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LETTER TO THE EDITORS

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Exclusion of linkage with chromosome 21 in families with recurrence of non-Down's atrioventricular canal

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We read with interest the report of Cousineau et al. (1994), presenting a linkage analysis study of a large pedigree with autosomal dominant non-syndromic atrioventricular canal (AVC). Because of the high incidence of AVC in patients with Down's syndrome, candidate loci on chromosome 21 have been investigated in order to demonstrate their involvement in non-syndromic familial AVC. The results excluded a linkage between polymorphic markers on chromosome 21 and AVC in this family. The Down's syndrome "critical region" was previously analysed by Wilson et al. (1993) in a large pedigree with recurrence of non-syndromic AVC in three generations, but no linkage was demonstrated.

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We have recently described five families with recurrence of isolated AVC (Digilio et al. 1993a). All pedigrees were compatible with an autosomal dominant pattern of inheritance, although the presence of normal individuals who have transmitted the cardiac defect suggests incomplete penetrance of the AVC gene. Two families with multiple affected individuals were selected for linkage analysis. In family A (Fig. 1 a) 7 affected individuals, 4 obligate carriers and 13 normal relatives were available for the study. In family B (Fig. 1 b) 5 affected, 1 carrier and 13 normal individuals were analysed. Chromosome 21 linkage was evaluated using three short tandem repeat polymorphisms (STRPs) (D21S265, D21S269, D21S263) mapping within the region 21q22.1-q22.2 (Weissenbach et al. 1992). Alleles were detected using the polymerase chain reaction (PCR) and polyacrylamide gel electrophoresis (Weissenbach et al. 1992). Two-point linkage analysis was performed using the MLINK program from the LINKAGE package (version 5.1; Lathrop and Lalouel 1984); two values (50% and 90%) of penetrance were assumed. The negative lod score values (Table 1) confirm the exclusion of linkage between our non-syndromic AVC families and 21q22.1–q22.2 markers.

The results obtained in the four pedigrees investigated for linkage with markers of the Down's syndrome critical region argue for genetic heterogeneity of AVC. Genes located on different chromosomes could be responsible for AVC, as illustrated by its association with different chromosomal imbalances, including trisomy 21, partial monosomy 8p (Marino et al. 1992; Digilio et al. 1993b), trisomy 9 (Marino et al. 1989), and trisomy 18 (Digilio et al. 1991; Carmi et al 1992). This is also in agreement with previous personal observations on the anatomical differences of AVC in patients with trisomy 21 compared with those with normal chromosome in terms of prevalence of left side obstructions and right malalignment of the AVC, including hypoplasia of left ventricle (De Biase et al. 1986; Marino et al. 1990; Carmi et al. 1992).

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Table 1 Results of pairwise two-point linkage analysis at penetrance levels of 90% and 50% in the two AVC families

Short tandem repeat polymorphism	Recombination fraction							
	0.000	0.001	0.010	0.050	0.100	0.200	0.300	0.400
90% penetrance								
D21S265	–15.430	–12.180	–8.500	–4.880	–3.120	–1.400	–0.570	–0.600
D21S269	–5.370	-3.350	–2.260	–1.210	–0.640	–0.130	0.010	0.020
D21S263	–16.260	–9.970	–6.640	–3.650	–2.160	–0.760	–0.180	0.010
50% penetrance								
D21S265	–7.390	–5.900	–4.300	–2.290	–2.390	–0.590	–0.230	–0.050
D21S269	–3.570	–2.500	–1.310	–0.700	–0.130	0.090	0.100	0.040
D21S263	–9.730	–6.350	–3.700	–1.460	–0.680	–0.070	0.100	0.090

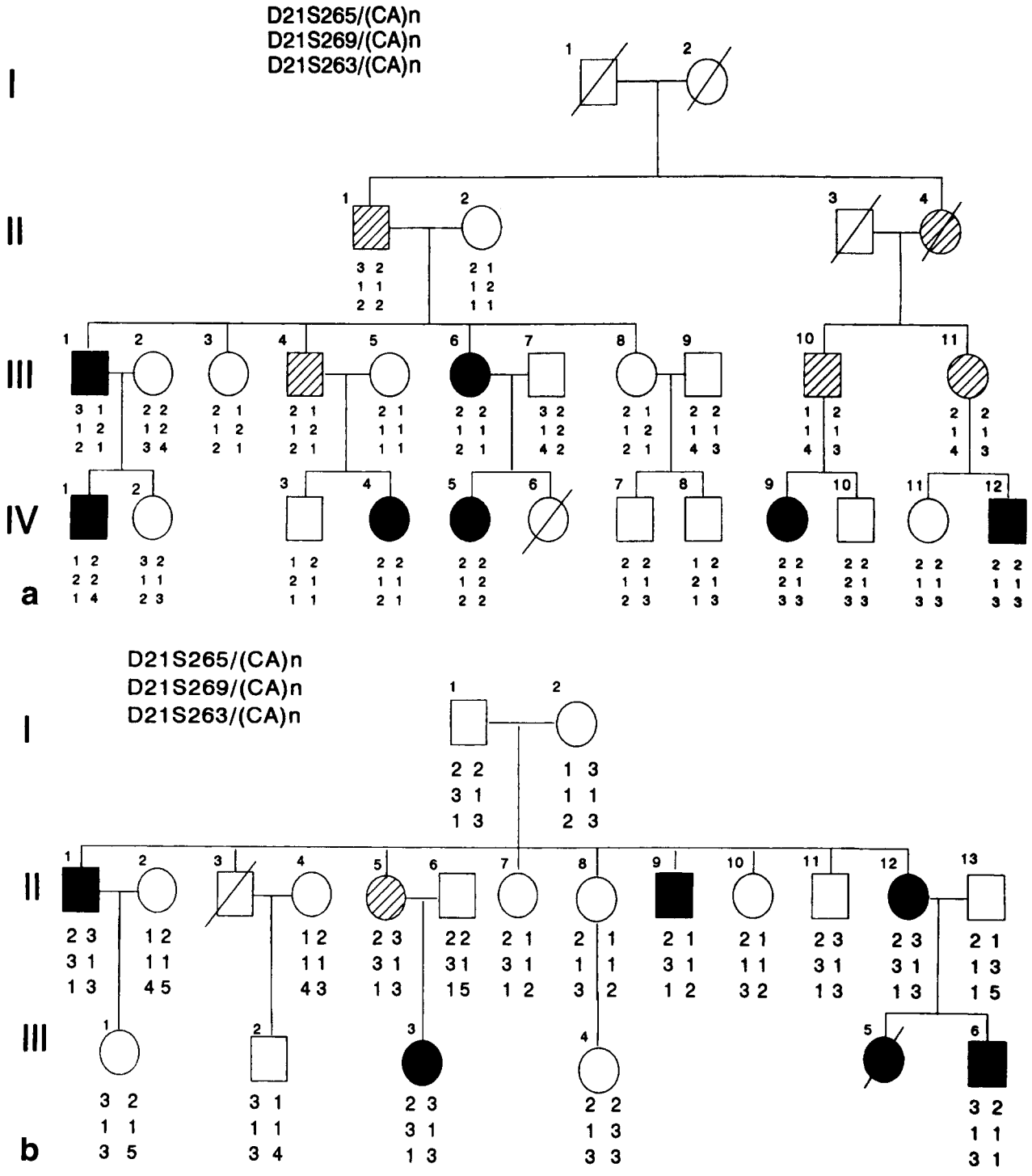

Fig. 1 a, b Family A (**a**) and family B (**b**) pedigrees with indication of alleles of markers D21S265, D21S269 and D21S263 detected in the analysed individuals. Affected individuals with atrioventricular canal (AVC) are represented by *solid symbols*. Obligate carriers of the AVC gene are indicated by *hatched symbols* and unaffected individuals by *open symbols*

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