approval for screening random schizophrenics for mutations was granted by Lothian Area Health Authority before the initiation of this study.

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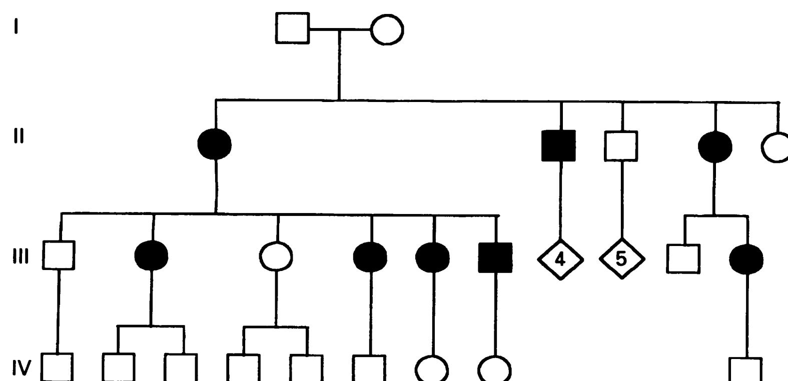
Further family with autosomal dominant patent ductus arteriosus

Occasionally, families have been reported with apparent autosomal dominant inheritance of a patent ductus arteriosus (PDA), although the condition usually appears to be sporadic.[1-6] We report a further family with eight affected members in two generations.

The pedigree is shown in the figure. The grandfather (I·1) died suddenly after a tooth extraction at the age of 40; his wife died of old age. II·1 was diagnosed and operated upon for a PDA at the age of 35 years. Despite having a sister with a PDA and two children requiring PDA ligations, it was not until she brought her third affected child into hospital that she herself was examined. Mild right ventricular hypertrophy was found and a small PDA was closed. She also had coeliac disease. II·2 has been in good health all his life. Because of the family history of patent ductus arteriosus he sought a cardiology opinion at the age of 54 years. A PDA was found with moderate biventricular dilatation and he was operated on successfully. II·4 had been a sickly child throughout her life but became progressively less well in her teenage years. At the age of 18 years bacterial endocarditis and a PDA were diagnosed. Both were eventually successfully treated. In later life she developed myasthenia gravis, scleroderma, and Reynaud's phenomenon. III·2 was referred to a cardiologist at the age of 7 years with an asymptomatic murmur. After two years of follow up, ventriculomegaly began to develop and the PDA was ligated. III·4 was diagnosed as having a PDA at the age of 5 years, had always been mildly exercise restricted, had ventriculomegaly, and was operated on at 6 years. III·5 was found to have an asymptomatic murmur at the age of 6 years and her PDA was tied at $6\frac{1}{2}$ years. She also had coeliac disease. III·6 had frequent upper respiratory tract infections as a young child and was exercise restricted. At the age of 4 years he was referred to a cardiologist who found a typical PDA murmur. He was operated on at the age of $4\frac{1}{2}$ years. His karyotype is normal. III·17 was referred to a cardiologist at the age of 3 years for an asymptomatic murmur. A PDA was diagnosed and ligated forthwith.

Family members are of normal appearance and intelligence and have no symptoms suggestive of a prostaglandin metabolic defect, such as atopy or difficulties during labour. Although all occurrences of PDA have been inherited from an affected mother in this family, paternal-offspring transmission has been described previously.[1,3,4,6] The PDAs found in this family were not unusual in their position and varied greatly in the symptomatology they caused.

The empirical recurrence risk for a PDA is 3% whether it is a parent or a sib that is affected.[7] Most cases are thought to be the result of polygenic/multifactorial inheritance. In families such as this, where so many members are affected, autosomal dominant inheritance seems likely and the recurrence risk is probably 50%. In order to give realistic recurrence risks to a family where a child has a PDA, the facial phenotype described by Davidson[6] should be sought, and both parent's cardiovascular systems should be examined. Referral to a cardiologist of any children born to a family with possible autosomal dominant PDA seems sensible whether or not they have a detectable murmur.



Family pedigree.

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Molecular basis of the common electrophoretic polymorphism (Fu1/Fu2) in human α-L-fucosidase

α-L-fucosidase (EC.3.2.1.51) is a lysosomal hydrolase involved in the catabolism of fucose-containing glycolipids and glycoproteins. A deficiency of this enzyme leads to the lysosomal storage disease, fucosidosis.[1,2] α-L-fucosidase exists as multiple molecular forms, which can be separated by various procedures.[3,4] The precise molecular basis of this heterogeneity is not understood but it is probably post-translational. All the forms are encoded by a single locus on the short arm of chromosome 1 at 1p34.1-1p36.1 which encodes the structural gene for the enzyme, FUCA1[5,6] The enzyme shows a genetically determined, common, electrophoretic polymorphism (Fu1/Fu2), which can be detected in blood and tissues[7] and maps to the structural gene locus (FUCA1).[8] The minor allele, Fu2, produces more cathodal forms of the enzyme.

The structural gene for α-L-fucosidase has been isolated and sequenced.[9,10] It is 23 kb in length and has eight exons. Two common RFLPs obtained with *Pvu*II and *Bgl*I are in almost complete linkage disequilibrium and can be used to haplotype subjects.[11] Several disease-causing mutations have been identified in patients with fucosidosis.[2,12-14] In addition, an A to G transition in exon 5 causing substitution of an arginine for glutamine, Q281R, has been found homozygously in both patients and controls, indicating it is a polymorphism rather than a disease-causing mutation.[14] All homozygotes for this substitution showed the RFLP *Pvu*II-*Bgl*I haplotype, 2-2, 2-2. It was postulated that Q281R might be the molecular basis of the Fu1/Fu2 electrophoretic polymorphism.[14] Evidence to support that suggestion is presented in this paper.

The Q281R polymorphism creates a new site for the restriction enzymes *Dsa*I and *Bsa*JI in exon 5. It can be readily detected by amplifying exon 5 with the two primers used for mutation analysis (F42 and F43 in reference 14), followed by digestion with *Dsa*I or *Bsa*JI (fig 1). Analysis of the *Bsa*JI digestion products by electrophoresis in 3% agarose (BRL)/

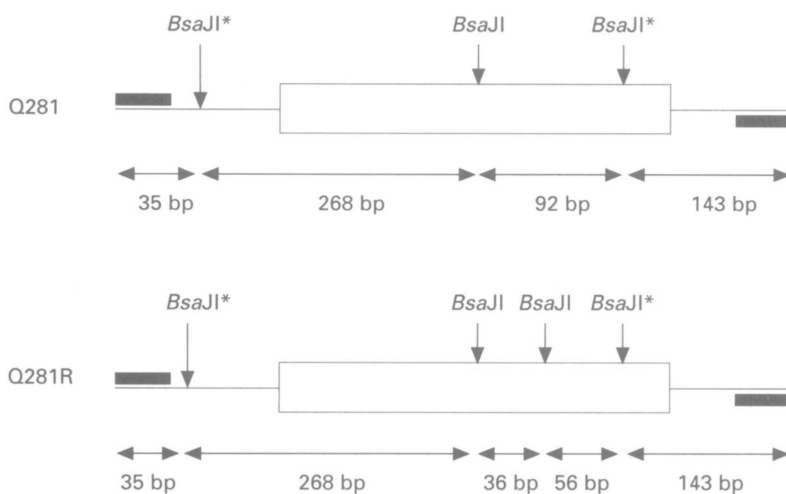

Figure 1 Diagram showing the detection of the polymorphism in exon 5 of FUCA1.

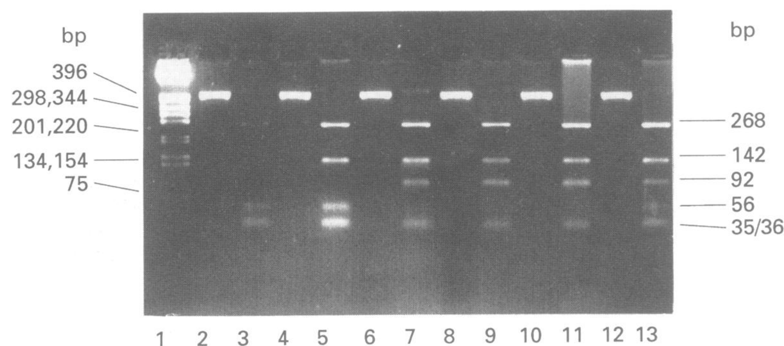

Figure 2 Detection of Q281R polymorphism by amplification of exon 5 by PCR and digestion of products with BsaJI, followed by electrophoresis in agar/Nusieve in ethidium bromide. Genomic DNA from persons of known Fu1/Fu2 genotype was analysed. Lane 1, λ1kb ladder; lanes 2 and 3 fucosidosis patient; lanes 4 and 5 Fu2 homozygote; lanes 6 and 7, 8 and 9, and 10 and 11 Fu1 homozygotes; lanes 12 and 13 Fu1/Fu2 heterozygote. Lanes 2, 4, 6, 8, 10, and 12 undigested DNA and lanes 3, 5, 7, 9, 11, and 13 DNA digested with BsaJI.

1% Nusieve (Flowgen) in the presence of ethidium bromide shows the appearance of a 56 bp band and the concomitant loss of a 92 bp band (fig 1). The bands obtained with *DsaI* have different sizes[14] (fig 1). Representative analyses are shown in fig 2. DNA from eight persons who had been phenotyped previously for the Fu1/Fu2 electrophoretic polymorphism[8] was analysed for the Q281R polymorphism. Two persons who were homozygous for the Fu2 allele were also homozygous for the Q281R allele. Conversely four persons who were homozygous for the Fu1 allele did not have the Q281R allele. Two heterozygotes for the Fu1/Fu2 polymorphism were heterozygous for the Q281R allele. A fucosidosis patient homozygous for the Q281R polymorphism (lanes 2 and 3 in fig 2) had the *PvuII-BglI* haplotype, 2-2, 2-2. The frequency of the Q281R allele was 0·38 both in 27 controls and in 11 patients with fucosidosis. A frequency range of 0·27–0·50 at a confidence limit of 95% is predicted for the Q281R allele in the population from analysis of this sample. A frequency of 0·25 was obtained for a smaller sample analysed previously.[14] The frequency of the Fu2 allele ranges from 0·05 in American blacks to 0·36 in northern Europeans, with a mean value of 0·28 for all the samples analysed.[15]

The complete concordance of the DNA genotypes and protein phenotypes together with the fact that the glutamine to arginine substitution causes an increase in positive charge supports the notion that Q281R is the causative substitution for the Fu1/Fu2 polymorphism. The Q281R polymorphism was discovered during mutation analysis of patients with fucosidosis. It was originally thought to be a disease-causing mutation, because of the nature of the resulting amino acid change. Although the mutation does affect the electrophoretic mobility of the enzyme it does not appear to affect its catalytic function. This illustrates the importance of checking the normal population for sequence changes found in patients and for relating them to known phenotypic variations.

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