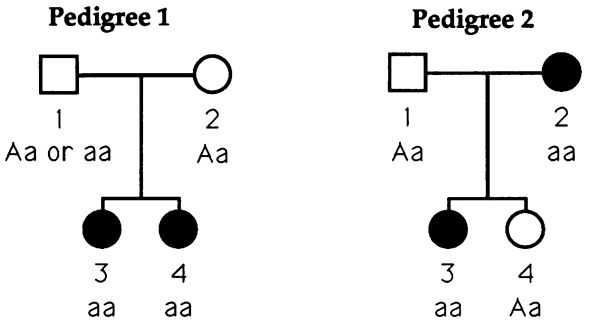

Figure 1 The two example pedigrees presented by Hayward and Brock (1993). The disease genotypes are indicated, with the a allele defined as the disease allele. The pedigrees were drawn by the Pedigree/Draw program (Mamelka et al. 1988).

replicates indicate that, as expected, pedigree 1 is, on average, more informative for linkage than is pedigree 2.

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An A-to-G Transition at Nucleotide Pair 11084 in the ND4 Gene May Be an mtDNA Polymorphism

To the Editor:

In the September 1992 issue of the *Journal*, Lertrit et al. (1992) reported a new disease-related mutation of mtDNA in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS). They reported two Caucasian patients with the classical features of MELAS and found different mtDNA mutations in each patient: in one, an A-to-G transition at nucleotide pair (nt) 3243 in the $tRNA^{Leu(UUR)}$ gene (3243 mutation), commonly seen in MELAS patients (Goto et al. 1990), and, in the other, an A-to-G transition at nt 11084 in the ND4 gene (11084 mutation), a mutation which Lertrit et al. claimed is a novel disease-related mutation.

In 50 MELAS patients studied in our laboratory, we found the 3243 mutation in 34 patients, a T-to-C transition at nt 3271 in the $tRNA^{Leu(UUR)}$ gene (3271 mutation) in 4 patients (Goto et al. 1991; Sakuta et al. 1993), and the 11084 mutation in 3 patients. To determine whether the 11084 mutation was a disease-related mutation, we further analyzed 90 patients with a variety of other mitochondrial myopathies, as well as 105 normal Japanese individuals (fig. 1 and table 1). The 11084 mutation was found in 9 patients (10%) with mitochondrial myopathies, including MELAS, chronic progressive external ophthalmoplegia (CPEO), and other miscellaneous mitochondrial disorders, and in 15 (14%) normal individuals.

However, none of the 109 normal and diseased Caucasians (Lertrit et al. 1992), American blacks (Wallace et al. 1988; Shoffner et al. 1990), or several patients with mitochondrial diseases, including 7 patients with

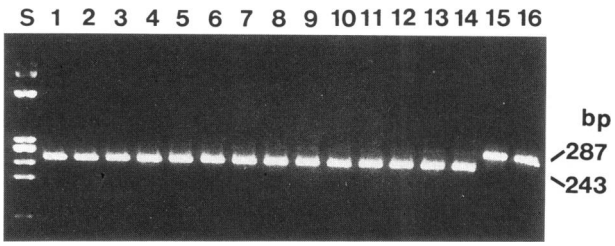

Figure 1 Analysis of the 11084 mutation in patients with mitochondrial myopathies and in normal Japanese, using PCR and *Nhe*I digestion. Total DNA was extracted from biopsied muscles (mitochondrial myopathies) and placenta (normal individuals). PCR was carried out according to the method described in this letter (Lertrit et al. 1992), by using the primers P1 (nt 11039–11083) and P2 (nt 11302–11325). PCR products were digested with *Nhe*I and were electrophoresed onto a 4.0% NuSieve 3:1 agarose gel. PCR products (287 bp) having an A-to-G substitution at nt 11084 were cleaved into two fragments of 243 and 44 bp. New bands were detected in nine mitochondrial myopathies (lane 1, MELAS without 3243; lanes 2 and 3, MELAS with 3243; lanes 4–6, CPEO without deletion; lane 7, CPEO with 3243 mutation; lanes 8 and 9, miscellaneous mitochondrial myopathies; and lanes 10–14, normal controls). Normal controls without 11084 mutation are also shown (lanes 15 and 16). Size-standard DNA (lane S) was ϕx174 DNA digested by *Hae*III.

Table 1

Clinical Diagnoses and mtDNA Mutations

Clinical Features and Observed Mutations	No. of Patients	No. with nt 11084 Mutation
MELAS:		
With 3243 mutation	34	2
With 3271 mutation	4	0
With no 3243 or 3271 mutation	12	1
Myoclonus epilepsy with ragged-red fibers:		
With 8344 mutation	4	0
With no 8344 mutation	3	0
CPEO:		
With deletion	2	0
With no deletion	16	3
With 3243 mutation	1	1
Miscellaneous mitochondrial myopathies	14	2
Total	90	9 (10%)
Normal controls	105	15 (14%)

Leber hereditary optic neuropathy (Howell and McCullough 1990; Huoponen et al. 1990), had the 11084 mutation. On the other hand, 1 of 10 Japanese patients with mitochondrial respiratory disorder showed the 11084 mutation (Ozawa et al. 1991). The high incidence of the A-to-G substitution at nt 11084 in mtDNA in the Japanese population suggests that this substitution may be a polymorphism prevalent in the Japanese. Although nt 11084 is an evolutionarily conserved site, and although the amino acid residues are highly invariant in various species, our findings suggest that an A-to-G substitution at nt 11084 may be a polymorphism and may not be responsible for inducing the clinical phenotype of MELAS.

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