Review

The non-syndromic clinical spectrums of mtDNA 3243A>G mutation

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ABSTRACT

الطفرة m.3243A >G في جين الحمض النووي الريبي (MT-TL1) من الحمض النووي للميتوكوندريا هي الطفرة المرضية الأكثر انتشارًا والتي لها اختلافات نمطية رئيسية. يشمل النمط الظاهري السريري أعضاء مختلفة مثل الدماغ والأعصاب وعضلات الهيكل العظمي والقلب ونظام الغدد الصماء والجهاز الهضمي والجلد. تتوافق بعض الأنماط الظاهرية مع متلازمات راسخة، بينما تظهر معظم الأعراض بشكل فردي أو مصاحبة لمتلازمات أخرى، مما يجعل التعرف عليها أمرًا صعبًا. علاوة على ذلك، تم إحراز بعض التقدم في المظاهر القلبية وكذلك المضاعفات أثناء الحمل وفترة ما حول الولادة. تقدم هذه المقالة مراجعة منهجية للأنماط الظاهرية غير المتلازمية وآخر التطورات في طفرة m.3243A >G .

The m.3243A >G mutation in the tRNA Leu (UUR) gene (MT-TL1) of the mitochondrial DNA is the most widely seen pathogenic mtDNA mutation which has major phenotypic variations. The clinical phenotype involves various organs such as the brain and nerves, skeletal muscles, heart, endocrine system, gastrointestinal tract, and skin. Some phenotypes conform to well established syndromes, while most of the symptoms appear individually or concomitant to other syndromes, making identification difficult. Furthermore, some progress has been made on cardiac manifestations as well as complications during pregnancy and perinatal period. This article provides a systematic review of the non-syndromic phenotypes and latest developments in m.3243A>G mutation.

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Mitochondrial disease is a group of genetic metabolic diseases involving multiple systems related to mitochondrial DNA (mtDNA) or/and nuclear DNA (nDNA) mutations.[1,2] Mitochondrial disease is fairly common. The overall incidence of mitochondrial diseases related to mtDNA and nDNA mutations reported in the United Kingdom is about one in 4800 people. The mtDNA mutations conform to material inheritance while the nDNA mutation conform to Mendelian inheritance.[2] The m.3243A> G mutation in the tRNA Leu (UUR) gene (MT-TL1) is among the most common pathogenic mtDNA point mutation.[3-5] The general prevalence of the m.3243A>G mutation in the population is about one in 400 people,[4] but the reported incidence of manifestations in patients due to this mutation is only about 3.5 per 100000,[3] indicating low penetrance of m.3243A> G mutation.

The phenotypes of m.3243A>G mutation are in great variety in manifestations and severity, ranging from fatal to asymptomatic. The affected tissues or organs include the nervous system, skeletal muscles, heart muscles, ears, eyes, kidneys, liver and endocrine system. Some phenotypes conform to well established syndromes, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like attack (MELAS) syndrome, Leigh syndrome (LS), Keams- Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), neurogenic weakness, ataxia, and retinitis pigmentosa (NARP), and Maternally Inherited Diabetes and Deafness (MIDD), etc.,[6] which can be easily defined (**Table 1**). However, most of the patients do not develop the complete manifestations of any syndrome, including hypertrophic cardiomyopathy, migraine, deafness, peripheral neuropathy, myopathy, pancreatitis, etc.[7] These symptoms appear individually or concomitant to other syndromes, which are ignored as common diseases (**Table 1**). Furthermore, some progress has been made on cardiac manifestations,[3,8] as well as complications during pregnancy and perinatal period.[9] This article provides a review of the non-syndromic phenotypes and latest developments in m.3243A> G mutation.

Neurological and mental impairment. Psychiatric disorders. Mental disorders including depression, personality disorders, schizophrenia, and panic disorders in m.3243A>G mutation patients were first reported in 1997,[10] and have been rapidly increasing and becoming more specific in recent years. Verhaak et al[11] studied 122 patients carrying m.3243A > G mutation and found that 37% of them exhibited mental health problems, such as depression and anxiety, which was significantly more than healthy normal people. A study comprising 202 m.3243A>G mutation patients from Newcastle (UK) found that half of the patients had mild psychiatric symptoms such as reactive depression, while 19% had moderate to severe psychiatric symptoms. The Newcastle study also proposed a hypothesis that mental illness may be related to abnormal brain function because they found that 22 out of 202 patients had both encephalopathy and mental disorders, and 19 patients had evidence of encephalopathy before the onset of psychiatric symptoms.[12] The heritability of psychiatric problems in m.3243A>G muation patients is larger than that of major depression in the population, which is estimated to be 31-42%.[13]

Headache and migraine. Migraine is defined as recurrent, mostly unilateral, moderate to severe, and pulsatile headaches, with an annual incidence of about 12% in the general adult population.[14] The prevalence of migraine happened in patients with m.3243A>G mutation varies from 29-58%,[15,16] which is higher than that of the general population. Two recent research from Europe have focused on headaches in mitochondrial disease. Tiehuis et al[17] has reported 56 % headache out of 62 mitochondrial disease patients, of which 48% met the ICHD-3 Migraine-criteria. Report from the UK Newcastle group showed that 66.7% of patients had primary neuropathic chronic pain. The m.3243A > G MTTL1 mutation patients showed higher pain severity and higher possibility of neuropathic pain compared to other causative mtDNA and nuclear DNA mutations.[18] Smeitink J et al[19] proposed that the disentangling of the angiopathy paradigm, ROS-redox metabolism, or ROS-induced inflammation pathways might be the mechanisms of mitochondrial migraine. In the study from The Newcastle Group,[12] migraine related to m.3243A>G mutation showed a moderate correlation with gastrointestinal dysfunction (r~0.45). Thus, they hypothesized that a similar biological mechanism underlying these two conditions may be involved in the genes of smooth muscle function.[12]

Other neurological symptoms. Multiple peripheral neuropathy is very common in m.3243A>G mutation patients.[20] The clinical manifestations range from subclinical peripheral nerve damage to severe peripheral neuropathy, which can be one of the multiple system damages or exist alone. Cerebellar ataxia appears in about 66% patients with m.3243A>G mutation, which indicated moderate to large possibility of heritability in-line with migraine, psychiatric involvement, and hearing impairment.[12] Progressive cognitive regression, brain volume shrinkage, and extensive white matter lesions are also important features of syndromic and non-syndromic patients with m.3243A> G mutations.[21,22]

Mitochondrial myopathy. The main manifestations of mitochondrial muscle involvement are exercise intolerance, muscle weakness, myalgia and muscle atrophy.[23] Muscle weakness is a common symptom of various clinical syndromes such as MELAS, CPEO, KSS, MERRF, etc. Occasionally, it manifests as isolated myopathy.[15] The majority of mitochondrial myopathies are chronic. However in some conditions, it can manifest as acute onset muscle pain, muscle weakness, palpitations, dyspnea, and lactate acidosis.[24,25] This life-threatening condition can be trigged by strenuous exercise, fatigue, drinking, sedative drugs, etc. Zhou et al.[24] reported three cases of severe mitochondrial myopathy, of which one case had cardiac arrest and died after the first attack, while two cases survived the metabolic crisis and remained in stable condition with long-term medication. Pan et al[25] reported five patients with respiratory failure and lactate acidosis caused by m.3243A>G mutation triggered by sedative drugs.

Endocrine system involvement. The common endocrine system involvements in m.3243A>G mutation include the pancreas, thyroid, parathyroid, pituitary, and gonads.[26] In an observational study of 35 patients carrying m.3243A>G mutation, the incidence of endocrine-related manifestations were as follows: 18 (51.4%) cases with diabetes, 8 (22.9%) cases of short stature, 8 (22.9%) cases with elevated lactate, 3 (8.6%) cases with elevated pyruvate and 2 (5.7%) cases with hypothyroidism.[7] The most common disease of the endocrine system is mitochondrial diabetes, which accounts for 0.5-2.8% of diabetes mellitus.[27] About 85% of mitochondrial-derived diabetes can be attributed to m.3243A> G mutations,[27,28] which is often concomitant with low body mass index. Short

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Table 1 - Clinical phenotypes due to m.3243A>G mutation in the $tRNA^{Leu}$ gene (UUR).

	Syndromic phenotypes	Non-syndromic symptoms
Neurological disorders	MELAS, LS, MELAS/LS, KSS, CPEO, MERRF, NARP,	Migraine, cerebella ataxia, seizures, autism, depression, anxiety, mental retardation, tension-type cluster headaches, polyneuropathy, myelopathy, calcification of basal ganglia
Muscle disorders	CPEO, MERRF	exercise intolerance, muscle atrophy, myalgia, muscle cramp, hypercreatine kinase
Cardiovascular disorders	SADS, WPW syndrome,	Hypertrophic cardiomyopathy, dilated cardiomyopathy, conduction block, ventricular extrasystoles, supraventricular tachycardia, atrial fibrillation, regurgitation of various valves
Endocrine disorders	MIDD	Diabetes, growth hormone deficiency, hyperparathyroidism, hypoparathyroidism hypogonadism, hypothyroidism
Ocular impairment	NARP, CPEO	Pigmentary retinopathy, cortical blindness, visual field defect, night blindness, cataract, macular dystrophy and optic atrophy
Otolaryngologic impairment	MIDD	sensorineural hearing loss; bilateral vestibular loss
Digestive system	IPO	Vomiting, diarrhea, constipation, acute pancreatitis, celiac disease
Kidney impairment	none	renal failure, nephropathy, maternal hereditary recurrent kidney stone, renal tubular acidosis
Pregnancy and delivery	none	Miscarriage, gestational diabetes, premature delivery, intrauterine growth retardation, preeclampsia, cesarean section
Others	none	short statures, stuttering, hypertriglyceridaemia, hair loss, Hypertrichosis, Dark complexion

MELAS - mitochondrial encephalomyopathy, lactic acidosis, stroke-like attack; LS - Leigh syndrome; KSS - Keams- Sayre syndrome; CPEO - chronic progressive external ophthalmoplegia; NARP - neurogenic weakness, ataxia, and retinitis pigmentosa; MERRF - myoclonic epilepsy and ragged-red fiber disease; SADS - sudden adult death syndrome; WPW - Wolff-Parkinson-White syndrome; MIDD - Maternally Inherited Diabetes and Deafness; IPO - Intestinal pseudo-obstruction

stature is another common feature in m.3243A> G mutation carriers, which may be partially related to growth hormone deficiency.[7]

Cardiovascular involvement. Cardiac manifestations in m.3243A>G mutation patients are common and serious. The presentations include hypertrophic or dilated cardiomyopathy, heart failure, conduction block, Wolff-Parkinson-White (WPW) syndrome,[29,30] and ventricular or supraventricular tachycardia. Malfatti et al. analyzed cardiac abnormalities in 41 individuals carrying m.3243A>G mutation, of which 18 patients had left ventricular hypertrophy and dysfunction, while seven patients had WPW syndrome.[30] They indicated that left ventricular hypertrophy independently predicted adverse cardiac events.[30] Wahbi et al.[31] studied predictors of severe adverse cardiac events in 260 mitochondrial disease patients, including 64 cases with m.3243A>G mutations. They found that patients with m.3243A>G point mutation or single large-scale deletions are mostly vulnerable to major cardiac adverse events. The main causes of death were heart failure and cardiac arrest. In recent years, sudden adult death syndrome (SADS) in asymptomatic patients has also been recognized as a clinical entity in m.3243A>G mutation.[3] Thus, it is important to conduct regular cardiac arrhythmia surveillance and cardiac echo in m.3243A>G mutation carriers.

Visual and hearing impairment. The most common ophthalmological manifestation due to m.3243A> G mutation is pigmented retinopathy, which can cause symptoms such as vision loss, visual field defect, night blindness, etc.[32] Cortical blindness is also common when mitochondrial encephalopathy involves the visual cortex or posterior visual pathway in MELAS syndrome.[32,33] The ocular complications of mitochondrial diabetes are cataracts, macular degeneration, or optic atrophy.[28] This is different from type 1 and type 2 diabetes complications, which is primarily diabetic retinopathy.[29] A study found that approximately 86% of MIDD patients exhibited macular dystrophy and pigmented retinopathy.[27]

Hearing impairment is one of the most common clinical features of mitochondrial disease, accounting for 62.8% of m.3243A>G mutation carriers.[7] The Newcastle group studied 238 m.3243A>G mutation patients found that up to 81% of patients had hearing impairment.[12] Hearing impairment may present alone

or as a symptom of syndromic MIDD and MELAS syndrome. The types of hearing impairment are mainly sensorineural hearing loss.[34] Peripheral vestibular functional impairment was also reported.[32,35] Therefore, combining visual and hearing impairments can be a useful clinical indicator for MT-TL1 m.3243A> G mutation diagnosis.[7]

Gastrointestinal involvement. Gastrointestinal symptoms include vomiting, diarrhea, constipation, and gastrointestinal discomfort. Most of them are considered non-specific symptoms of mitochondrial disease. Vomiting and headache often present as the first symptom in MELAS syndrome patients and are recurrent.[36] In the study of the Newcastle group, 76% of patients with m.3243A> G mutations had gastrointestinal symptoms, with the frequency secondary to deafness.[12] In a study of 190 MELAS patients in China, the incidence of vomiting was 65.58%.[37] Intestinal pseudo-obstruction (IPO) is a severe but easily ignored symptom in mitochondrial disease. The IPO is a clinical syndrome, which includes long-term nausea, vomiting, abdominal pain, and significant abdominal distension associated with severe constipation, imaging shows intestinal loop dilation, with the absence of any lesion occluding the gut.[38] The presentation of IPO is often an indicator of poor prognosis.[23] In a study involving 226 patients with m.3243A> G mutations, 30 cases had IPO, of which 14 cases had concurrent IPO and MELAS syndrome.[39] Rare cases such as IPO with diabetes and recurrent pancreatitis have also been reported.[40]

Pregnancy and delivery. Women carrying mtDNA mutations are vulnerable to obstetric complications such as miscarriage, gestational diabetes, premature delivery, intrauterine growth retardation, and preeclampsia than normal women and nDNA mutation carriers.[41,42] Feeney et al analyzed the complications of 67 pregnant women and found that pregnant women with m.3243A> G mutations had a higher risk of gestational diabetes, cesarean section and premature delivery than those with other types of mitochondrial diseases.[9] Of the 67 live births, the premature birth rate was as high as 53.3%, and extremely premature babies (<32 weeks old) accounted for 12.9%. De Laat et al[5] analyzed 46 pregnant women with m.3243A> G mutation, including 98 pregnancies. The obstetric complications were preterm birth (25.3%), preeclampsia (12%), and gestational diabetes (11%). These results suggested that pregnant women carrying m.3243A>G mutations have a very high risk of perinatal complications, miscarriage, and premature delivery, which require close monitoring for genetic counseling and maternal care.

Heteropasmy and phenotype variety. The reason for phenotypes variety of m.3243A>G mutation is not fully clear to date. Heteroplasmy level (a state that wild-type and mutant mtDNA co-exist in the same cell at different ratio) contribute to the phenotype properties.[43] Higher heteroplasmy level often present more severe clinical phenotypes such as seizure, MELAS, myopathy and related to younger onset age. While lower heteroplasmy level were more likely to suffer from hearing loss, decreased vision, and gastrointestinal disturbance.[44,45] Phenotype is also modulated by nuclear gene and environmental factors. Recent report based 238 patients carrying 3243A>G mutation from New Castle found that nuclear factor may contribute larger than other known factors such as age, gender, and heteroplasmy.[12]

Disease course and prognosis. The course and prognosis of mitochondrial disease due to m.3243A>G mutation are affected by many factors. Higher heteroplasmy level, nervous system involvement, presentation of IPO are closely related to poor prognosis.[23,46] Recent 6 year follow up on 151 m.3243A>G mutation carriers showed that slowly progression of clinical score by 0.47 point increase of Newcastle Mitochondrial Disease Adult Scale (NMDAS) score per year.[47] Sun et al.[48] analyzed 64 patients with MELAS syndrome and found that the medium survival time was 12 years. The medium survival time of patients with onset before 14 years old was eight years, which was significantly shorter than those with onset after sexual maturity (21 years). In adults, the most common reason of death included sudden cardiac death, epilepticus status, stroke-like attacks, aspiration failure, paralytic intestinal obstruction, sepsis, and metabolic acidosis.[49,50]

Conclusion. The phenotype of mtDNA m.3243A>G mutation is highly heterogeneous. It is crucial to identify key symptoms, such as repeated vomiting, early onset diabetes, deafness, family history of miscarriage and multi-system involvement, in order to facilitate an earlier diagnosis. Moreover, screening asymptomatic carriers is particularly important to prevent sudden adult death syndrome. Furthermore, high pregnancy complications in m.3243A>G mutation cases poses great challenges in obstetrics and gynecology, pediatrics, and genetic counseling.

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