Novel *IBA57* Mutations in Two Chinese Patients and Literature Review of Multiple Mitochondrial Dysfunction Syndrome

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Abstract

Multiple mitochondrial dysfunction syndrome (MMDS) refers to a class of mitochondrial diseases caused by nuclear gene mutations, which usually begins in early infancy and is classically characterized by markedly impaired neurological development, generalized muscle weakness, lactic acidosis, and hyperglycinemia, cavitating leukoencephalopathy, respiratory failure, as well as early fatality resulted from dysfunction of energy metabolism in multiple systems. So far, six types of MMDS have been identified based on different genotypes, which are caused by mutations in *NFU1*, *BOLA3*, *IBA57*, *ISCA2*, *ISCA1* and *PMPCB*, respectively. *IBA57* encodes a protein involved in the mitochondrial Fe/S cluster assembly process, which plays a vital role in the activity of multiple mitochondrial enzymes. Herein, detailed clinical investigation of 2 Chinese patients from two unrelated families were described, both of them showed mildly delay in developmental milestone before disease onset, and the initial symptoms were all presented with acute motor and mental retrogression, and brain MRI showed diffused leukoencephalopathy with cavities, dysplasia of corpus callosum and cerebral atrophy. Exome sequencing revealed three *IBA57* mutations, one shared variant (c.286T > C) has been previously reported, the remaining two (c.189delC and c.580A > G) are novel. To enhance the understanding of this rare disease, we further made a literature review about the current progress in clinical, genetic and treatment of the disorder. Due to the rapid progress of MMDS, early awareness is crucial to prompt and proper administration, as well as genetic counseling.

Introduction

Mitochondrial encephalopathies represent a heterogeneous group of neurodegenerative disorders related to a defect in energy metabolism, which can be associated with progressive leukoencephalopathy in infant patients (Uziel et al. 2011). A new class of mitochondrial diseases presenting with white matter abnormalities and multiple respiratory chain disorders has been defined as multiple mitochondrial dysfunction syndrome (MMDS) (Lill and Freibert 2020). Clinically, the disease onset usually occurred in early infancy, with main symptoms of motor regression, feeding problems, muscle weakness, spastic paralysis, arthrogryposis, seizures, cognitive impairment, severe lactic acidosis and hyperglycinemia. Brain imaging showed progressive and diffuse vacuolar leukoencephalopathy (Maio and Rouault 2020; Wachnowsky et al. 2018). To date, six types of MMDS have been classified, namely MMDS1-MMDS6, which are attributed to the mutations in *NFU1*, *BOLA3*, *IBA57*, *ISCA2*, *ISCA1*, and *PMPCB*, respectively (Ajit Bolar et al. 2013; Al-Hassnan et al. 2015; Cameron et al. 2011; Shukla et al. 2017; Vögtle et al. 2018). Except for the *PMPCB*, which encodes the catalytic subunit of the mitochondrial processing protease, all the remaining genes are encoding a protein implicated in the mitochondrial iron-sulfur clusters (ISCs) assembly process (Lill and Freibert 2020). Protein-bound ISCs are among the most structurally and functionally versatile cofactors, with varied functions that include electron transport, regulation of gene expression, substrate binding and activation, radical generation, and DNA repair (Wachnowsky et al. 2018). The protein encoded by *IBA57* is a late-acting component of the Fe-S cluster machinery and assists the insertion of the (4Fe-4S) clusters in recipient protein or enzymes (Gourdoupis et al. 2018). In 2013, mutations in *IBA57* were first identified in two consanguineous Moroccan siblings with multiple mitochondrial dysfunction syndrome-3 (MMDS3) (Ajit Bolar et al. 2013). Since then, more additional cases have been reported, while the exact prevalence of the disease remains unclear. The disease is rapidly progressive, leading to early death. Due to the extreme rarity and high variability, the disorder can be easily misdiagnosed or delayed. Herein, two Chinese MMDS patients with novel *IBA57* mutations were described and a comprehensive literature review of MMDS was made to summarize the current progress in clinical, genetic and treatment to enhance the early recognition, and to shed light on the pathogenic and therapeutic study for this disorder.

Methods

Patients

Two individuals from two unrelated families were included based on clinical evaluation and radiologic examinations. Genomic DNA was extracted using the standardized phenol/chloroform extraction protocol. Exome sequencing was performed on the proband of each family. This study was approved by the local ethics committee. Written informed consent, which also included the consent for the publication of medical information, was obtained from the guardians.

Exome sequencing and data analysis

Exome sequencing was performed using Agilent SureSelect v6 reagents for capturing exons and Illumina HiSeq X Ten platform for sequencing. The variants were analyzed as follows: The 1000 Genomes Project (<http://www.internationalgenome.org>), dbSNP (<http://www.ncbi.nlm.nih.gov/projects/SNP>), and Exome Aggregation Consortium (ExAC, <http://exac.broadinstitute.org/>) were as references to exclude all variants present in the population at greater than 5% frequency. In addition, Mutationtaster (<http://www.mutationtaster.org>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2>) and SIFT (<http://sift.jcvi.org>) were used to predict the pathogenicity of the nucleotide and amino acid conservation. Then the pathogenic of the variant was interpreted and classified following the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines (Richards et al. 2015). Sanger sequence, and co-segregation analysis were further confirmed among family members.

Results

Clinical findings

Clinical profiles of the two cases are summarized in Table 1. All patients were children of non-consanguineous parents. Both of them showed mildly delay in developmental milestone before disease onset, and the initial symptoms were all presented with acute motor and mental retrogression, and brain MRI found diffused leukoencephalopathy with cavities, dysplasia of corpus callosum and cerebral atrophy (Fig. 1). Serum amino acid, acylcarnitine and acetone succinate levels were normal based on tandem mass spectrometry. Different from patient 1, patient 2 showed marked slow reaction and lost acquired skills due to repeated respiratory tract infections, these episodes induced aggravated psychomotor regression with hypertonia, limbs rigid, and trunk opisthotonos. Due to the rapid progress, patient 2 had died in the following two months after the medical visit.

Table 1
Clinical and genetic aspects of the patients

Patient no.	Gender /Age	Age of onset	Preceding infection	Initial symptoms	Physical examination	EEG	Brain MRI	<i>IBA57</i> mutations/ ACMG classification
Patient 1	M/10 mon	6 mon	No	Motor regression (can't crawl and sit alone, and lost head control), stiff limbs.	Muscular hypertonia of extremities, positive pyramidal sign.	Normal	Patchy leukoencephalopathy, dysplasia of corpus callosum, and cerebral atrophy.	c.189delC (p.D65Tfs*7) "Pathogenic" c.286T > C (p.Y96H) "Pathogenic"
Patient 2	F/1 y 1 mon	1 y	Yes	Psychomotor regression (fatigue, poor activity, drowsy, slow response, less talk), involuntary movement.	Regular involuntary twitch of limbs, muscle weakness, spasticity, opisthotonus.	Not done	Diffused leukoencephalopathy with cavities and diffusion restriction, dysplasia of corpus callosum, and cerebral atrophy.	c.580A > G (p.M194V) "Likely Pathogenic" c.286T > C (p.Y96H) "Pathogenic"
M: male, F: Female. mon: month; y: year; EEG: Electroencephalogram;								
ACMG: American College of Medical Genetics and Genomics Standards and Guidelines.								

Genetic findings

Patient 1 carried the compound heterozygous *IBA57* mutations with c.189delC (p.D65Tfs*7) and c.286T > C (p.Y96H), which were transmitted from his heterozygous father and mother, respectively (Fig. 1A). Patient 2 had the compound heterozygous *IBA57* mutations with c.580A > G (p.M194V) and c.286T > C (p.Y96H), which came from her asymptomatic father and mother, respectively (Fig. 1B). The shared variant c.286T > C has been previously documented, while both c.189delC and c.580A > G are

novel, which were not found in 1000Genomes Project, dbSNP, and ExAC database, and Mutationtaster predicted the mutations to be disease-causing.

Discussion

Our present study described two cases with a genetically confirmed diagnosis of MMDS3. Both two individuals displayed acute and progressive psychomotor regression with a brain MRI profile of diffuse vacuolar leukoencephalopathy. MMDS is a rare mitochondrial disorder which has a broad phenotypic spectrum with a heterogeneous course, ranging from fatal early-onset to acute and severe psychomotor regression after the first year of life, followed by recovery of symptom control and longer survival (Debray et al. 2015; Hamanaka et al. 2018; Torraco et al. 2017). Prenatal ultrasound had found intra-uterine dysplasia in two siblings with homozygous *IBA57* mutation (Ajit Bolar et al. 2013). In infantile cases, the average onset age was 8 months (4–18 months), with initial symptoms of motor regression or feeding difficulties. Encephalopathy, myopathy, vision impairment, seizures, and respiratory failure can be presented as disease progressed. Symptomatic fluctuation with transient stability or turn to severe phenotypes which are usually associated with early fatal or debilitating conditions have been described (Alfadhel 2019; Ishiyama et al. 2017; Liu et al. 2018; Uzunhan et al. 2020). In line with the previous report, the patient 2 in our study suffered from a recurrent preceding infection which may induce or aggravate the symptoms, this may be associated with the increased level of lactate (Liu et al. 2018). The milder phenotype which is presented with slowly progressive neurological symptoms characterized by spastic paraparesis, optic atrophy, and peripheral neuropathy is more common in childhood or more older cases (Lossos et al. 2015). MMDS often show the similar biochemical features with lactic acidosis in serum and cerebrospinal fluid, and hyperglycinemia (Ajit Bolar et al. 2013; Nizon et al. 2014; Toldo et al. 2018). Moreover, deficient activity and expression of the respiratory chain complexes I and II, and a decrease in mitochondrial protein lipoylation can be detected in the affected patients (Ishiyama et al. 2017; Lill and Freibert 2020). Brain MRI showed diffuse leukoencephalopathy that completely implicated in the white matter around the lateral ventricle, splenium of the corpus callosum, and posterior limb of the internal capsule. An extension or progression of infratentorial white matter involvement in the cerebellum, brainstem, or cervical spinal cord were frequently found in late MRI. In both the peak and recovery stages, cavitating lesions could be observed (Al-Hassnan et al. 2015; Ishiyama et al. 2017; Liu et al. 2018; Torraco et al. 2017). Cavitating leukoencephalopathies was described as irregular, asymmetric, patchy areas of white matter abnormalities that evolve to develop cystic degeneration, which indicates a high clinical diagnostic significance in patients with mitochondrial defects (Naidu et al. 2005). What's more, a variable degree of cerebral atrophy was also found (Ajit Bolar et al. 2013; Vögtle et al. 2018).

So far, based on different genotypes, mutations in *NFU1*, *BOLA3*, *IBA57*, *ISCA2*, *ISCA1* and *PMPCB* have been identified lead to MMDS types 1 to 6, respectively. All the first five genes play a vital role in the biogenesis of mitochondrial (4Fe–4S) cluster-binding proteins (Lill and Freibert 2020). Located in mitochondria, cytosol, endoplasmic reticulum and nucleus, ISCs contribute to respiration, iron homeostasis, heme biosynthesis, oxidative phosphorylation, citric acid cycle, and DNA repair, among regulation of other pathways (Lill 2009; Maio and Rouault 2020). Assembly of ISCs usually begins in mitochondria, where ISCs work as essential protein cofactors of numerous key mitochondrial enzymes, including respiratory chain complexes I and II, mitochondrial aconitase and lipoic acid synthase (Lill and Freibert 2020; Stehling and Lill 2013). At present, there are approximately 20 different proteins involved in the mitochondrial ISC assembly machinery, which is mainly composed of three consecutive steps: firstly, the de novo synthesis of a (2Fe-2S) cluster on the scaffold protein; secondly, chaperone assisted release of the Fe-S cluster and mitochondrial trafficking; finally, the conversion of (2Fe-2S) cluster into a (4Fe-4S) type by proteins ISCA1, ISCA2, and IBA57, then followed by transfer and insertion into target recipient apoproteins either directly or through some specific proteins, like NFU1, NUBPL, and BOLA3 (Alfadhel et al. 2017). Therefore, the proteins ISCA1, ISCA2, IBA57, NFU1, IND1, and BOLA are crucial late-acting ISC factors required for (4Fe-4S) protein maturation and dedicated insertion (Lill and Freibert 2020). Mutations in late-acting ISC genes are usually associated with neurological impairments, respiratory deficiencies, and metabolism disturbance. However, the severity of functional defects caused by different mutations within MMDS1-5 genes differs dramatically, which may have great relevance with the extent of biochemical alterations (Lebigot et al. 2017). Mutations in *PMPCB*, which encoding the catalytic subunit of the essential mitochondrial processing protease, have been found in patients presented with leigh-like neurodegeneration in childhood with prominent cerebellar atrophy. Functional study showed that biallelic *PMPCB* mutations cause defects in mitochondrial processing protease proteolytic activity accompanied by dysregulation of ISC biogenesis (Vögtle et al. 2018).

IBA57 located in 1q42.13, contains 3 exons and encodes the mitochondrial Fe-S protein assembly factor, which has a globular shape and consists of three tightly packed domains arranged in a rigid ring-like structure, and forms a heterodimeric complex with ISCA2 upon (2Fe-2S) cluster binding (Gourdoupis et al. 2018; Nasta et al. 2019). The clinical presentations of *IBA57*-mutated MMDS can range from severe early fatality to childhood or adolescent-onset spastic paraplegia, optic atrophy, neuropathy or asymptomatic cavitating leukoencephalopathy (Ajit Bolar et al. 2013; Hamanaka et al. 2018; Lossos et al. 2015). Moreover, the highly clinical variability even among siblings with identical genotypes, pointing to the possibility of significant interaction among genetic, epigenetic, and environmental factors (Hamanaka et al. 2018). Up to now, total 28 patients with *IBA57*-mutated MMDS from 25 different families (including the present cases) have been described, including 16 females and 12 males, the average age of onset was 10 months (range from prenatal to 22 months). About 28 *IBA57* mutations have been identified, including missense, nonsense, and frameshift variants (Ajit Bolar et al. 2013; Debray et al. 2015; Hamanaka et al. 2018; Ishiyama et al. 2017; Liu et al. 2018; Torraco et al. 2017) (Fig. 2B). It is noteworthy that including present study, almost all the Chinese patients carried the same mutation c.286T > C, which might show a founder mutation effect in Chinese sufferers (Liu et al. 2018). Cellular functional assays showed that mutation leads to substantial decreases in IBA57 protein expression, and partial functional impairment, which mainly resulted from its proteolytic degradation (Ajit Bolar et al. 2013). Moreover, *IBA57* mutations resulted in defect of respiratory chain complexes, and deficiency of lipoic acid synthetase through aberrant NFU1 function (Debray et al. 2015; Ishiyama et al. 2017). All mutations in our study were highly conservative in the related species (Fig. 2A). The mutation c.189delC caused frame shift and a premature termination codon, resulting in abnormal truncated protein, and both c.189delC and c.580A > G were located in the helix structure, thus we speculated the novel mutations in the present study have an impaired function. Further functional assays are needed to confirm the influences.

Due to the highly heterogeneous clinical spectrum of mitochondrial diseases, when concurrence of neurodegeneration, optic atrophy, and leukoencephalopathy, many other diseases such as different types of MMDS, Leigh syndrome, Leber's hereditary optic neuropathy, vanishing white matter disease, as well as Kearns–Sayre syndrome can also be considered (Ashrafi et al. 2020; Lerman-Sagie et al. 2005). Thus, it's appropriate to perform the molecular genetic analysis for reliable diagnosis, and further make a MMDS genotype. The current overall administration of MMDS is symptomatic and supportive treatment, and exercise, nutrition and supplements, social care, and mental wellbeing were used as a framework to guide the disease management (Long et al. 2021; Parikh et al. 2017). Previous studies have suggested that cocktail therapy (a mix of supplements and vitamins) for mitochondrial diseases may have a certain effect (Tarnopolsky 2008). Since the rapidly progressive course and high mortality of the disease, earlier recognition and diagnosis with multidisciplinary collaboration is much more crucial to provide timely intervention and accurate genetic counseling.

Conclusions

In conclusion, we reported two Chinese MMDS patients with novel *IBA57* mutations. MMDS is a progressive neurodegeneration with a poor prognosis. By studying and reviewing the disorder, we summarized the phenotype, expanded the genotype spectrum to enhance learning and awareness-raising of MMDS. Early observation is crucial to prompt the timely administration, as well as genetic counseling. However, we are still far from a comprehensive picture of the detailed molecular pathogenesis of the disease. Further deep combination of structural, biochemical, cell biological, genetic, and clinical study is warranted to clarify the molecular basis of the disease and lead to potential therapeutic approaches.

Declarations

Conflict of interests

All authors in this study have no conflict of interest.

Data availability

The raw data are available upon reasonable request.

Code availability

Not applicable

Authors' contributions

Feixia Zhan: Data acquisition, analysis and interpretation of data, and drafted the manuscript for intellectual content.

Xiaoli Liu: Funding, data acquisition, interpreted the data, and revised the manuscript for intellectual content.

Ruilong Ni: Data acquisition.

Tiaotiao Liu: Data acquisition.

Yuwen Cao: Data acquisition.

Jingying Wu: Data acquisition.

Wotu Tian: Data acquisition.

Xinghua Luan: Data acquisition, analysis and interpretation of data, and revised the manuscript for intellectual content.

Li Cao: Funding, study design and conceptualization, analysis and interpretation of data, manuscript revision, and supervision.

Ethics approval

This study was approved by the local ethics committee. Written informed consent, which also included the consent for the publication of medical information, was obtained from the guardians.

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Figures

Figure 2

A. The mutations located in the highly-conserved region of proteins. B. Diagram of all IBA57 mutations (NM_001010867). The novel mutations detected in this paper are marked in red. The previously reported homozygous mutations are marked in blue, and heterozygous mutations in black.