4

Mitochondrial disorders

Introduction

Mitochondria are present in virtually all eukaryotic cells. They are membrane-bound, cytoplasmic organelles and are primarily involved in oxidative energy metabolism (Figure 1). Mitochondria have their own, self-replicating chromosomes and it was discovered in 1988 that faults in the mitochondrial genes can cause human diseases. Since these initial

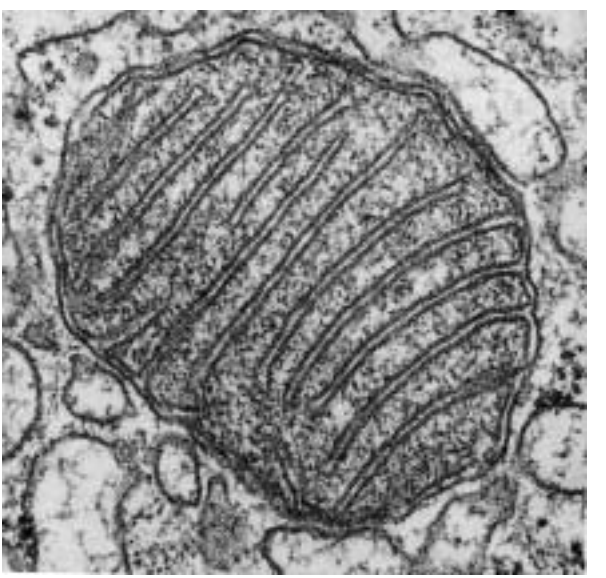

Figure 1. Electron micrograph of a mitochondrion magnified 140000 times.

observations, a large number of defects in mitochondrial DNA (mtDNA) have been reported in association with a broad spectrum of multi-system disorders, usually with prominent neuromuscular disease.

The mitochondrial genome

The human mitochondrial genome consists of a single, circular double-stranded DNA molecule of 16569 base pairs, which has been completely sequenced. It is present in thousands of copies in most cells and in multiple copies per mitochondrion. The genome contains 37 genes: 28 are encoded on one of the strands of DNA and 9 on the other. These genes encode 22 transfer RNAs and two types of ribosomal RNA required for mitochondrial protein synthesis (see Bullied, 1992, in the Background reading section) in addition to 13 proteins, which are involved in cellular oxidative phosphorylation [11]. The mitochondrial genome thus encodes only a small proportion of the proteins required for its specific functions; the bulk of the mitochondrial polypeptides are encoded by nuclear genes and are synthesized on cytoplasmic ribosomes before being imported into the mitochondria. The mitochondrial genome resembles that of a bacterium in that genes have no introns, and that there is a very high percentage of coding DNA (about 93% of the genome is transcribed as opposed to about 3% of the nuclear genome) and a lack of repeated DNA sequences. Consequently, mitochondria are believed to have originated as aerobic bacteria living within bigger cells that could not themselves carry out oxidative phosphorylation [11].

Inheritance of the mitochondrial genome

Human cells usually contain thousands of copies of the double-stranded mtDNA molecule. During zygote formation a sperm cell contributes its nuclear genome but not its mitochondrial genome to the egg cell. Consequently, the fertilized zygote contains only the mitochondria that were present in the unfertilized egg and are maternal in origin. Thus the mitochondrial genome is maternally inherited: males and females both inherit their mitochondria from their mother, and males cannot transmit their mitochondria to subsequent generations (Figure 2). Thus a typical mitochondrially inherited condition can affect both sexes but is passed on only by affected mothers.

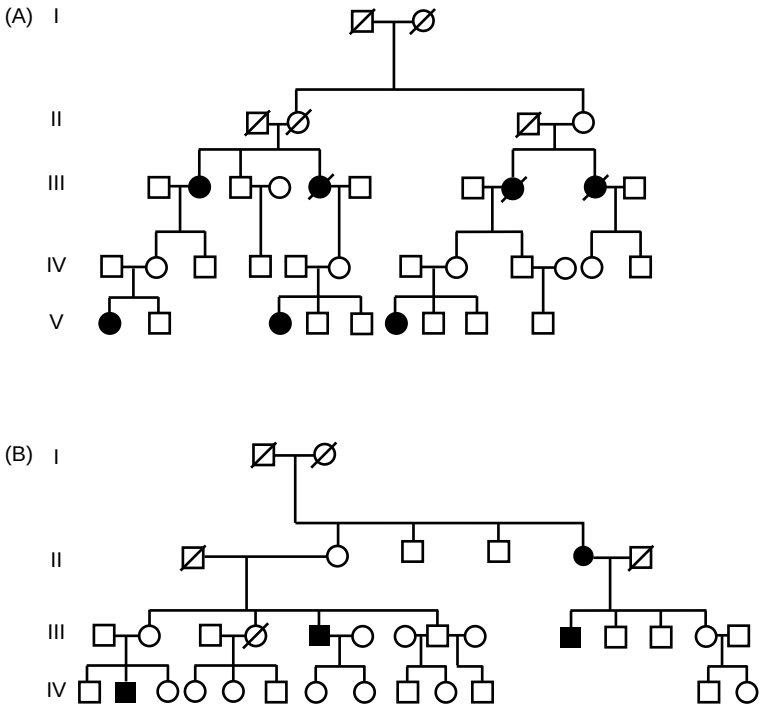

Figure 2. Pedigrees of mitochondrial diseases. (A) A typical pedigree pattern for a mitochondrial disorder; (B) the atypical pattern of Leber's hereditary optic neuropathy, which affects mainly males. Reproduced from Strachen, T. and Read, A. (1996) *Human Molecular Genetics*, Bios Scientific Publishers, Oxford, with permission; ©1996, Bios Scientific Publishers. (See Figure 1 in Chapter 3 for key to symbols used.)

Mitochondrial diseases

In comparison with the nuclear genome, the mitochondrial genome is a small target for mutation (about 1/200000 of the size of the nuclear genome). The proportion of clinical disease due to mutations in the mitochondrial genome might therefore be expected to be extremely low. However, due to the large amounts of non-coding DNA in the nuclear genome, most mutations in the nuclear genome do not cause diseases. In contrast, the bulk of the mitochondrial genome is composed of coding sequence and mutation rates in mitochondrial genes are thought to be about 10 times higher than those in the nuclear genome (probably

because mtDNA replication is more error-prone and the number of replications is much higher). Accordingly, mutation in the mitochondrial genome is a significant contributor to human disease.

Mitochondrial diseases can be caused by the same range of mutations as cause disorders of the nuclear genome. An important aspect of the molecular pathology of mtDNA disorders, however, is whether every mtDNA molecule carries the causative mutation (homoplasmy) or whether the cell contains a mixed population of normal and mutant mitochondria (heteroplasmy). Where heteroplasmy occurs, the disease phenotype may therefore depend on the proportion of abnormal mtDNA in some critical tissue. Also, this proportion can be very different in mother and child because of the random segregation of mtDNA molecules at cell division.

The idea that defects in mitochondrial respiratory chain function might be the basis of disease has been considered for some time but it was not until 1988 that molecular analysis of mtDNA provided the first direct evidence for mtDNA mutations in neurological disorders, notably Leber's hereditary optic neuropathy.

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) is an inherited form of blindness that presents in mid-life and is characterized by rapid bilateral central vision loss due to atrophy of the optic nerve. A major focus of early studies of LHON was the elucidation of the mode of inheritance of the disorder. Perplexing features of the disease were its maternal inheritance pattern and that more males than females were affected (Figure 2). In 1988 it was demonstrated that LHON was caused by mtDNA mutations and it is now known that three primary mutations are present in at least 90% of affected families. These mutations all cause substitutions of highly conserved amino acids. Thus the mtDNA mutations explain the maternal transmission of LHON but the reasons why more males are affected than females remain unknown. Hypotheses for the male bias have included that expression of the phenotype may require the co-inheritance of the mtDNA mutation plus an X-linked recessive mutation, that LHON could be hormonally influenced by androgens or that environmental factors may contribute. In terms of environmental effects, heavy tobacco smoking has been proposed and is still being con-

sidered as one possible factor influencing the penetrance of the condition.

mtDNA mutations in aging

In the course of investigating mtDNA deletions in disease it became apparent that normal individuals can also be heteroplasmic for deleted mtDNA and that the fraction of deleted DNA increases exponentially with age. These observations raised interest in the role played by mtDNA mutations in aging. One hypothesis is that continuous oxidative damage to mtDNA is responsible for an age-related decline in oxidative phosphorylation capacity. Whether a causal relationship exists between mtDNA mutations and aging, however, remains to be established.