A healthy woman sought preconceptional genetic counseling regarding a family history of a mitochondrial myopathy in her brother and retinitis pigmentosa (RP) in her two maternal aunts. Several questions were raised: (1) What is the likelihood of a familial mitochondrial condition? (2) What molecular tests or prenatal screening can we offer? (3) How would these tests help assess the likelihood of a familial mitochondrial condition? A mitochondrial mutation previously identified in the brother consisted of a heteroplasmic 2.9 kb deletion. We detected this deletion in the peripheral blood of the brother by PCR amplification of the deletion breakpoint, but not in his mother, the consultand, nor in one of the two aunts affected with RP. Although the molecular analysis was encouraging to the consultand, a familial mitochondrial disorder could not be eliminated with certainty. The pros and cons of prenatal testing for mitochondrial disorders are discussed in general, and as specifically related to this family.

KEY WORDS: mitochondrial disorders; retinitis pigmentosa; genetic counseling.

INTRODUCTION

Mitochondrial disorders are quite diverse in their clinical presentation ranging from isolated ocular disease to diffuse neuromuscular involvement.

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They can be classified into distinct groups based on the phenotypic features, modes of inheritance, and biochemical and pathological information.

Myopathies are associated with the majority of mitochondrial conditions and have varying severity and clinical course (DiMauro et al., 1985, 1987). Some of the more common mitochondrial encephalomyopathies include: myoclonic epilepsy with ragged red fibers (MERRF); mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); Kearns-Sayre syndrome (KSS); and chronic progressive external ophthalmoplegia (CPEO). This group of disorders is characterized morphologically by the hallmark finding of ragged-red fibers (DiMauro et al., 1985; 1987).

Isolated or pure encephalopathies comprise another group of disorders consisting of Leber hereditary optic neuropathy (LHON) (Newman et al., 1991) and neuropathy, ataxia, and retinitis pigmentosa (NARP) (Ortiz et al., 1993). In the United States, autosomal recessive inheritance accounts for up to 84% of RP cases, the remainder being transmitted by autosomal dominant, X-linked recessive or other modes (Boughman et al., 1980). Of note, RP is associated with certain mitochondrial disorders. In several families with NARP, a point mutation has been noted in the mitochondrial DNA (mtDNA) (Puddu et al., 1993; Ortiz et al., 1993). Furthermore, retinal pigmentary changes have been observed commonly in individuals with KSS (Moraes, 1989).

Mitochondria are unique cellular organelles with the primary purpose of energy (ATP) production via oxidative phosphorylation. The five enzyme complexes involved in oxidative phosphorylation are located in the inner mitochondrial membrane and the approximately 65–70 protein membrane units are encoded by over 50 nuclear and 13 mitochondrial genes (Nonaka, 1992). The mtDNA is contained in a small circular chromosome which occurs in hundreds to thousands of copies in each cell. The mitochondrial genome comprises 16,569 bp encoding the 13 structural subunits of the respiratory chain complexes, 22 transfer RNAs and 2 ribosomal RNAs (Anderson et al., 1981; Attardi and Schatz, 1988).

The presence of chromosomes in the mitochondrion leads to the unique inheritance of mitochondrial traits. Mitochondria in the zygote are derived exclusively from the ova, hence the inheritance is entirely from the maternal side (maternal inheritance). This means that mitochondrial traits are passed only through the female to her offspring, and transmission of mitochondrial traits ends with each son (Giles et al., 1980).

In the normal state, mtDNA is homoplasmic, meaning that all mitochondrial chromosomes have an identical sequence (Monnat and Loeb, 1985). In disease states, however, mitochondria can show heteroplasmy, containing two or more populations of mtDNA. Thus, mitochondrial disease mutations can be present in all of the mtDNA (homoplasmic muta-