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LETTER

MtDNA-related idiopathic dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is a heart muscle disease characterised by impaired myocardial contractility and ventricular dilatation. This disorder is an important cause of morbidity and mortality among children and represents the primary indication for heart transplantation.[1] Although the pathogenesis of DCM remains uncertain, a heritable cause is detected in 20–30% of children, with any mode of transmission being possible.[2]

There is now convincing evidence that proper mitochondrial DNA (mtDNA) functioning is critical to normal cellular metabolism and that mtDNA mutations can result in disease phenotypes.[3] In terms of cardiovascular diseases, evidence suggests that an accumulation of mutant forms of mtDNA in the myocardium results in cardiac conduction block and sudden death.

We studied 10 children with impaired myocardial contractility associated with left ventricular or biventricular dilatation to establish the extent to which mtDNA mutations affect the natural history of their heart disease. Cases studied belong to eight different families; family history and clinical symptoms were compatible with a mitochondrial disorder in four. None showed alterations in the dystrophin gene. Using direct sequencing, we searched for mtDNA alterations in regions implicated in mitochondrial protein synthesis, including rRNA and tRNA genes. Mutations in such sequences are likely to affect mitochondrial respiratory chain and ATP production. We identified a novel T12297C mutation in the mitochondrial $tRNA^{Leu(CUN)}$ gene in two brothers showing DCM and endocardial fibroelastosis (EMCF) (Figure 1). A 7-year-old boy, the youngest of three children born to unrelated parents, collapsed while playing. At admission, he was found in ventricular fibrillation and was converted. Past medical history was significant for developmental delay and an episode of congestive heart failure at the age of 6 months. Echocardiography had suggested EMCF and a diagnosis of DCM was entertained. A skeletal muscle biopsy showed increased lipid droplets, subsarcolemmal mitochondrial aggregates, and giant mitochondria by electron microscopy. Histochemistry showed about 10% cytochrome *c* oxidase-negative fibers. Arterial plasma lactate was normal at rest (1.8 mM/L, normal < 2 mM/L). An older brother had died at the age of 15 months because of cardiac failure. A 9-year-old sister has DCM.

General consensus exists that a novel pathogenic mtDNA mutation should (i) be absent in normal individuals; (ii) exhibit heteroplasmy, a condition rarely observed in neutral mtDNA polymorphisms; and (iii) affect an evolutionary preserved nucleotide, important for the function of the molecule. The T12297C mutation alters a highly conserved nucleotide in the anticodon loop of the $tRNA^{Leu(CUN)}$ gene, was very abundant in the patient and his sister ($> 95\%$) and heteroplasmic in their asymptomatic mother (65%), and it was not found in 170 normal controls. Also, it has never been reported in high resolution studies of normal population.[4] Thus, all the criteria for pathogenicity were satisfied.

Although current findings link abnormalities in mtDNA structure and function with a broad group of cardiac pathologies, the pathophysiological events that give rise to specific forms of heart disease associated with mtDNA mutations still remain obscure,[5] mostly because they occur in the context of a multisystem disorder. Our novel findings add to the clinical and genetic spectrum of mitochondrial cardiomyopathies. In our opinion, the frequent heritable nature of familial DCM deems it important to undertake a diligent search for all potentially affected genes, including mtDNA. Identification of the responsible genes permits reliable preclinical diagnosis to be made and enables carriers of the condition to be identified. In addition to the impact on genetic counselling and pathogenesis, this might have important consequences for clinicians heralding a new era in understanding and treatment of this condition.

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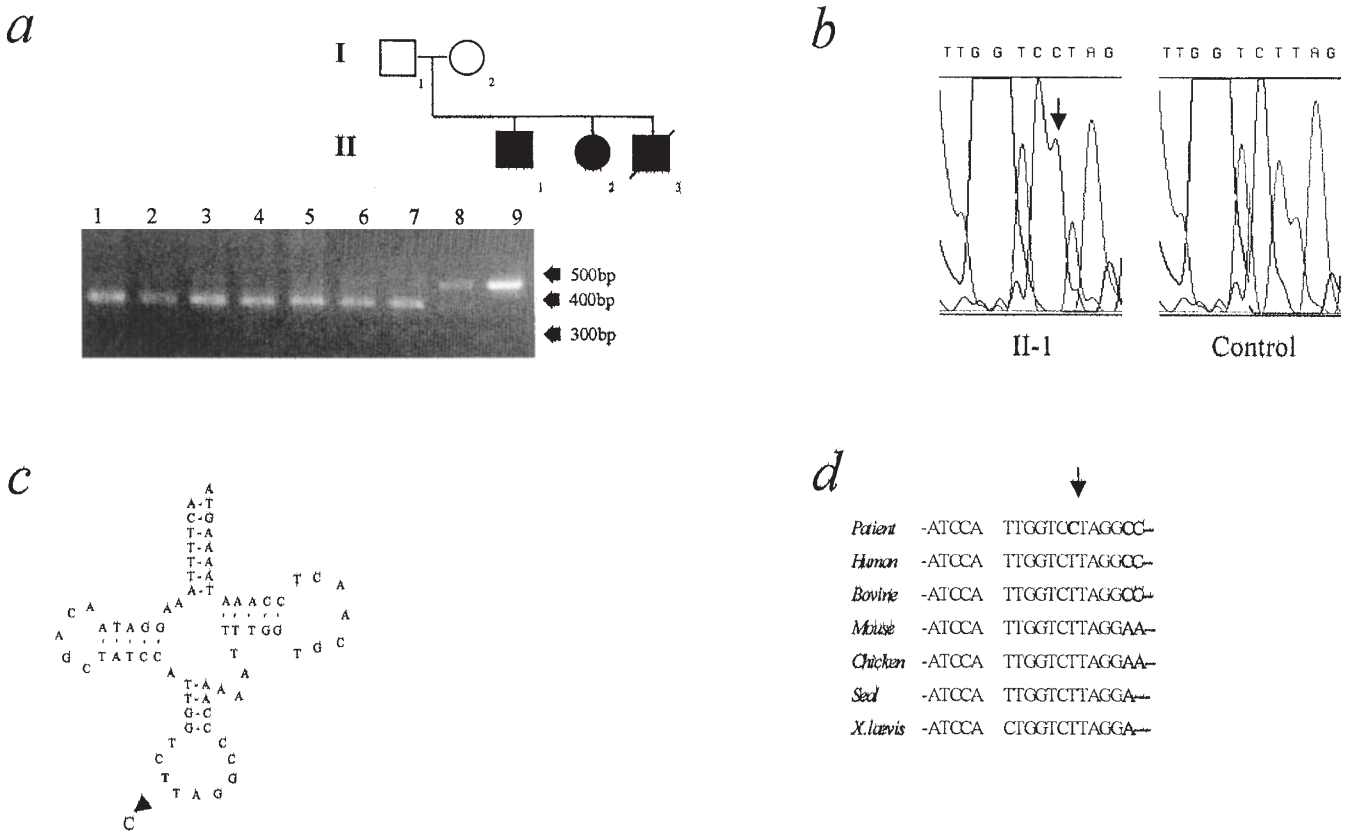

Figure 1 **a** *Family pedigree and RFLP analysis. A 470-bp PCR-amplified fragment is normally cut by the endonuclease* Dde*I into two fragments, sized 390 and 80 bp. The T12297C mutation abolishes the unique site of cleavage. Lanes 1–7 are normal controls; lane 8 is I–2; lane 9 is the proband (II-1). Sequence analysis of the region flanking the T12297C mutation;* **b** *cloverleaf of the mitochondrial* $tRNA^{Leu(CUN)}$ *gene with the position of the novel mutation (arrow);* **c** *and homology with other species;* **d** *are also shown*

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