Familial atrioventricular septal defect: possible genetic mechanism

Sirs.—We read with interest the report of Kumar et al describing a family in which the mother and her two daughters by different fathers had atrioventricular septal defects not associated with trisomy 21.1 They suggest that an autosomal dominant pattern of inheritance may be involved in this pedigreed, albeit a multifactorial or cytological mechanism cannot be ruled out.

We recently described five families in which two or more members had isolated atrioventricular septal defect. Parent-to-son transmission of concordant cardiac defect was documented in four cases. The mother was affected in three cases and the father in one.

Lately we found an additional example of atrioventricular septal defect in four members in two generations of the same family (figure). None of the family members showed phenotypic anomalies and all had a normal karyotype. They were examined by echocardiography and cardiac catheterisation. A partial atrioventricular septal defect was diagnosed in one case (II 5) and a complete defect in two cases (III 1 and III 2). The daughter of a patient with atrioventricular septal defect had an isolated cleft of the mitral valve (III 3).

Anatomical differences between isolated mitral clefts and clefts associated with an atrioventricular septal defect have been described. 1 The height and shape of isolated mitral cleft in families with atrioventricular septal defects, 1,2 including our family, and its prevalence in patients with Down's syndrome (4/420 = 0.52/200 in our experience), however, suggests that this malformation should be included in the spectrum of atrioventricular septal defects.

Monogenic autosomal dominant inheritance with incomplete penetrance could explain the atrioventricular septal defects in the families we studied and those reported by other workers. Normal parents of affected children could be obligate carriers of the gene involved in familial atrioventricular septal defects. The father-to-daughter transmission of cardiac malformation in two cases excludes cytoplasmic inheritance in these families. Moreover, atrioventricular septal defects in patients with and without Down's syndrome differ not only in terms of the prevalence of partial or complete forms 3 3 but also in terms of the distribution of associated cardiac malformations. 4 4 These anatomical differences and the absence of linkage in the molecular analysis of chromosome 21 in families with atrioventricular septal defect 5 5 suggest that the gene or genes involved in the pathogenesis of atrioventricular septal defect in "normal" children are different from those in patients with Down's syndrome.
