



Advances in Gene Analysis of Mitochondrial Cytopathies

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Abstract

Mitochondrial cell disease is a relatively special clinical disease. The occurrence of this disease is due to a defect in the respiratory chain-oxidative phosphate system, which in turn causes damage to the nervous system and muscle tissue of the patient. In this paper, the molecular characteristics of mtRNA are discussed and analyzed accordingly, the concept of mitochondrial cell disease is studied, and the single mutation hotspot gene and detection methods of mtRNA are reviewed, aiming to provide a basis for mitochondrial cell disease in clinical medicine. Provide help and reference for the follow-up diagnosis and treatment of the disease.

Keywords

Mitochondrial cell disease; disease characteristics; monitoring analysis; clinical research

Mitochondrial cell disease presents with a unique clinical manifestation. It arises from a defect in the respiratory chain-oxidative phosphorylation system, leading to damage to the central nervous system and muscle tissue. Recent clinical studies have revealed that mitochondrial cell disease can threaten all organs of the body. However, skeletal muscle and the nervous system have relatively high energy requirements and are highly susceptible; therefore, most patients with mitochondrial defects present with encephalomyopathy as the primary symptom. Mitochondria are crucial organelles in the cytoplasm, found in all eukaryotic cells except for animal cells and mature red blood cells. They are vital sites for oxidation and energy conversion, providing approximately 80% of the energy needed for cellular life processes. Mitochondria also play a vital role in cell growth, metabolism, and human heredity. Problems with mitochondria significantly impact bodily functions and metabolism, necessitating close attention from researchers and the development of effective treatments to ensure the success of mitochondrial cell disease management.

1. Related Concepts of Mitochondrial Cell Diseases

Mitochondrial cell disease is caused by defects in the phosphomonoamine monoxide of the respiratory chain, which leads to the accumulation of damage to the central nervous system and muscle tissue. Mitochondrial cell disease is mainly encephalomyopathy, but the manifestations of this disease are relatively complex and can damage multiple systems in the human body. Common damages include nervous system damage, muscle damage, and cardiac conduction block, which can lead to diabetes or short stature. Laboratory tests [1] on patients can reveal elevated levels of lactic acid in serum and cerebrospinal fluid, and broken red fibers in skeletal muscle cells. Electroencephalography and imaging diagnosis of patients show certain abnormalities. Clinical analysis of patients can still reveal that patients have mitochondrial encephalomyopathy accompanied by lactic acidosis, and some patients may have chronic progressive extraocular muscle paralysis syndrome. At present, when diagnosing mitochondrial diseases in clinical practice, the diagnosis can be made based on the patient's clinical symptoms and disease characteristics. At the same time, it is also necessary to use biochemical tests, electrophysiological and imaging examinations to determine the patient's condition. Recent studies suggest that mutations in mtRNA, nuclear DNA, or both can lead to mitochondrial

dysfunction, resulting in related diseases. Clinical treatment must be tailored to each patient's specific condition. Currently, only symptomatic treatments exist; there is no cure for the disease, necessitating further in-depth research.

2. Molecular Genetic Characteristics Of mtRNA

Mitochondrial DNA is a circular, double-stranded molecule that exists independently of the chromosomes in the cell nucleus. It consists of 16,569 bp and contains 37 gene codes and 2 rRNAs. Twenty-two mitochondrial proteins require tRNAs for assembly, and 13 key subunits of the respiratory chain are involved. Analysis of its molecular genetic characteristics reveals many distinct features, as detailed in the following research.

Genetic code: The mtRNA genetic code differs from that of other mammals. Overall, the mtRNA genetic code has relatively low repetition and higher information density. In the same amount of mtRNA, the total amount of genetic information contained is relatively higher.

Maternal inheritance: During the inheritance of mtRNA, all the information it contains originates from the oocyte. If the mother carries a mutation, the mtRNA will be passed on to all offspring, regardless of sex. However, from a genetic perspective, only female offspring will further inherit this mutated mtRNA. Therefore, mtRNA inheritance exhibits characteristics of maternal inheritance.

Mitosis: During cell division and growth, the proportion of mutated mitochondrial genome changes in daughter cells, and changes in clinical manifestations occur due to related factors during division. This phenomenon can lead to varying degrees of symptoms in patients.

Mutation: Within each cell, the composition and molecular characteristics of mtRNA are completely identical. Once mtRNA mutates, it affects the entire genome; this type of mutation is called homologous mutation. Besides homologous mutations, heterologous mutations are also very common. Heterogeneous mutations refer to the coexistence of common characteristics between wild-type and mutant mtRNAs within the same cell or tissue. Most pathogenic mutations are heterologous variations. Most cells contain thousands of mitochondria, each containing 2-10 copies of mtDNA.

Currently, over 170 mutations of mtRNA have been reported, and more than 1,000 known polymorphisms have been recorded. Non-pathogenic polymorphisms are usually homotypic, while most pathogenic mutations are heterotypic.

3. Routine detection methods for single mutant hotspot genes of mtRNA

3.1 MELES

MELES refers to a syndrome that occurs when patients have mitochondrial disease and lactic acidosis-related symptoms. MELES was first reported by American medical personnel in 1984, and in 1990, relevant researchers analyzed the pathological characteristics of MELES and found that all MELES patients had mtRNA 3243A → G mutation, and 3243A → G mutation was a major factor leading to MELES. This mutation leads to mutation of the *tra* gene, which in turn affects the total amount of protein synthesis in mitochondria, resulting in a reduction in the total amount of protein synthesis in mitochondria, affecting the overall function of mitochondria, and ultimately affecting the function of cells [2]. When testing for this site, relevant researchers usually use polymerase chain reaction restriction fragment length polymorphism to detect it. When conducting the test, researchers first amplify the corresponding fragment of this site and digest it with *ApaI*, while simultaneously using 10% PAGE electrophoresis for identification. When identifying mutation sites, a new restriction enzyme site is often generated. Therefore, electrophoresis analysis shows that there are two bands in the mtRNA of mutant patients, while wild-type patients only have one band. Researchers believe [3] that the mutation rate of this mutation site in muscle is significantly higher than that in blood. In the study, it was also shown that the mutation rate in blood of younger patients was significantly higher than that of adults. This is due to the large differences in the function of tissues and cells in patients. Mutated mtRNAs accumulate in these tissues. This also suggests that when detecting gene mutation levels, researchers should try to select tissues with higher content, such as muscle and hair tissue. Otherwise, false negative results may occur when detecting lymphocytes.

3.2 MERRF

MERRF includes myoclonic epilepsy, cerebellar syndrome and lactic acidosis. In 1988, when relevant clinical researchers analyzed the patients' conditions, they found that the severity of neurological symptoms in MERRF patients

was closely related to the degree of reduction in cytochrome C oxidase activity and NADH dehydrogenase activity in the respiratory chain. When analyzing the conditions of MERRF patients, they further discovered the 8344A →G base substitution in mtRNA in the patient's family [3]. When analyzing this feature, it was found that this mutation is located on the tRNA^{Lys} gene of mtRNA and is closely related to the TUC loop of tRNA^{Lys}. This loop is involved in the connection between tRNA and ribosome, and the final result will affect the synthesis of mitochondrial proteins, resulting in the mitochondrial oxidative phosphorylation function being affected, ultimately leading to MERRF - related multisystem lesions in the patient's body. When analyzing the patients' conditions, a new enzyme cleavage site was found at position 8344, and this enzyme cleavage site can also be used in the diagnosis of this disease. When conducting the test [4], the PCR product of tRNA^{Lys} mutation can be identified by using NaeI to digest the PCR product. The electrophoresis speed is faster than that of the PCR product of wild-type mtRNA. Furthermore, since NaeI restriction enzyme is readily available in clinical practice, this diagnostic method can achieve good results in the diagnosis of MERRF and is worth promoting [5].

4. Discussion and Summary

To more quickly analyze mutations at detection points, researchers targeted Agilent 2100. Research has been conducted on the conventional site mutation detection capabilities of bioanalyzer. This analyzer can simulate the principle of gel electrophoresis and real-time quantitative analysis [6], integrating multiple functions into one. It can perform mixing, warming, reaction, and sample separation and detection. When conducting the test, researchers only need to amplify the extracted DNA using PCR, then digest it with restriction enzymes, and then add it to the reaction well of the analyzer. The instrument can then automatically analyze the data and display the results in the form of gel electrophoresis patterns. After analyzing the images, the staff can confirm the DNA fragments and their size and concentration. In this way, mutations can be detected. Researchers believe that this analyzer can replace the commonly used gel film restriction fragment length analysis method and can perform detailed analysis of mtRNA mutation quantification. It plays an indispensable role in clarifying the patient's condition and carrying out subsequent treatment.

Genetic diagnosis of mitochondrial encephalomyopathy has good clinical application value. For some mitochondrial diseases with subtle symptoms, genetic diagnosis can be applied to make it relatively easy to determine the patient's condition. However, researchers need to optimize the genetic diagnosis method, especially by studying the virulence of mtRNA and its impact on the disease. It is believed that in the future, with the support of biological and clinical medical technologies, the genetic diagnosis and clinical treatment of mitochondrial encephalomyopathy will become even better.

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