Coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome in three generations

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Abstract
Five members in three generations of a family were affected by a congenital heart disease. Four of them had mild or severe coarctation of the aorta (CoA), either isolated or in association with other cardiac defects. Fetal echocardiography allowed prenatal diagnosis in one pregnancy at risk. This family suggests that a rare form of CoA could be the result of an autosomal dominant mutation with high penetrance and variable expressivity rather than polygenic inheritance (J Med Genet 1993;30:328-9)

Most cases of coarctation of the aorta (CoA) are attributed to multifactorial inheritance. However, sporadic families presenting with CoA in two or more generations have suggested that sometimes this malformation could be inherited as an autosomal dominant trait with high penetrance and variable expressivity. We report on a family in which CoA was segregating through at least three generations and in which fetal echocardiography allowed prenatal diagnosis in a pregnancy at risk.

Case report
The proband, a 25 year old pregnant woman, requested echocardiographic monitoring of her second pregnancy. She was the third born of a sibship of three (III-3) (fig 1). She was born at term after an uncomplicated pregnancy. A diagnosis of CoA with interventricular septal defect (VSD) and patent ductus arteriosus (PDA) had been made at 20 months. The defect was corrected at 8 years. At that time chromosome analysis showed a 46,XX karyotype. One younger sister (III-1) died at 6 years of unspecified congenital heart disease (CHD). According to hospital records she had no features of any syndrome associated with cardiac outflow tract defect, such as Di George syndrome (DGS) and velocardiofacial syndrome (VCS). One younger brother (II-2) was healthy with normal cardiac function and structure, as shown by echocardiography.

At 22 years this woman became pregnant. In the 33rd week of gestation she delivered a male infant with a birthweight of 2300 g. The baby (IV-1) had interruption of the aortic arch and died at 6 days of age. An echocardiographic examination was performed in her second pregnancy at 26 weeks. A single fetus was found in cephalic position with a normal heart position and situs. A transverse thoracic sec-
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Family pedigree.

1·8% by Zetterquist and Nora et al. According to Beekman and Robinow, CoA did not affect more than two generations in 25 of 26 families reviewed. In one family, five members in four generations were affected, suggesting the segregation of an autosomal dominant trait with high penetrance and variable expressivity. An additional familial case of CoA associated with aplasia cutis congenita in the midline of the scalp vertex has been reported by one of us (BD). The possibility that these defects were the result of a Mendelian mutation has been put forward.

Interestingly, a study of relatives of infants with hypoplastic left heart syndrome (HLHS), which was present in one of our family members, has shown that cardiac defects occur in first degree relatives of probands at a higher frequency than predicted by an additive multifactorial model of inheritance. It was also found that first degree relatives of HLHS probands may have an increased risk of subclinical cardiac defects.

The present observation, together with a limited number of known families, supports the conclusion that a rare form of CoA could be the result of an autosomal mutation. This possibility should be taken into account when providing genetic counselling. Recent observations have shown that 22q11 deletions are associated with both DGS and VCS. This deletion can cause apparently isolated heart defects whose range may be wider than previously recognised in the two syndromes. Admittedly no patient in our family had the clinical features of DGS or VCF. However, the possibility that patients with a cardiac outflow tract defect, including isolated ventricular septal defects or coarctations, have an undetected deletion of 22q11 cannot be excluded.