Mitochondrial tRNA<sub>Thr</sub> Mutations and Lethal Infantile Mitochondrial Myopathy

To the Editor:

Recently, Yoon et al. (1991) attributed certain cases of lethal infantile mitochondrial myopathy (LIMM) to mutations in the mtDNA threonine transfer RNA (tRNA<sub>Thr</sub>) gene. The two patients in their study had severe respiratory chain enzyme deficiency and associated lactic acidosis and died within days after birth. Separate mtDNA tRNA<sub>Thr</sub> mutations were detected by DNA sequence analysis at nucleotide pair (np) 15924 in one patient and at np 15923 in the other patient. Both mutations occur within the tRNA anticodon stem-loop structure. No unaffected controls were screened for the presence of these mutations.

We have screened three LIMM and multiple control subjects for these mutations and report here that the np 15924 mutation found in one of the above patients is not a primary cause of LIMM. mtDNA was isolated from transformed lymphocytes of three LIMM patients, all of whom had mitochondrial respiratory enzyme deficiency and lactic acidosis. The tRNA<sub>Thr</sub> genes from all three were sequenced, but only one was found to differ from the normal sequence. It contained the np 15924 A-to-G mutation. This Caucasian male died at 4 mo postpartum, of severe lactic acidosis and heart and muscle mitochondrial defects (Zheng et al. 1989). His mother had the same mutation, and both individuals were homoplasmic. However, the mother showed no evidence of disease even after extensive biochemical, histological, and clinical analyses (Zheng et al. 1989).

In order to determine the frequencies of the np 15924 and 15923 mutations in the general population, mutation-specific restriction-endonuclease digestion assays were developed. PCR primers were prepared in which the sequence near the mutation was altered to create a diagnostic restriction enzyme-recognition site after PCR amplification (Seibal et al. 1990). To test for the np 15924 mutation, a Fnu4HI site was created using PCR primers at np 15409–15428 and np 15925–15944 (mismatched G at np 15928). To test for the np 15923 mutation, a Mael site was generated using PCR primers at np 15903–15922 (mismatched C at np 15920) and at np 16527–16557. With this procedure, a number of unaffected controls were screened for the mutations.

The np 15924 mutation was confirmed in our Caucasian LIMM patient and his mother, but it was also detected in approximately 11% (11/103) of Caucasian controls. Thus, while deleterious interactions with other genes cannot be completely excluded, the presence of the np 15924 mutation in the unaffected mother and its polymorphic frequency in the general population strongly suggest that this mutation is a common mtDNA polymorphism and not the primary cause of LIMM.

The np 15923 mutation was not detected in 91 Caucasians, 35 Africans, and 57 Asians. Consequently, the role of this mutation in causing LIMM remains to be clarified.

In conclusion, recent studies have demonstrated both the genetic heterogeneity of LIMM (Zheng et al. 1989; Tanaka et al. 1990; Moraes et al. 1991) and the extensive sequence variation of human mtDNAs (Wallace et al. 1991). Therefore, it is extremely important to ascertain the frequency of a sequence variant in the general population before attributing a pathological role to it.

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Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. Science 232:193–202


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References


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