Genetics of Fallot’s tetralogy

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A genetic analysis of 126 correlative cases of Fallot’s tetralogy has been performed. The isolated cases showed male predominance and a higher risk for the sibs of female cases, suggesting a multifactorial causative mechanism. Dermatoglyphs were typical, with a high number of whorls on the fingers and a tendency to distal t triradius. There were 13 cases belonging to polymalformative syndromes, such as mongolism, Turner, triplo-X, among others.

Knowledge of inheritance mechanisms in heart disease has been considered as one of the four major topics for cardiac research in the seventh decade of this century (Shirley Smith, 1970). While the genetics of ischaemic heart disease and hypertension is by no means unimportant, congenital heart malformations represent the main field open to investigation.

In the past few years several papers have dealt with the aetiology of different types of congenital heart disease. Among them, Polani and Campbell (1955) have reported a genetic study of a large series of cyanotic cardiac anomalies, most of them Fallot’s tetralogy. Data on Fallot’s genetics were also reported by Lamy, de Grouchy, and Schweisguth (1957). Additional information on this point is also available from Nora (1968) and Neil (1970), among others. But a complete, recent investigation on this subject, including cytogenetic and dermatoglyphic analysis, has not been found.

Fallot’s tetralogy is one of the most common types of cardiac malformation. The dramatic lengthening of life expectancy after operation is changing the until-now secondary problem of recurrence in offspring. The genetics of Fallot’s tetralogy emerges as a subject for research.

Subjects and methods
Studies have been made of 126 correlative cases of Fallot’s tetralogy. They represent about 21 per cent in a series of 600 cases of congenital heart disease. The diagnosis of Fallot’s tetralogy was soundly proved through angiocardiography and/or heart operation in all cases. Familial data were collected from parents. Date of birth, birth rank, parental ages (when the proband was born), and pathological events during pregnancy or delivery were recorded. The proband’s sibs were classified as concordant (also having Fallot’s tetralogy), normal, and bearing extracardiac anomalies; the number of abortions and stillbirths was also recorded.

All the cases belonging to general syndromes or having extracardiac anomalies, and many others, were karyotyped, performing standard peripheral leucocyte cultures.

Dermatoglyphs were taken of all the 10 fingers and right palm. Both qualitative and quantitative analyses were performed. We shall only refer to (see also Fig. 1) the following: (1) Finger pattern: arch (A) is the pattern with no triradius; loops have one triradius, being named ulnar (U) or

![FIG. 1 In thecentre a typical Fallot's palm, showing duplication of t triradius (t° and t'). In the corners an arch, a loop, and the two common types of whorls.](image)
radial (R) loops, according to the radial or ulnar position of the triradius; whorls (W) have two triradii, ulnar and radial. (2) Total finger ridge count: this important quantitative parameter is calculated by counting the number of ridges between the triradius and core for all the 10 fingers. (3) Axial palm triradius (t). The atd angle (a and d triradii are beneath the 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 measurement.

People born in Madrid during 1968 were used as models for familial data (Ayuntamiento de Madrid, 1968). A control series of 50 normal men and 100 normal women was used as a dermatoglyphic model.

Results

Isolated cases and those belonging to general polymalformative syndromes will be considered separately.

(a) Isolated cases (113 cases, 75 male, 38 female)

Month of birth Neither male nor female cases presented significant deviations.

<table>
<thead>
<tr>
<th>TABLE 1 Birth order</th>
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<tr>
<td>Order</td>
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<td>Fallot cases (%)</td>
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<td>All sibs (%)</td>
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<th>TABLE 2 Parental ages</th>
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<tr>
<td>Years</td>
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<td>Fallot's fathers (%)</td>
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<td>Normal fathers (%)</td>
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<td>Fallot's mothers (%)</td>
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<td>Normal mothers (%)</td>
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Birth order (Table 1) Here again no significant deviation was found.

Parental ages (Table 2) Mean ages were 33.0 ± 6.8 for the father and 29.5 ± 5.3 for the mother. These values do not deviate from normal ones.

Sibs (Table 3) 1.1 per cent of the sibs of boys with Fallot's tetralogy and 1.4 per cent of the sibs of girls were concordant. Extra-cardiac anomalies were also more frequent among sibs of affected females and the number of abortions was again higher in the latter.

Pregnancy and delivery No relevant data were recorded.

Finger pattern (Table 4) Both sexes, but particularly girls, had a reduced number of U (63% and 62% vs. 67% and 68% in controls) and a proportional increase in W (27.5% and 25% vs. 22% in controls). Girls had a high

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<th>TABLE 3 Pedigree</th>
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<td>Sex</td>
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<tr>
<td>Male</td>
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<td>Female</td>
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<tr>
<th>TABLE 4 Dermatoglyphs (% values)</th>
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<tr>
<td>Sex</td>
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<tr>
<td>Fallot</td>
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<td>Fallot</td>
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t°, t', and t" are the different positions for axial triradius (see text).
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proportion of arches (11% vs. 5% in controls). These differences were statistically significant for both sexes.

Total finger ridge count This was measured in 71 boys and 33 girls. The former had a mean of 109 ± 45 ridges, while the girls had 99 ± 46 ridges (Fig. 3 and 4). Both values were low and the deviation from models was significant.

Palm axial triradius (Table 4) Both boys and girls showed a clear increase in the t' and t" proportions, these deviations being statistically significant.

Karyotype All analysed cases had normal chromosomes.

(b) Syndrome cases (13 cases)

Down's syndrome (mongolism) 5 cases (3 male, 2 female). Trisomy for chromosome no. 21 existed in all. Birth order and maternal ages were high, as typical for this syndrome. One case has had a brother concordant both for mongolism and congenital heart disease. The remaining 19 sibs were normal. Dermatoglyphs were typical for mongolism (96% ulnar loops, 100% t', and low total finger ridge count).

XXX syndrome One girl with 47 chromosomes and XXX trisomy. No relevant data were present except a high proportion of whorls.

Turner's syndrome One case presenting mosaicism 46,XXp-/45,X. A first cousin was affected with a cyanotic type of congenital heart disease.

Turner's phenotype in a male case (Bonnevie-Ulrich or Noonan syndrome) One case having pterygium colli, low implantation of the hair, and cryptorchidism. Karyotype was 46,XY (normal male). There were many whorls on the fingers and t' on the palms.

Lewis's syndrome (radioventricular dysplasia) There was a boy with absence of the left thumb and hypoplasia of the left radial epiphysis (Fig. 4). Cryptorchidism, hypospadias,
and cataract were also present. No other cases existed in the family. Parental ages were particularly high. \( t \) was absent on the left palm and normal on the right. The electrocardiogram was unusual (Fig. 5) for aberrant Q waves in II, III, and aVF.

**Klippel-Feil syndrome**  
One girl without any other relevant data.

**Other non-specified syndromes with normal chromosomes** (3 cases) A boy with hyperuricaemia, persisting at high levels even after total correction, plus mental retardation. Lesch-Nyhan syndrome was enzymatically ruled out. There was a \( t' \) on both palms.

A girl presented lateral asymmetry. Parental ages were high. There was a \( t' \) triradius.

A girl presented severe mental retardation and agenesis of the corpus callosum. Palm dermatoglyphs were very unusual, each palm presenting 3 whorls plus 10 triradii – duplication of \( b, c, \) and \( d, \) and triplication of \( t. \)

**Discussion**

Difficulties in genetic analysis of human malformations are well known, mainly due to the small number of members of most families, even smaller after a malformed child’s birth. On the other hand, knowledge of inheritance patterns of congenital heart disease is essential today, when people suffering from these anomalies are prone to marry and could have affected children.

In the past few years major improvements in the analysis of inheritance of congenital malformations have been provided by, (i) the introduction of practical models based on polygenic inheritance (Edwards, 1960; Nora, 1968; Carter, 1969); (ii) the isolation of many new polymalformative syndromes with a cytogenetic basis in some of them; (iii) the use of dermatoglyphic analysis, with specific patterns in some malformations.

Many families have been reported in which several cases of Fallot’s tetralogy existed (Eihlers and Engle, 1966; Molz, 1968; Emanuel, 1970). The most impressive of all these families was published by Pitt (1962), with 6 Fallot’s and 5 other cases of congenital heart disease, among 275 members. These families are sometimes presented in support of dominant or recessive inheritance, but a multifactorial mechanism also results in familial aggregation of cases, simulating mendelism (Edwards, 1960).

For a polygenically determined trait the recurrence in first degree relatives (parents, sibs, and offspring) is \( V_p \), where \( p \) is the incidence of the trait in the normal population. In our series there were 126 cases of Fallot’s tetralogy in 600 cases with congenital heart disease. This incidence is probably high as our series included only a few infants in whom other more severe types of cardiac anomalies are usually found; a figure of 20 per cent seems to be more appropriate. Accepting a general incidence for all types of congenital heart disease of about \( 0.005 \) live newborns (McKeown, McMahon, and Parsons, 1953; Carlgren, 1959), the natural occurrence of Fallot’s tetralogy should be of the order of \( 0.001. \) If a multifactorial mechanism is the underlying cause the risk of recurrence in sibs (and also in offspring) would be as high as \( \sqrt{0.001} \approx 3 \) per cent. Neil (1970) has found 2.6 per cent affected offspring of 235 cases of Fallot’s tetralogy (60% of them concordant) and Nora (1968) 2.2 per cent affected sibs of 118 patients. In Lamy’s series (Lamy et al., 1957), 238 patients with Fallot’s tetralogy had 1 per cent affected sibs. The series of Polani and Campbell (1955) is not useful as it included other congenital heart disease besides Fallot’s tetralogy. Our series presented 1.2 per cent recurrence risk in the sibs; this figure seems to be a little low, and the reason for that could be: (i) the truncation of the family, after voluntary reduction in the number of children; (ii) heterogeneity of the condition, some cases being phenocopies – in fact Fallot’s tetralogy can be produced by thalidomide (Vickers, 1967) or diabetic embryopathy (Kučera, Lenz, and Maier, 1965); (iii) bias in the ascertainment of the cases, those more severe being prone to die in infancy and not to be included in this series, and one should remember that the more severely affected the cases are, the higher risk for their sibs.
According to the multifactorial mechanism also, patients of the more rarely affected sex are a higher risk to their relatives. This was found in our series in which the risk for sibs of female patients was 1.4 per cent and for male patients 1.1 per cent. In addition, the number of abortions and stillbirths was considerably higher in the former, and this could be a reason for the deviation from unity for the sex ratio in the series. High parental consanguinity is also in accordance with a multifactorial hypothesis.

We have previously reported typical dermatoglyphic findings in several types of congenital heart disease (Sánchez Cascos, 1964, 1965). In the present series a high proportion of whorls was present on the fingers and the number of ulnar loops was proportionally diminished. Similar results have been noted by Emerit, Vernant, and Corone (1968): 28.7 per cent of whorls in Fallot’s tetralogy, for 24.5 per cent in controls. Total finger ridge count is the most useful quantitative parameter, and its multifactorial determination has been proved (Holt, 1961; Penrose, 1963; Holt, 1968). We have found low total finger ridge count values, both in boys and girls, with Fallot’s tetralogy. On the palm a high proportion of distal t (t’ or even t”) was found; similar results have been reported by Emerit et al. (1968) and by Alter and Schulenberg (1970). The deviation from normal values was always wider in girls with Fallot’s tetralogy, and this could represent a further proof for multifactorial inheritance.

In the past years intensive investigation of polymalformative syndromes has proved cardiac involvement in many of them. We shall only refer to those represented in this series:

(1) Down’s syndrome (mongolism) Two old papers (Berg, Crome, and France, 1960; Rowe and Uchida, 1961) reported that about 50 per cent of mongoloid patients have heart involvement, and that Fallot’s tetralogy was a rare condition in mongolism, being present in less than 4 per cent of them. Two recent series (Ward and Ducasse, 1968; Cullum and Liebman, 1969) report a higher proportion of Fallot cases. Our results support this thesis.

(2) XXX syndrome These slightly retarded female patients rarely have congenital heart disease, atrial septal defect being the common anomaly (Barr et al., 1969; Sánchez Cascos, Lautre, and Sokolowski, 1969).

(3) Turner’s syndrome Heart involvement is found in about one-third of the cases and aortic coarctation is the most common anomaly (Sánchez Cascos et al., 1969; Emanuel, 1970), Fallot’s tetralogy being rarely found.

(4) Turner’s phenotype (Bonnevie-Ulrich or Noonan syndrome) Though pulmonary stenosis seems to be the typical anomaly in this condition, Fallot’s tetralogy is by no means rare, particularly in male patients (Chaves-Carballo and Hayles, 1966; Emerit et al., 1967; Ando, Mori, and Takao, 1969).

(5) Lewis’s syndrome (radioventricular dysplasia) While in the well-known Holt–Oram syndrome an ostium secundum atrial septal defect is associated with thumb anomalies and an autosomal dominant inheritance is the rule (Sánchez Cascos, 1967), patients with more severe heart and radial involvement have been considered to represent a different syndrome and the term Lewis’s syndrome has been proposed by McKusick (1966). Nevertheless, Murdoch (1969) has recently proved that both syndromes can be present in the same family, so that different expression of the same gene seems to be the cause for both.

(6) Klippel-Feil syndrome Congenital heart disease existed in 13 instances from 400 collected cases of this syndrome (Gray, Romaine, and Skandalakis, 1964). Ventricular septal defect seems to be a common finding, either isolated or as a part of a complex as in Fallot’s tetralogy (Nora, Cohen, and Maxwell, 1961).

We can see that, though some polymalformative syndromes sometimes cause typical heart anomalies, such as atrioventricular communis in mongolism, coarctation in Turner’s, or pulmonary stenosis in Noonan, in many instances there is a lack of specificity: Fallot’s tetralogy, as with other types of congenital heart disease, can be present in different syndromes.

References
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