Genetics of Atrial Septal Defect

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Sánchez Cascos, A. (1972). Archives of Disease in Childhood, 47, 581. Genetics of atrial septal defect. Of 109 cases of atrial septal defect, cases with an isolated defect (92 cases) showed a female preponderance (sex ratio 0·64), but there was a higher risk to the sibs of the male patients, suggesting a multifactorial mechanism. Dermatoglyphs showed a large number of whorls on the fingers.

In 17 cases there were multiple malformations, such as Holt-Oram syndrome (hypoplastic and triphalangic thumb, with ostium secundum atrial septal defect), polydactyly plus ostium primum defect, and tracheo-oesophageal fistula.

Atrial septal defect (ASD) is one of the commoner types of congenital heart disease. Clinical diagnosis is easy and surgical correction has become a routine procedure with virtually no mortality. Even unoperated cases usually do well, so that they frequently marry and have children. These facts make ASD a suitable heart anomaly for the purposes of a genetic survey.

It is nowadays agreed that most heart anomalies are determined by a polygenic mechanism. This type of inheritance has been proved for valvular aortic stenosis (Zoethout, Bonham Carter, and Carter, 1964; Jürgensen, 1969), Fallot’s tetralogy (Fuhrmann, 1968a; Sánchez Cascos, 1971), ventricular septal defect (Fuhrmann, 1968a), pulmonary stenosis (Sánchez Cascos, 1972), and transposition of the great vessels (Fuhrmann, 1968b). With regard to ASD, Nora, McNamara, and Fraser (1967), Emanuel et al. (1968), and Williamson (1969) have presented evidence in favour of a polygenic causation though some other authors (Johansson and Sievers, 1967; Bizarro et al., 1970; Zetterqvist et al., 1971) think that a monogenic dominant mechanism may be present. This was indeed an early view based on the observation of families with multiple cases of ASD in successive generations.

In this study we hoped to settle the question of polygenic versus monogenic inheritance, and also to define the genetics of ASD when this is part of a multiple malformation syndrome, whether chromosomal, monogenic, or sporadic.

Material and Methods

109 cases of ASD were studied; 84 of them belonged to the ostium secundum type (OS), and 25 to the ostium primum (OP). Cases of the so-called sinus venosus type either with or without anomalous drainage of pulmonary veins, are included in the OS variety. Cases of common atrioventricular canal (atrioventricularis communis) have been excluded.

These cases of ASD formed 15·5% of a series of 700 consecutive cases of congenital heart disease (CHD). In all cases the diagnosis was confirmed by cardiac catheterization and/or cardiac surgery. Familial data were collected from parents. All living parents, nearly half of the sibs, and all the proband’s children were personally examined, clinically and by ECG and x-ray. Date of birth, birth rank, parental ages (at the time when the proband was born), and pathological events during pregnancy or delivery were recorded. The proband’s sibs were classified as concordant (i.e. having also CHD, ASD unless otherwise stated), normal, or bearing extracardiac anomalies; the number of abortions and stillbirths was also recorded.

All cases with multiple malformations or those having extracardiac anomalies, and many others, were karyotyped.

Dermatoglyphs were taken of all 10 fingers and the right palm. We shall refer only to these parameters: (i) Finger pattern: arch (A) is the pattern with no triradius; ulnar loop (U) has one triradius in radial position; radial loop (R) has an ulnar triradius; and whorl (W) has two triradii, ulnar and radial. (ii) Total finger ridge count (TFRC) is calculated by adding the number of ridges between triradius and core for all 10 fingers. (iii) Axial palm triradius (t). The atd angle (a and d triradii are beneath forefinger and little finger) defines a proximal t° (atd < 45°), medial t' (atd between 46° and 70°), and distal t'' (atd wider than 70°). When t is duplicated only the most distal is used in atd measurements).

Individuals born in Madrid during 1968 were used as controls for familial data (Madrid, Ayuntamiento,
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1968). 50 normal males and 100 normal females provided the controls for dermatoglyphs.

Results

Table I gives the numbers of cases of each type of ASD. Isolated cases and those forming part of a multiple malformation syndrome will be considered separately, as they usually have a different genetic mechanism.

**TABLE I**

Distribution of Ostium Secundum and Ostium Primum Defects in 92 Cases of Isolated ASD

<table>
<thead>
<tr>
<th>Type of ASD</th>
<th>Sex</th>
<th>Isolated</th>
<th>With Extracardiac Malformations</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secundum (OS-ASD)</td>
<td>Male</td>
<td>28</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>42</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Both sexes</td>
<td>70</td>
<td>14</td>
<td>84</td>
</tr>
<tr>
<td>Primum (OP-ASD)</td>
<td>Male</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Both sexes</td>
<td>22</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

**TABLE II**

Birth Order in 92 Cases of Isolated ASD

<table>
<thead>
<tr>
<th>Birth Order (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 or more</th>
<th>$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 OS-ASD cases</td>
<td>27·0</td>
<td>26·0</td>
<td>14·5</td>
<td>14·5</td>
<td>18·0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sibs</td>
<td>21·5</td>
<td>20·5</td>
<td>17·0</td>
<td>13·0</td>
<td>28·0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 OP-ASD cases</td>
<td>27·0</td>
<td>18·0</td>
<td>32·0</td>
<td>4·5</td>
<td>18·5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sibs</td>
<td>22·0</td>
<td>22·0</td>
<td>19·0</td>
<td>15·0</td>
<td>22·0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 92 isolated ASD cases</td>
<td>27·0</td>
<td>24·0</td>
<td>18·5</td>
<td>12·0</td>
<td>21·5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sibs</td>
<td>21·0</td>
<td>20·5</td>
<td>17·0</td>
<td>13·0</td>
<td>28·5</td>
<td>5·9</td>
<td>&lt;0·3</td>
</tr>
</tbody>
</table>

**TABLE III**

Parental Ages in 92 Cases of Isolated ASD

<table>
<thead>
<tr>
<th>Years</th>
<th>Fathers</th>
<th>70 OS-ASD cases %</th>
<th>22 OP-ASD cases %</th>
<th>Total ASD %</th>
<th>Normal controls</th>
<th>$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1·9</td>
<td>&lt;0·9</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2·2</td>
<td>&lt;0·8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>
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TABLE IV
Pedigree in 92 Cases of Isolated ASD

<table>
<thead>
<tr>
<th>Consanguinity</th>
<th>Sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>First Degree</td>
</tr>
<tr>
<td>28 OS-ASD cases</td>
<td>1</td>
</tr>
<tr>
<td>8 OP-ASD cases</td>
<td>1</td>
</tr>
<tr>
<td>Total 36 ASD cases</td>
<td>2</td>
</tr>
<tr>
<td>Females</td>
<td>42 OS-ASD cases</td>
</tr>
<tr>
<td>14 OP-ASD cases</td>
<td>1</td>
</tr>
<tr>
<td>Total 56 ASD cases</td>
<td>1</td>
</tr>
</tbody>
</table>

CHD = congenital heart disease.

TABLE V
Dermatoglyphs (% distribution) in 92 Cases of Isolated ASD

<table>
<thead>
<tr>
<th></th>
<th>U</th>
<th>W</th>
<th>R</th>
<th>A</th>
<th>χ²</th>
<th>P</th>
<th>t²</th>
<th>t’</th>
<th>t”</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS-ASD cases</td>
<td>52</td>
<td>37</td>
<td>4</td>
<td>7</td>
<td></td>
<td>80</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP-ASD cases</td>
<td>66</td>
<td>20</td>
<td>9</td>
<td>5</td>
<td></td>
<td>87</td>
<td>13</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ASD cases</td>
<td>55</td>
<td>34</td>
<td>5</td>
<td>6</td>
<td>29-7</td>
<td>&lt;0-001</td>
<td>82</td>
<td>18</td>
<td>0</td>
<td>1-1</td>
<td>&lt;0-3</td>
</tr>
<tr>
<td>Controls</td>
<td>67</td>
<td>22</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td>86</td>
<td>14</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS-ASD cases</td>
<td>63</td>
<td>32</td>
<td>2</td>
<td>3</td>
<td></td>
<td>78</td>
<td>17</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP-ASD cases</td>
<td>53</td>
<td>31</td>
<td>3</td>
<td>13</td>
<td></td>
<td>58</td>
<td>33</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ASD cases</td>
<td>61</td>
<td>32</td>
<td>2</td>
<td>6</td>
<td>39-5</td>
<td>&lt;0-001</td>
<td>73</td>
<td>21</td>
<td>6</td>
<td>5-9</td>
<td>&lt;0-1</td>
</tr>
<tr>
<td>Controls</td>
<td>68</td>
<td>22</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td>83</td>
<td>16</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For dermatoglyphic notation, see text.

children, all normal. Two uncles and one cousin of the probands also had ASD.

a5. Pregnancy and delivery. Nothing relevant was found.

a6. Finger pattern (Table V). Both sexes had a reduced number of ulnar loops (55% and 61% versus 67% and 68% in controls) and a proportional increase in whorls (33.5% and 32.3% versus 22% in controls). These differences were significant for both sexes.

a7. TFRC. This measured 127±50 in OS males and 126.5±41 in females. These values did not differ from controls (normal males had TFRC = 150±54; SD = 12.14, t = 1.8; normal females had TFRC = 127±40; SD = 8.1, t = 0.06).

a8. Palm axial triradius (Table V). The proportions of t”, t’, and t” positions did not differ from controls.

a9. Karyotype. All analysed cases had normal chromosomes.

Multiple malformation syndromes with OS-ASD. There were 14 cases in this category, 6 male, 8 female.

b1. Down’s syndrome (mongolism). One boy, also having persistent ductus arteriosus had trisomy-21, and showed the typical high maternal age and t” position of the axial triradius.

b2. Edwards’ syndrome. One boy with trisomy-18; he had young parents; his dermatoglyphs were not recorded.

b3. XXX syndrome. A girl with 47, XXX had middle-aged parents (56 and 36 years). Dermatoglyphs were unremarkable.

b4. Turner’s syndrome. A girl with typical features and chromosomes XO, had 9 W on her fingers.

b5. Turner’s phenotype in a female with normal karyotype (46, XX) (Bonnevie-Ulrich or Noonan’s syndrome). This girl also had pulmonary valve stenosis and aortic coarctation. She had hypertelorism, webbing of the neck, kyphoscoliosis,
and other somatic anomalies. Her dermatoglyphs showed 9 W on the fingers, a high TFRC (162), and a t' position of the axial triradius. Her ECG was atypical and has been published elsewhere (Sánchez Cascos, 1972).

b6. Holt-Oram syndrome. 4 cases (2 of each sex) belonged to the atrio-digital dysplasia syndrome of Holt-Oram. One was a sporadic case, the other three formed a sibship that has been reported previously (Sánchez Cascos, 1967). Fig. 1 and 2 show the typical hypoplastic, syndactylc, distally placed, and sometimes triphalangistic thumb; also the distal placement or even absence of the axial palm triradius (t). Sinus arrhythmia with AV

Fig. 1.—Holt-Oram syndrome. See the hypoplastic, triphalangic, syndactylc thumb, and the absence of the t triradius on the palm (partly reproduced from Sánchez Cascos, A.—(1967), Acta Paediatrica Scandinavica, 56, 313, Fig. 2, with permission of the Editor).

Fig. 2.—Holt-Oram syndrome. Absence of the metacarpal, hypoplastic thumb, distal t'' axial triradius, and thenar pattern.
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junctional escapes is characteristic, and was present in two cases.

b7. Cleido-cranial dysplasia. One girl showed absence of both clavicles, cervical hemivertebrae, visceral situs inversus, and the skull deformities typical of the cleido-cranial dysplasia. She had a low TFRC (50) and high t' axial triradius.

b8. Deaf mutism. This was present in two cases, one of each sex. The boy had a sib, also a deaf-mute, and a high t' triradius.

b9. Tracheo-oesophageal fistula. This was present in one girl, who also had ventricular septal defect and persistent ductus arteriosus.

b10. Cerebral sclerosis plus optic atrophy. This was present in one boy; 2 of his 4 sibs had died with a similar neurological condition, but their heart condition was unknown.

Multiple malformation syndromes with OP-ASD. There were 3 cases, 2 male, 1 female.

c1. Polydactyly. Two cases, one of each sex, presented with polydactyly. The boy also had ungual dysplasia (Fig. 3). The girl had a t''

distal triradius; in her pedigree were 4 polydactylic members in 2 generations, but their heart condition is unknown.

c2. Cleft lip, tracheo-oesophageal fistula, hypertelorism, and hypospadias. This boy presented 7 arches on his fingers and consequently his TFRC was very low (18); the axial triradius was in t' position. This patient seems to be an example of the so-called BBB syndrome (see below).

Discussion

Several previous papers contain impressive records of families with multiple cases of ASD, in one or successive generations (Carleton, Abel-mann, and Hancock, 1958; Weinstein, 1958; Campbell, 1959; Weil and Allenstein, 1959; Allenstein and Weil, 1960). Campbell and Polani (1961) reported one of these families, with 5 proved plus 4 suspected cases in 5 generations, and collected from the literature 51 families with multiple cases of ASD.

Kahler et al. (1966), Ehlers and Engle (1966), Nora et al. (1967), Amarasingham and Fleming (1967) have also published families with multiple cases of ASD, and recently Zetterqvist et al. (1971) reported a family with a least 16 cases. Bizarro et al. (1970) have emphasized the common occurrence of a long PR interval in familial cases of ASD, a feature already noted in the reports of Kahler and Amarasingham, and suggested that a long PR interval is indicative of a dominant inheritance in ASD.

We have reviewed the PR interval in our familial cases of ASD. Only one case had a long PR, but it was an OP case and in OP defects this feature is not uncommon. Nevertheless, the possibility remains that cases of 'OS-ASD with long PR' belong to a monogenic syndrome, in relation to the Holt-Oram syndrome (see below).

Familial aggregation occurs in polygenic inheritance (Edwards, 1960; Nora, 1968; Carter, 1969). In this situation the incidence of the anomaly in first degree relatives (parents, sibs, and offspring) is \( \sqrt{p} \), where \( p \) is the incidence of the trait in the normal population. In our series there were 109 cases of ASD in 700 consecutive cases of CHD (15.5%). Accepting a general incidence for all types of CHD of about 0-005 live newborns (McKeown, McMahon, and Parsons, 1953; Carlgren, 1959) the natural occurrence of ASD should be 0-005 \( \times 0-155 \approx 0-0008 \). If a multifactorial mechanism is the underlying cause, the risk of recurrence in sibs (and also in offspring) would be as high as \( \sqrt{0-0008} \approx 3\% \).

Nora et al. (1967) reported 3.7% affected sibs and 3.5% affected parents in a series of 100 cases of ASD. Williamson (1969) found 3.7% affected sibs and 3.8% affected children in another series of 135 cases of ASD. Emanuel et al. (1968) in 92 cases of OP-ASD found 1.1% affected parents, 1.7% affected sibs, and 10% affected children. In two older series (Lamy, de Grouchy, and Schweig Guth, 1957; Campbell and Polani, 1961) the incidence in sibs was 1.24% and 1.1%; in the latter study 1.3% of the parents were also concordant. All these figures agree with theoretical expectations. Our results were similar, with 3.3% concordant sibs.

In multifactorial inheritance patients of the less
affected sex are found to be associated with the greater incidence among their relatives. This was so in our series, where the incidence of ASD in the sibs of male patients was 5%, while that for female patients was only 2·5%. The higher risk for the more severe type (12·5% for the sibs of OP males) also is in keeping with this pattern of inheritance, as is the high rate of parental consanguinity, 3·2% of first degree, compared with less than 2% in the Spanish population (Valls, 1967). Another feature of polygenic inheritance is a sex ratio which deviates from 1, and this series gave 0·64 males to 1 female.

We have found that both Fallot's tetralogy (Sánchez Cascos, 1971) and pulmonary stenosis (Sánchez Cascos, 1972) present dermatoglyphic features that deviate from the normal. In the present series of ASD we found a high proportion of whorls, and a parallel diminution in the numbers of ulnar loops. The other dermatoglyphic findings were not significant (position of i axial triradius and TFRC).

With regard to the specific types of heart lesion found in multiple malformation syndromes, we shall only refer to those syndromes represented in the present series.

(i) Chromosome imbalance syndromes. Both 21-trisomy (Down's syndrome) and 18-trisomy (Edwards' syndrome) are often associated with CHD. Though the commonest heart lesions are atroventricularis communis in the former and ventricular septal defect in the latter, ASD is by no means uncommon (Taylor, 1968; Cullum and Liebman, 1969).

In the X chromosome imbalance syndromes heart involvement is not so frequent. Aortic coarctation is the typical anomaly in X monosomy (Turner's syndrome), but ASD is also found (Bishop, Lessof, and Polani, 1960; Emerit et al., 1967). On the other hand, the XXX syndrome rarely coexists with CHD, though ASD seems to be the commonest anomaly (Barr et al., 1969). The lesions in the Noonan or Bonnevie-Ulrich syndrome, where the karyotype is normal, often include CHD; pulmonary stenosis is the most frequent anomaly, but ASD is also found (Chaves-Carballejo and Hayles, 1966; Emerit et al. 1967; Noonan, 1968).

(ii) Holt-Oram and related syndromes. It is now well known that a number of conditions can produce CHD plus regression of the first ray of the hand. Apart from the Dr syndrome (ring chromosome in the group 13–15), Fanconi's anaemia, and other rarer conditions, there are two major syndromes, the Holt-Oram and Lewis syndromes, both autosomal dominant, with this phenotypic expression.

The Holt-Oram syndrome (Holt and Oram, 1960; McKusick, 1961; Zetterqvist, 1963; Sánchez Cascos, 1967; Antia, 1970, etc.) comprises OS-ASD, AV junctional escapes, or AV block, and a hypoplastic syndactylic, and triphalangic thumb, with hypoplasia of the first metacarpal and external carpal bones. The term atriodigital dysplasia, coined by McKusick (1961), seems to be appropriate.

The Lewis syndrome (Kuhn, Schaaf, and Wagner, 1963; Lewis, Bruce, and Motulsky, 1964; Holmes, 1965; Gall et al., 1966; Simcha, 1971; Sánchez Cascos, 1971) comprises a more severe type of CHD—ventricular septal defect, Fallot's tetralogy or transposition of the great arteries—hypoplasia of the radius with subsequent aplasia of the first carpometacarpal ray, and sometimes aberrant ECG (Sánchez Cascos, 1971). McKusick's term ventriculo-radial dysplasia seems appropriate.

We believe the two syndromes to be different, though their phenotypes may overlap. The typical palm dermatoglyphs, shown in Fig. 1 and 2, are related to the absence or hypoplasia of the thumb.

Another syndrome with involvement of the heart and the hand is represented by our two cases of OP-ASD with polydactyly and nail dystrophy. A case of OP-ASD plus polydactyly has been published by Cleland et al. (1969). Fuhrmann (1968a) has reported two cases of CHD with polydactyly, one with ventricular septal defect, the other with truncus arteriosus. Other cases of polydactyly presented septal defects (Tunte, 1968), aortic coarctation (Veno, Bansho, and Kawashima, 1968), and truncus arteriosus (Van Praagh and Van Praagh, 1965). This syndrome seems to be related to the well-known autosomal recessive syndrome of Ellis-van Creveld, in which polydactyly, dwarfism, dysplastic nails, and abnormal teeth co-exist with CDH—usually common atrium, but also ventricular septal defect or atrioventricularis communis (Tubbs, Crevasse, and Green, 1962; Giknis, 1963; McKusick, 1964; Behar and Rachmilewitz, 1964; Goor et al., 1965; Lynch et al., 1968).

(iii) Other syndromes with ASD. Many other syndromes have been reported in which ASD is present. In tracheo-oesophageal fistula (with or without oesophageal atresia) ASD was present in 20 of 183 cases (Mellins and Blumenthal, 1964) and in 9 of 87 cases (Daum, Hecker, and Rüter, 1969), but was not represented in a series.
of 39 necropsied cases (Mehrizi, Folger, and Rowe, 1966).

Opitz, Summit, and Smith (1969) have coined the term **BBB syndrome** for the association of hypertelorism, hypospadias, and CHD—OP-ASD in one of their two cases. One case in our series would conform to this description.

Finally we have two cases of deaf-mutism plus OS-ASD previously reported in detail (Sánchez Cascos, Sánchez-Harguindey, and de Rábago, 1969).

In many of these syndromes, the type of heart lesion is not specific, while in others it is, such as OS-ASD in Holt-Oram syndrome and perhaps OP-ASD in polydactyly.

**References**


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