A common cause of congenital heart disease

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The schematic of a family tree shows the facial appearance of three women (fig 1). The woman in panel A is in her mid 50s and her two daughters (panels B and C) are both in their 30s. All three women are well and in full time employment. On examination the woman shown in panel A has a soft systolic murmur in the pulmonary area. She has a past history of heart valve surgery performed at the age of 19 years and correction of unilateral ptosis as a child. The woman shown in panel B also has a soft systolic murmur at the upper left sternal edge. She has a daughter (D) who is well and of normal phenotype. The woman in panel C has a normal cardiovascular examination. All three women are just under 5 feet (1.5 m) in height.

QUESTIONS

(1) What is the likely unifying diagnosis?

- (2) What clinical features, illustrated above, typify this condition?
- (3) What is the most likely cardiac abnormality in both women A and B?
- (4) What is the mode of inheritance?
- (5) What are the differential diagnoses?

ANSWERS

- (1) The diagnosis is Noonan syndrome. Dr Jacqueline Noonan first described this condition in the early 1960s in Iowa, USA. Surprisingly, it is the most common non-chromosomal cause of congenital heart disease. The incidence is 1:1000–2500 live births. Often described as the male equivalent of Turner syndrome, it is, however, present in both sexes and with equal incidence.
- (2) Noonan syndrome is characterised by short stature, congenital heart defects,

broad or webbed neck, and characteristic facial dysmorphism as demonstrated above. The main facial features are hypertelorism with down slanting palpebral fissures, ptosis, a flattened nasal bridge, epicanthic folds, malar hypoplasia and low set anterior rotated ears. Developmental delay of varying degrees may be a feature. Chest deformities include superior pectus carinatum, inferior pectus excavatum, and wide set nipples. Cryptorchidism, bleeding diatheses, and lymphatic dysplasias are also associated.

(3) The most common cardiac defects seen are valvular pulmonary stenosis and hypertrophic cardiomyopathy. Both women in panels A and B have a diagnosis of pulmonary valvular stenosis. The cardiac surgery mentioned in the case of the woman in panel A at the age of 19 years was a pulmonary valvotomy. Noonan syndrome is the most common single gene cause of congenital heart disease. A documented heart defect is reported in 50–80% of patients. Other structural cardiac defects observed include:

- atrial and ventricular septal defects
- branch pulmonary artery stenosis
- tetralogy of Fallot
- coarctation of the aorta.

(4) Noonan syndrome is a heterogeneous condition with autosomal dominant inheritance. It demonstrates incomplete penetrance and variable expression. New sporadic mutations are also seen. In 50% of cases there is a single gene mutation (PTPN11) on chromosome 12 encoding for tyrosine kinase. The majority of cases with pulmonary stenosis have this genotype.¹ Further gene mutations (SOS1 and KRAS) have been identified, accounting for a further 25% of cases. Until very recently the genes responsible for the remainder of cases have been unknown. A further five different mutations of RAF1 were described in patients with Noonan syndrome in 2007, the majority of which were associated with hypertrophic cardiomyopathy.²

(5) Important differential diagnoses to consider include:

- Turner syndrome
- cardiofaciocutaneous syndrome
- Leopard syndrome

Turner syndrome occurs exclusively in females and is differentiated from Noonan syndrome by demonstration of a sex chromosome abnormality. It is not a possible differential in the women we

Figure 1 Family tree schematic. Informed consent was obtained from all three individuals for publication of this figure.

describe, as Turner syndrome results in infertility. The phenotype in Turner syndrome is actually quite different. Left sided cardiac abnormalities are the rule, and renal abnormalities and developmental delay are more common.

Cardiofaciocutaneous syndrome occurs sporadically. It has similar cardiac findings to Noonan syndrome; however, developmental delay is severe with a higher likelihood of structural central nervous system abnormalities.

Leopard syndrome is an autosomal dominant syndrome characterised by multiple lentigines and café au lait spots, electrocardiographic conduction abnormalities, ocular hypertelorism/obstructive cardiomyopathy, abnormalities of the genitalia in males, retardation of growth,

and deafness. Leopard syndrome shares many features with Noonan syndrome, in which lentigines and deafness are usually not present. Molecular studies have shown that Noonan syndrome and Leopard syndrome are caused by different mis-sense mutations in the same PTPN11 gene.

It is clearly important to identify Noonan syndrome in order to allow evaluation of associated cardiac abnormalities. Interestingly, the signs and symptoms of Noonan syndrome lessen with age and most adults do not require specialist medical intervention.

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REFERENCES

- 1 **Roberts AE**, Araki T, Swanson KD, *et al.* Germ line gain of function mutations in SOS1 cause Noonan Syndrome. *Nat Genet* 2007;**39**:8–9.
- 2 **Razzaque MA**, Nishizawa T, Komoike Y, *et al.* Germ line gain of function mutations in RAF1 cause Noonan syndrome. *Nat Genet* 2007;**39**:1013–17.