ages in the study were 29-6 years (range 26-35 years) and 27-6 years (range 25-35 years) respectively, as compared with the general population figures of 30-19 and 27-15 years respectively.

Penetrance was complete. Careful examination of all 17 obligate heterozygotes showed clinically detectable abnormalities.

Biological fitness was calculated from the numbers of offspring born to affected and unaffected subjects. Twelve affected parents had 13 unaffected sibs. The affected parents had 24 offspring, indicating that there was no reduction in fitness.
SEVERITY

When scored separately, skeletal and cardiac abnormalities showed a statistically significant positive correlation (table 7). Although only two of the total number of affected patients (4-5%) had severe phocomelia, 39% patients had a skeletal severity score of $\geq 3$ indicating a serious reduction anomaly of the upper limb; 34% had abnormalities of the forearms and hands only and 27% had only minor abnormalities of the hands. For cardiac abnormalities 36% scored 3, indicating a structural lesion requiring surgery or symptomatic arrhythmia, 23% scored 2 denoting an asymptomatic structural defect, and 39% scored 1 owing to an ECG abnormality.

There was no difference in severity between males and females (fig 4). Mean scores for offspring of affected mothers were greater than for offspring of affected fathers (fig 5). Analysis of severity of abnormalities in different generations within a family showed increasing severity in successive generations with a significant increase in severity from generation I to III (fig 6A). There appeared to be a greater correlation between severity in sib pairs than between parent and offspring (fig 6B).

**Discussion**

In this study we have reviewed the clinical and genetic features of HOS based on the largest known series, consisting of 72 patients, 57 of whom have been personally examined. This has allowed us to define the clinical phenotype and delineate the spectrum of abnormalities seen in familial cases. In this paper we have focused particularly on those clinical features which help to distinguish the diagnosis in isolated cases and those which enable affected parents to be alerted to the range of severity likely to be seen in future affected children.

**Table 7** Correlation between severity scores for cardiac and skeletal abnormality

<table>
<thead>
<tr>
<th>Skeletal score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac score</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>2</td>
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<tr>
<td></td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Spearman rank $r=0.4894$, p = 0.001.

**Figure 4** Mean combined severity score with 95% confidence interval for 22 females and 22 males showing no difference in severity. (Mann–Whitney $U=221$, p = 0.52.)

**Figure 5** Maternal effect in HOS. Mean combined severity score for 11 offspring of affected fathers showing greater severity among offspring of affected mothers. (Mann–Whitney $U=305$, p = 0.0473.)

**Figure 6** Evidence for anticipation in HOS. (A) Mean combined severity score for nine three generation families showing significant increase in severity in third generation. Kruskall Wallis $\chi^2=10.89$, p = 0.0043. (B) Mean combined severity score for sib pairs compared to parent-offspring pairs showing greater correlation between sibs than between parent and offspring.
Limb Abnormalities

These involved primarily the radial ray. Proximal abnormalities of the arm and forearm were always accompanied by distal abnormalities in the hand, though the thumb was not necessarily abnormal. The shoulders were often involved even when involvement of the hands was minor. This feature seems to be specific to HOS and is not seen in cases of isolated radial ray defects, so the presence of a relatively subtle abnormality such as narrow sloping shoulders is a useful diagnostic pointer. Characteristically there was asymmetry of the limb abnormalities with a tendency for the left side to be more affected than the right. This contrasts with other radial ray defects which generally show right-sided preponderance. Asymmetry is otherwise unusual for single gene disorders affecting the upper limb.

Cardiac Abnormalities

The incidence of cardiac defects (95%) was similar to that seen in previous studies. While ASD was the structural lesion in the first family described, subsequent reports have included VSD and other defects. Five families in this study had no ASD. For example in one family a father with a conduction abnormality but no septal defect had two sons both of whom had a VSD and the same conduction disturbance. In another family a father with a conduction abnormality had a daughter with a VSD. All had radial ray abnormalities which were indistinguishable from families with an ASD. Following localisation of a gene for HOS to 12q, analysis in these two families was consistent with linkage to this locus. This supports the notion that an ASD is not a requirement for the diagnosis.

All families had at least one member with a septal defect. First degree heart block was the commonest defect and may be seen with or without a septal defect. Two affected subjects from one family showing linkage to 12q had mitral valve prolapse in conjunction with first degree heart block. Mitral valve prolapse has previously been described in HOS. Seven patients had a combination of left axis deviation with first degree heart block. This ECG pattern may be seen in families with dominantly inherited non-syndromic ASD. A conduction defect may therefore be a form of HOS, possibly reflecting previous spontaneous closure of a septal defect. None of the rarer cardiac conditions seen in the isolated group and reported previously in isolated cases, for example, tetralogy of Fallot, was seen in the familial group in whom the most complex defect was an atrioventricular septal defect.

Data from this study have enabled us to define the HOS phenotype based on the features seen in familial cases and to set minimal diagnostic criteria (table 8). It has become evident that a number of isolated cases have features outside this spectrum and possibly represent other heart-hand associations.

Differential Diagnosis

The differential diagnoses include the dominantly inherited heart-hand syndromes. Heart-hand syndrome II (Tabatznik) involves the combination of type D brachydactyly with supraventricular tachycardia. Patients may also have mild facial dysmorphism and mild mental retardation. Ruiz De La Fuente and Prieto described heart-hand syndrome III with type C brachydactyly plus sick sinus syndrome. The long thumb brachydactyly syndrome described by Hollister and Hollister shows similarities to HOS. There is dominant inheritance of a long thumb owing to elongation distal to the PIP joint with index finger brachydactyly, clinodactyly, narrow shoulders owing to short clavicles and pectus excavatum. The cardiac abnormality is a conduction defect. There is also rhizomelic limb shortening.

Isolated cases of HOS need to be distinguished from recessive conditions which include heart-hand abnormalities, for example, thrombocytopenia-absent radius (TAR). This differs from HOS in that radial aplasia is seen with the thumb present. In HOS radial aplasia would invariably be accompanied by hypoplasia or absence of the thumb. ASD may be seen and also tetralogy of Fallot. A number of other abnormalities may be found in TAR, including involvement of the lower limb, which are not seen in HOS. Radial ray defects are well recognised in Fanconi syndrome and specific investigation to exclude chromosomal breakage is required. Radial defects in the sporadic VACTERL association are more usually unilateral. Radial defects occur with Duane anomaly in the DR or Okihiro syndromes as well as being reported in HOS. Two patients (mother and son) from this series had Duane anomaly and HOS. Both had cardiac and upper limb involvement. There was no history of deafness.

Variation in Expression

Our observations have confirmed previous reports of marked intra- and interfamilial variation with cardiac involvement varying from asymptomatic arrhythmias to large or multiple septal defects leading to death in infancy. Skeletal defects ranged from minor features such as clinodactyly or hypoplasia of the thenar eminence to severe reduction defects of the upper limb. In larger families there was evidence of a specific intrafamilial pattern as has been described previously.

Three families showed a tendency to more severe cardiac involvement and mild limb abnormalities, whereas showed more severe limb defects and less severe cardiac involvement.

Incidence of Severe Anomalies

Families seeking information regarding HOS usually want to know both the spectrum of

Table 8 Minimal diagnostic criteria for Holt-Oram syndrome

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Holt-Oram Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial defect</td>
<td>Yes</td>
</tr>
<tr>
<td>Septal defect (atrial or ventricular)</td>
<td>Yes</td>
</tr>
<tr>
<td>AV block in at least one family member</td>
<td>Yes</td>
</tr>
</tbody>
</table>
the condition and the likelihood of serious abnormality. In this study one in three cases had a significant reduction deformity of the upper limb although only 1 in 22 had phocomelia. The only previous estimate of the incidence of phocomelia was 1 in 10. This difference may reflect underascertainment of milder cases in previous studies. The most severe heart cases in cardiac terms were three premature deaths and two children who required surgery in the first year of life because of severe cardiac failure. Many septal defects either did not require treatment or, in the case of ASD, were treated electively in childhood or adulthood.

A statistically significant correlation was observed between the severity of limb and heart abnormalities in a given person. No difference in severity between the sexes was observed. This is in contrast to previous studies which have shown greater severity in females.38

GENETIC ASPECTS

The pedigrees were clearly indicative of autosomal dominant inheritance. A previous finding of abnormal segregation with more affected than unaffected offspring born to affected parents29 was not confirmed. It has been suggested in previous studies that abnormal segregation is the result of maternal fetal loss.2324 No such effect was observed in this study.

Penetration was found to be complete. Although x rays sometimes showed additional findings, all obligate heterozygotes showed clinical abnormalities on detailed examination. No examples of non-penetrance or gonadal mosaicism were encountered. Previous reports of the proportion of isolated cases attributable to new mutations vary from 0·3 to 0·85. Of the cases referred to in this study only 8% were considered to be sporadic after examination of both parents and investigation with x ray, ECG, and echocardiography. This lower figure may reflect incomplete ascertainment because of preferential referral of families for linkage analysis in our study. In three cases referred with no significant family history, clinical abnormalities were found in one of the parents.

ANTICIPATION

Several reports of families with HOS have mentioned an observed tendency to increasing severity of abnormalities in successive generations.103825 McKusick259 was the first to report this in a family in which the grandparent had an ASD and triphalangeal thumbs, the parent had an ASD and absent thumbs, and the grandchild was born with a VSD and bilateral phocomelia. We examined this phenomenon in this study. Although families with three or more affected generations showed increasing severity of both skeletal and cardiac abnormalities as measured by severity scores (fig 6A) this is not in itself proof of anticipation. We would expect a degree of ascertainment bias since previous generations are often detected retrospectively and families are more likely to be identified if the index case is severe. Furthermore, in a dominant disorder with a severe phenotype one would expect to see such an increase in severity since mildly affected cases are more likely to reproduce, and following the birth of a severely affected child family size is restricted. However, fig 6B indicates that there is a greater correlation between offspring than between parent and offspring, which is supportive evidence for anticipation. The mean severity score for each generation increased significantly although not all individual meioses led to an increase in severity score. Maternal meioses were never accompanied by a decrease in severity. However several paternal meioses did lead to a decrease in severity as measured by this method. This does not in itself rule out anticipation, as similar observations have been made in myotonic dystrophy where the proposed underlying genetic mechanism is a “re-treat of the triplet repeat.”27

The evaluation of anticipation and a parental effect in a genetic disorder usually involves documentation of age of onset. This approach cannot be applied to a congenital abnormality for which ranking or grading of severity for statistical analysis is necessary. Complete objectivity in clinical assessment of severity is difficult to achieve. However, our observations are consistent with both anticipation and a maternal effect although we recognise that confirmation or otherwise awaits isolation and characterisation of the HOS gene(s).

Meanwhile prospective parents can be alerted to the fact that a child born with HOS to an affected parent has a 1 in 3 chance of having a severe reduction abnormality of the upper limb with a 1 in 22 risk of phocomelia. If an ASD is present there is a greater risk of a serious limb abnormality than if a VSD or conduction defect occurs alone (table 9). Severity is likely to be greater if the transmitting parent is female. In our study there were no cases of severe limb abnormality occurring in isolation. Therefore the detection of a severe reduction defect before or after birth indicates that there is a high chance that a structural cardiac lesion will also be present.

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Table 9 Severity of skeletal defect as a function of cardiac defect

<table>
<thead>
<tr>
<th>Cardiac defect</th>
<th>Mean severity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect</td>
<td>2.66</td>
</tr>
<tr>
<td>Atrial ventricular septal</td>
<td>2.28</td>
</tr>
<tr>
<td>defect</td>
<td></td>
</tr>
<tr>
<td>No structural defect</td>
<td>1.85</td>
</tr>
</tbody>
</table>

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