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The role of mitochondrial DNA mutations in coronary heart disease

Y. DING[1], B.-B. GAO[2], J.-Y. HUANG[2]

[1]Central Laboratory, Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China
[2]Department of Cardiology, Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Abstract. – Coronary heart disease (CHD) is a leading cause of death worldwide. It is a multifactorial disorder resulting from harmful interactions between genetic and environmental factors. Due to the central role of mitochondria in cellular energy homeostasis, there is growing evidence supporting the role of damage to mitochondrial components such as mitochondrial DNA (mtDNA) in the pathogenesis and progression of CHD. However, the molecular mechanisms linking mtDNA and CHD remains unknown. In terms of mutations, we found that mitochondrial transfer RNA (mt-tRNA) genes are hot spots for pathogenic mutations associated with CHD. These mutations cause structural and functional changes in tRNA; specifically, failure of tRNA metabolism may impair mitochondrial protein synthesis and lead to mitochondrial dysfunction responsible for CHD. This review provides a detailed summary of the mtDNA mutations that have been reported to be associated with CHD and further discusses the possible molecular mechanisms behind the involvement of these mtDNA mutations in CHD.

Key Words:
CHD, mtDNA, Mutations, mt-tRNA metabolism, Mitochondrial dysfunction

Introduction

Coronary heart disease (CHD), also known as coronary artery disease (CAD), is one of the most common causes of human deaths worldwide[1]. It has been estimated that, annually, CHD annually results in 502,000 deaths in the US and more than 700,000 deaths in China[2,3]. The pathogenesis of CHD remains largely undetermined, although it has been found that hypertension, hyperlipidemia, smoking and family history are risk factors for this disease[4]. At the molecular level, it has been suggested that CHD is a complex disorder that can be caused by a single gene or a multifactorial condition resulting from interactions between environmental and inherited risk factors[5,6]. In recent years, most attention has been focused on assessing the impact of nuclear genes on the development of CHD, so the roles of mtDNA mutations in this disease context are not fully understood. In this review, we comprehensively summarize the recent progress in research on mtDNA function and dysfunction, oxidative stress, and CHD-associated mtDNA mutations. We also discuss the potential underlying mechanisms by which pathogenic mtDNA mutations lead to CHD.

Mitochondria

Mitochondria are important organelles whose primary role is to generate ATP through the electron transport chain (ETC) and oxidative phosphorylation (OXPHOS). Mitochondria also play significant roles in other vital aspects of cell functioning, including the regulation of programmed cell death (apoptosis), calcium homeostasis, and the production of reactive oxygen species (ROS)[7,8]. Separate from nuclear DNA, mitochondria also have their own genome, which is called mitochondrial DNA (mtDNA) (Figure 1). A cell contains hundreds of mitochondria, and each mitochondrion contains five to ten copies of mtDNA[9]. Human mtDNA is a double-stranded circular molecule of 16,569-bp encoding 37 genes: 13 for essential subunits of the OXPHOS system, 2 for rRNAs and 22 for tRNAs required for mitochondrial protein synthesis[10]. Since mtDNA is in the proximity of sites of ROS generation and mitochondria have relatively unsophisticated DNA protection and repair systems, this DNA is particularly susceptible to mutation[11].

mtDNA is predominantly transmitted maternally. Most mammalian cells contain many cop-

Corresponding Author: Jinyu Huang, MD; e-mail: zdsyhjy0902@zju.edu.cn

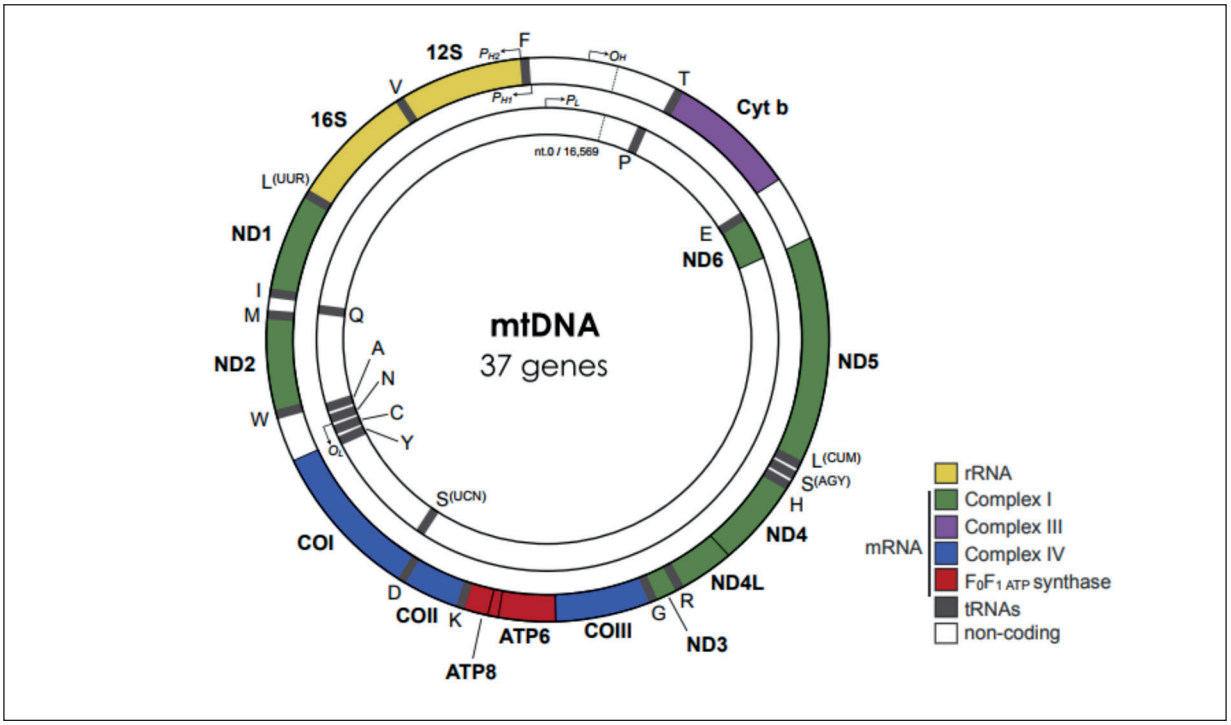

Figure 1. The genetic map of human mtDNA gene, it contained 13 peptides, 22 tRNA and 2 rRNA.

ies of the mitochondrial genome. mtDNA within a cell can be a mixture of both wild-type and mutant species, a condition called "heteroplasmy," while "homoplasmy" refers to the situation in which all mtDNAs are identical[12]. Pathogenic mutations are usually heteroplasmic in nature.

Oxidative Stress

Oxidative stress has been identified as a major factor contributing to the onset and development of CHD[13,14]. The term "oxidative stress" refers to an imbalance between the production of ROS and the ability of the body to detoxify the reactive intermediates. Under normal physiological conditions, the level of ROS production is tightly controlled through the activity of antioxidant enzymes, such as manganese-superoxide dismutase, catalase, glutathione reductase and peroxidase[15,16].

Mitochondria are the non-enzymatic source of ROS that mainly emerges from complexes I and III of the respiratory chain[17]. ROS within the mitochondrial intermembrane space, or in the cytosol, are involved in subsequent oxygen sensing modification *via* stabilization of the transcription factor hypoxia-inducible factor-1 alpha (HIF-1α)[18]. Therefore, ROS generated by the mitochondria, have the ability to modify multiple additional physiological pathways. For example, ROS can directly damage proteins by oxidation, or can oxidize lipids to form lipid peroxidation products, which can induce protein or phospholipid damage. ROS are also involved in DNA damage, in particular damage to mtDNA[19]. Moreover, ROS can generate peroxynitrite from nitric oxide (NO), causing intracellular nitrosylation and further impairment of mitochondrial respiration[20], which is detrimental to cardiac health.

mtDNA Deletions and CHD4977-bp Deletion

The mtDNA 4977-bp deletion, a common deletion that eliminates the region between nucleotides 8470 and 13447 of the human mitochondrial genome, was first identified in the muscle of a patient with neuromuscular diseases – (Kearns-Sayre/progressive external ophthalmoplegia plus syndrome) in 1989[21]. This common deletion removes five mt-tRNA genes, namely, $tRNA^{Gly}$, $tRNA^{Arg}$, $tRNA^{His}$, $tRNA^{Ser(AGY)}$ and $tRNA^{Leu(CUN)}$, as well as seven genes encoding four Complex I subunits (*ND3*, *ND4*, *ND4L*, partial *ND5*), one Complex IV subunit (COX III), and two Complex V subunits (*A6*, partial *A8*) that are crucial for supporting normal mitochondrial OXPHOS function[22]. Both animal studies[23] and cell model

analysis[24] have shown that the mtDNA 4977-bp deletion plays an important role during the course of tumorigenesis and aging. Studies[25,26] on cardiac tissues revealed the presence of the mtDNA 4977-bp deletion and showed a positive correlation between this deletion and CHD. It has been suggested[27] that continuous generation of intracellular free radicals during OXPHOS is a major underlying mechanism generating this deletion.

7.3-kb Deletion

In a previous study, 7.3-kb deletion breakpoints were found downstream of the *A8* gene and at the 3' end of the *Cytb* genes[28]. This deletion results in removal of the cytochrome b gene, the NADH dehydrogenase chain 6, 5, 4, 4L and 3 genes and the F_0-F_1 *A6* and *A8* genes. As these genes are essential for OXPHOS, their deletion would be expected to decrease ATP resynthesis during reperfusion[29]. Moreover, the incidence and prevalence of 7.3-kb deletion in patients with clinical indications of poor recovery suggest that this deletion could be an important indicator of surgical outcome in patients undergoing cardiac surgery.

Mitochondrial OXPHOS-Related Genes Mutations and CHD ND5 G13513A Mutation

The G to A mutation at nucleotide position 13513 in mtDNA affects an evolutionarily conserved amino acid (D393N) in the reduced form of the *ND5* gene, which encodes a subunit of respiratory chain complex I[30]. In fact, the amino acid at that position is critical for the functions of complex I. Mitochondrial complex I accepts electrons from NADH and then transfers them to coenzyme Q_{10}. Therefore, the G13513A mutation interferes with the function of complex I and causes mitochondrial dysfunction[31]. This mutation was first reported in adult mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)[30], as well as Leber's hereditary optic neuropathy (LHON)/MELAS syndromes[32]. Mitrofanov et al[33] analyzed the mtDNA heteroplasmic mutation G13513A in CHD patients and found a positive correlation between it and CHD.

CytB G15059A and C15452A Mutations

The point mutation G15059A results in the replacement of a glycine at amino acid position 190 with a stop codon. This change results in premature termination of translation, leading to a truncated *CytB* protein missing 244 amino acids at the C-terminus[33,34]. Initially, G15059A was described in a patient with mitochondrial myopathy[35]. Nikitin et al[36] examined the role of the *CytB* G15059A mutation in patients with type 2 diabetes with EH.

The C15452A mutation converts the 236th amino acid of *CytB* from leucine to isoleucine and was found to be correlated with decreased Complex III activities in the hearts of patients with severe ischemic cardiomyopathy III[37]. These findings suggest that mtDNA damage is a secondary effect of oxidative damage in the heart during aging and cardiomyopathy.

mtDNA D-loop Mutation and CHD D-loop T16189C Mutation

The mtDNA T16189C mutation, with a homopolymeric C-tract of 10-12 cytosines, was found to be a putative genetic risk factor for CHD in Saudi Arabians[38]. Nucleotide T16189 lies in the middle of a homopolymeric-C tract where the transition from a thymine (T) to a cytosine (C) causes a homopolymeric C-tract of 10-12 bp in the displacement loop (D-loop) region of mtDNA[39]. This mutation maps precisely to a novel point of origin of mtDNA replication (OriB), which makes it likely that T16189C alters mtDNA function[40] and subsequently plays a putative role in CHD progression.

mt-tRNA Mutations and CHD $tRNA^{Leu(UUR)}$ C3256T Mutation

The heteroplasmic mutation C3256T is located in the $tRNA^{Leu(UUR)}$ gene of the mitochondrial genome. This mutation has been reported in two families with diabetes mellitus[41,42] and one family with recurrent focal seizures, hemiplegia and hemianopia[43]. In fact, C3256T occurs at the D-stem of the $tRNA^{Leu(UUR)}$ gene (position 27) which is highly conserved from bacteria to humans[44]. It was anticipated that the C3256T mutation may interfere with protein synthesis and decrease mitochondrial function. In fact, this mutation was shown to significantly reduce the levels of mt-$tRNA^{Leu(UUR)}$ and *ND1* mRNA[45]. Sobenin et al[46] analyzed the frequency of the C3256T mutation in 45 CHD patients and 146 non-CHD controls, they found that this mutation was associated with atherosclerosis with a high level of statistical significance. Moreover, the heteroplasmic level of C3256T mutation in human white blood cells was regarded as a risk factor for atherosclerosis and can be used as an informative marker of genetic susceptibility to atherosclerosis, CHD and myocardial infarction.

tRNA^{Ala} T5592C Mutation

The T5592C mutation is localized at a highly conserved uridine (68U) on the acceptor stem of tRNA^{Ala}, a position that is important for the stability and identity of tRNA[47]. The U-to-C transition occurring at this position due to the T5592C mutation is expected to create a highly conservative base pairing (5G-68C) on the acceptor stem of this tRNA, altering its secondary structure (www.mitomap.org). Interestingly, the T12201C mutation occurring at the same position of the tRNA^{His} gene has been regarded as pathogenic and having an association with mitochondrial deafness[48]. A reduction in the steady state level of tRNA^{His} of approximately 70% has been observed in cybrid cells containing this mutation. Therefore, the T5592C mutation may have similar functional impact on CHD.

tRNA^{Lys} A8326G and A8344G Mutations

The A8326G mutation is located at the anticodon stem of the tRNA^{Lys} gene, adjacent to the first nucleotide of the triplet codon. The nucleotide at that position is invariant across species from yeast to human[49], and was previously described in a cystic fibrosis patient suspected of having mitochondrial cytopathy and CHD[50]. Hence, the A8326G mutation was considered to be deleterious because of the high degree of evolutionary conservation. Meanwhile, the A8344G mutation occurring in the TΨC loop of the cloverleaf-folded tRNA has been reported to be associated with CHD[51], myopathy, multiple lipomatosis, mild hearing loss, stroke-like episodes, and paralytic ileus[52], and myoclonus epilepsy with ragged red fibers (MERRF)[53]. This mutation was shown not to affect mitochondrial transcription and the global post-transcriptional modification pattern of tRNA[54], except modification at nucleotide 34[55]. However, A8344G was found to affect the steady-state level of tRNA^{Lys}, in addition, it was described as having altered capacity to read lysine codons[56].

tRNA$^{Leu(CUN)}$ G12315A Mutation

The G to A change at position 12315 in the tRNA$^{Leu(CUN)}$ gene was first described in a sporadic patient with chronic progressive external ophthalmoplegia, ptosis, limb weakness, sensorineural hearing loss, and pigmentary retinopathy[57]. The G12315A mutation was also presented in patients with myocardial infarction[58]. This heteroplasmic mutation disrupts the highly conserved G-C base pairing in the TΨC stem[47]. It has been suggested that the G12315A mutation could lead to defects in the tRNA and affect protein synthesis, which could in turn result in deficiencies of mitochondrial respiratory chain enzymes. This would eventually lead to energy deficiency in affected cells, which could play a role in myocardial infarction.

tRNA^{Glu} A14693G Mutation

The homoplasmic A14693G mutation occurs at an extremely conserved nucleotide of the TΨC-loop of tRNA^{Glu} (conventional position 54). In fact, nucleotides at that position of tRNA are often modified, thereby contributing to the structural formation and stabilization of functional tRNAs[59]. The A14693G mutation was implicated in MELAS[60] and suggested to influence the phenotypic expression of the deafness-associated 12S rRNA A1555G mutation[61], as well as CHD[62]. Thus, alteration of the tertiary structure of the mt-tRNA^{Glu} by these variants may lead to a failure in the metabolism of this tRNA.

tRNA^{Thr} G15927A Mutation

The mitochondrial G15927A mutation abolishes the highly conserved base-pairing (28C-42G) of the anticodon stem of tRNA^{Thr}. This mutation causes an unstable tRNA^{Thr} structure and decreases the efficiency of aminoacylation of this tRNA[63]. Moreover, the G15927A mutation was reported to markedly decrease the level of mtDNA-encoded polypeptides, to promote respiratory deficiency, to diminish membrane potential and to increase the production of ROS. An *in vivo* mitochondrial protein labeling analysis showed ~53% reduction in the rate of mitochondrial translation in mutant cells which may directly cause mitochondrial dysfunction responsible for CHD[64].

Molecular Mechanism Underlying mtDNA Mutations in CHD

Mitochondrial dysfunction and associated oxidative stress were strongly linked to cardiovascular diseases. In previous studies, we noted that CHD-associated mitochondrial pathogenic mutations were mainly located at OXPHOS-related and tRNA genes (Table I, Figure 2). mtDNA mutations have structural and functional effects, including altering the RNA structure and the processing of RNA precursors, reducing the tRNA or mRNA steady state level, and causing defects in tRNA modifications. These events lead to impaired mitochondrial translation, in particular, a decline in ATP production and an

Table I. CHD-associated mt-tRNA mutations.

Gene	Mutation	Position	Location in tRNA gene	Homoplasmy/ Heteroplasmy	Manifestation	Ref.
$tRNA^{Leu(UUR)}$	C3256T	27	D-stem	Heteroplasmy	CHD, myocardial infarction	45, 46
$tRNA^{Ala}$	T5592C	68	Acceptor stem	Homoplasmy	CHD	47, 62
$tRNA^{Lys}$	A8326G	32	Anticodon stem	Homoplasmy	Myocardial infarction	50
	A8344G	50	TΨC loop	Heteroplasmy	Myocardial infarction	51
$tRNA^{Leu(CUN)}$	G12315A	50	TΨC loop	Heteroplasmy	Myocardial infarction	58
$tRNA^{Glu}$	A14693G	54	TΨC loop	Homoplasmy	CHD	62
$tRNA^{Thr}$	G15927A	42	Anticodon stem	Homoplasmy	CHD	63, 64

increase in ROS generation in cardiovascular cells, which may in turn lead to the development of CHD.

Conclusions

In this review, we have summarized the CHD-associated mtDNA mutations, including large mtDNA deletions, and mutations in mtDNA OXPHOS-related genes and mt-tRNA genes. We found that mtDNA mutations are important causes of CHD. However, the molecular pathogenesis of CHD-associated mtDNA mutations needs to be further elucidated, especially the mechanism underlying the tissue-specific mtDNA mutations, and the interaction between mtDNA mutations and nuclear genes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

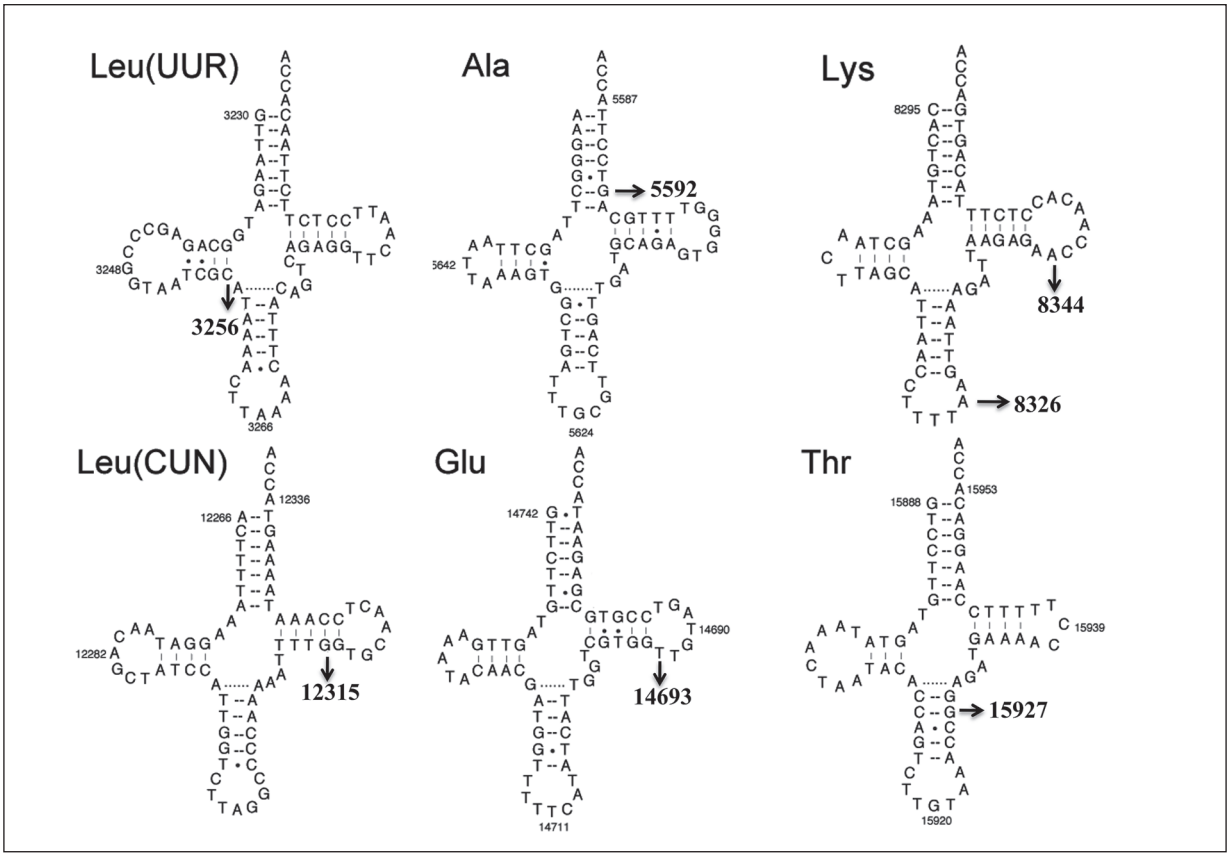

Figure 2. Secondary structures of CHD-associated mt-tRNA genes. Arrows indicated the mutation sites.

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References

1) GBD 2015 Mortality and Causes of Death Collaborators, "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the global burden of disease study 2015". Lancet 2016; 388: 1459-1544.
2) Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367: 1747-1757.
3) Zhang XH, Lu ZL, Liu L. Coronary heart disease in China. Heart 2008; 94:1126-31.
4) Brown JR, O'Connor GT. Coronary heart disease and prevention in the United States. N Engl J Med 2010; 362: 2150-2153.
5) Zhang MM, Zhang CG, Yang CJ, Zhao P, Li YL. The association between the D166E polymorphism of the lipoprotein associated phospholipase A2 and risk of myocardial infarction. Eur Rev Med Pharmacol Sci 2019; 23: 3960-3966.
6) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97: 1837-1847.
7) Picard M, Wallace DC, Burelle Y. The rise of mitochondria in medicine. Mitochondrion 2016; 30: 105-116.
8) Gnoni A, Ballini A, Trentadue R, Taurino F, Santacroce L, Ferrara P, Massaro F, Brienza N, Massari AM, Sardaro N, Dipalma G, Inchingolo F, Scacco S. Induction of mitochondrial dysfunction in patients under cardiopulmonary by-pass: preliminary results. Eur Rev Med Pharmacol Sci 2019; 23: 8115-8123.
9) Goto Y. Clinical and molecular studies of mitochondrial disease. J Inherit Metab Dis 2001; 24: 181-188.
10) Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJ, Staden R, Young IG. Sequence and organization of the human mitochondrial genome. Nature 1981; 290: 457-465.
11) DiMauro S, Schon EA. Mitochondrial DNA mutations in human disease. Am J Med Genet 2001; 106: 18-26.
12) Li H, Liu D, Lu J, Bai Y. Physiology and pathophysiology of mitochondrial DNA. Adv Exp Med Biol 2012; 942: 39-51.
13) Severino P, D'Amato A, Netti L, Pucci M, Infusino F, Maestrini V, Mancone M, Fedele F. Myocardial ischemia and diabetes mellitus: role of oxidative stress in the connection between cardiac metabolism and coronary blood flow. J Diabetes Res 2019; 2019: 9489826.
14) Zhang PY, Xu X, Li XC. Cardiovascular diseases: oxidative damage and antioxidant protection. Eur Rev Med Pharmacol Sci 2014; 20: 3091-3096.
15) Brigelius-Flohe R, Wingler K, Muller C. Estimation of individual types of glutathione peroxidases. Methods Enzymol 2002; 347: 101-112.
16) Zhao Q, Zhou L, Liu J, Cao Z, Du X, Huang F, Pan G, Cheng F. Involvement of CAT in the detoxification of HT-induced ROS burst in rice anther and its relation to pollen fertility. Plant Cell Rep 2018; 37: 741-757.
17) Al Ghouleh I, Khoo NK, Knaus UG, Griendling KK, Touyz RM, Thannickal VJ, Barchowsky A, Nauseef WM, Kelley EE, Bauer PM, Darley-Usmar V, Shiva S, Cifuentes-Pagano E, Freeman BA, Gladwin MT, Pagano PJ. Oxidases and peroxidases in cardiovascular and lung disease: new concepts in reactive oxygen species signaling. Free Radic Biol Med 2011; 51: 1271-1288.
18) Guzy RD, Schumacker PT. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. Exp Physiol 2006; 91: 807-819.
19) Chen X, Fang M. Oxidative stress mediated mitochondrial damage plays roles in pathogenesis of diabetic nephropathy rat. Eur Rev Med Pharmacol Sci 2018; 22: 5248-5254.
20) Turko IV, Li L, Aulak KS, Stuehr DJ, Chang JY, Murad F. Protein tyrosine nitration in the mitochondria from diabetic mouse heart. Implications to dysfunctional mitochondria in diabetes. J Biol Chem 2003; 278: 33972-33977.
21) Shoffner JM, Lott MT, Voljavec AS, Soueidan SA, Costigan DA, Wallace DC. Spontaneous Kearns-Sayre/chronic external ophthalmoplegia plus syndrome associated with a mitochondrial DNA deletion: a slip-replication model and metabolic therapy. Proc Natl Acad Sci U S A 1989; 86: 7952-7956.
22) Huang YH, Chen CM, Lee YS, Chang KH, Chen HW, Chen YC. Detection of mitochondrial DNA with 4977 bp deletion in leukocytes of patients with ischemic stroke. PLoS One 2018; 13: e0193175.
23) Lee HC, Hsu LS, Yin PH, Lee LM, Chi CW. Heteroplasmic mutation of mitochondrial DNA D-loop and 4977-bp deletion in human cancer cells during mitochondrial DNA depletion. Mitochondrion 2007; 7: 157-163.
24) Pavicic WH, Richard SM. Correlation analysis between mtDNA 4977-bp deletion and ageing. Mutat Res 2009; 670: 99-102.

25) Corral-Debrinski M, Shoffner JM, Lott MT, Wallace DC. Association of mitochondrial DNA damage with aging and coronary atherosclerotic heart disease. Mutat Res 1992; 275: 169-180.

26) Botto N, Berti S, Manfredi S, Al-Jabri A, Federici C, Clerico A, Ciofini E, Biagini A, Andreassi MG. Detection of mtDNA with 4977 bp deletion in blood cells and atherosclerotic lesions of patients with coronary artery disease. Mutat Res 2005; 570: 81-88.

27) Santos RX, Correia SC, Zhu X, Smith MA, Moreira PI, Castellani RJ, Nunomura A, Perry G. Mitochondrial DNA oxidative damage and repair in aging and Alzheimer's disease. Antioxid Redox Signal 2013; 18: 2444-2457.

28) Levitsky S, Laurikka J, Stewart RD, Campos CT, Lahey SJ, McCully JD. Mitochondrial DNA deletions in coronary artery bypass grafting patients. Eur J Cardiothorac Surg 2003; 24: 777-784.

29) Takeda N, Tanamura A, Iwai T, Nakamura I, Kato M, Ohkubo T, Noma K. Mitochondrial DNA deletion in human myocardium. Mol Cell Biochem 1993; 119: 105-108.

30) Santorelli FM, Tanji K, Kulikova R, Shanske S, Vilarinho L, Hays AP, DiMauro S. Identification of a novel mutation in the mtDNA ND5 gene associated with MELAS. Biochem Biophys Res Commun 1997; 238: 326-328.

31) Blok MJ, Spruijt L, de Coo IF, Schoonderwoerd K, Hendrickx A, Smeets HJ. Mutations in the ND5 subunit of complex I of the mitochondrial DNA are a frequent cause of oxidative phosphorylation disease. J Med Genet 2007; 44: e74.

32) Pulkes T, Eunson L, Patterson V, Siddiqui A, Wood NW, Nelson IP, Morgan-Hughes JA, Hanna MG. The mitochondrial DNA G13513A transition in ND5 is associated with a LHON/MELAS overlap syndrome and may be a frequent cause of MELAS. Ann Neurol 1999; 46: 916-919.

33) Mitrofanov KY, Zhelankin AV, Shiganova GM, Sazonova MA, Bobryshev YV, Postnov AY, Sobenin IA, Orekhov AN. Analysis of mitochondrial DNA heteroplasmic mutations A1555G, C3256T, T3336C, C5178A, G12315A, G13513A, G14459A, G14846A and G15059A in CHD patients with the history of myocardial infarction. Exp Mol Pathol 2016; 100: 87-91.

34) Andreu AL, Bruno C, Dunne TC, Tanji K, Shanske S, Sue CM, Krishna S, Hadjigeorgiou GM, Shtilbans A, Bonilla E, DiMauro S. A nonsense mutation (G15059A) in the cytochrome b gene in a patient with exercise intolerance and myoglobinuria. Ann Neurol 1999; 45: 127-130.

35) Andreu AL, Hanna MG, Reichmann H, Bruno C, Penn AS, Tanji K, Pallotti F, Iwata S, Bonilla E, Lach B, Morgan-Hughes J, DiMauro S. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. N Engl J Med 1999; 341: 1037-1044.

36) Nikitin AG, Lavrikova EY, Chistiakov DA. The hetero¬plasmic 15059G>A mutation in the mitochondrial cytochrome b gene and essential hypertension in type 2 diabetes. Diabetes Metab Syndr 2012; 6: 150-156.

37) Marin-Garcia J, Hu Y, Ananthakrishnan R, Pierpont ME, Pierpont GL, Goldenthal MJ. A point mutation in the cytb gene of cardiac mtDNA associated with complex III deficiency in ischemic cardiomyopathy. Biochem Mol Biol Int 1996; 40: 487-495.

38) Abu-Amero KK, Al-Boudari OM, Mousa A, Gonzalez AM, Larruga JM, Cabrera VM, Dzimiri N. The mitochondrial DNA variant 16189T>C is associated with coronary artery disease and myocardial infarction in Saudi Arabs. Genet Test Mol Biomarkers 2010; 14: 43-47.

39) Shaboodien G, Engel ME, Syed FF, Poulton J, Badri M, Mayosi BM. The mitochondrial DNA T16189C polymorphism and HIV-associated cardiomyopathy: a genotype-phenotype association study. BMC Med Genet 2009; 10: 37.

40) Yasukawa T, Yang MY, Jacobs HT, Holt IJ. A bidirectional origin of replication maps to the major noncoding region of human mitochondrial DNA. Mol Cell 2005; 18: 651-662.

41) Moraes CT, Ciacci F, Bonilla E, Jansen C, Hirano M, Rao N, Lovelace RE, Rowland LP, Schon EA, DiMauro S. Two novel pathogenic mitochondrial DNA mutations affecting organelle number and protein synthesis. Is the tRNA(Leu(UUR)) gene an etiologic hot spot? J Clin Invest 1993; 92: 2906-2915.

42) Hirai M, Suzuki S, Onoda M, Hinokio Y, Hirai A, Ohtomo M, Chiba M, Kasuga S, Hirai S, Satoh Y, Akai H, Miyabayashi S, Toyota T. Mitochondrial deoxyribonucleic acid 3256C–T mutation in a Japanese family with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1998; 83: 992-994.

43) Sato W, Hayasaka K, Shoji Y, Takahashi T, Takada G, Saito M, Fukawa O, Wachi E. A mitochondrial tRNA(Leu)(UUR) mutation at 3,256 associated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Biochem Mol Biol Int 1994; 33: 1055-1061.

44) Pütz J, Dupuis B, Sissler M, Florentz C. Mamit-tRNA, a database of mammalian mitochondrial tRNA primary and secondary structures. RNA 2007; 13: 1184-1190.

45) Rossmanith W, Karwan RM. Impairment of tRNA processing by point mutations in mitochondrial tRNA(Leu)(UUR) associated with mitochondrial diseases. FEBS Lett 1998; 433: 269-274.

46) Sobenin IA, Sazonova MA, Ivanova MM, Zhelankin AV, Myasoedova VA, Postnov AY, Nurbaev SD, Bobryshev YV, Orekhov AN. Mutation C3256T of mitochondrial genome in white blood cells: novel genetic marker of atherosclerosis and coronary heart disease. PLoS One 2012; 7: e46573.

47) Suzuki T, Nagao A, Suzuki T. Human mitochondrial tRNAs: biogenesis, function, structural aspects, and diseases. Annu Rev Genet 2011; 45: 299-329.

48) Yan X, Wang X, Wang Z, Sun S, Chen G, He Y, Mo JQ, Li R, Jiang P, Lin Q, Sun M, Li W, Bai Y, Zhang

J, Zhu Y, Lu J, Yan Q, Li H, Guan MX. Maternally transmitted late-onset non-syndromic deafness is associated with the novel heteroplasmic T12201C mutation in the mitochondrial tRNAHis gene. J Med Genet 2011; 48: 682-690.

49) Wong LJ, Liang MH, Kwon H, Park J, Bai RK, Tan DJ. Comprehensive scanning of the entire mitochondrial genome for mutations. Clin Chem 2002; 48: 1901-1912.

50) Wong LJ, Liang MH, Kwon H, Bai RK, Alper O, Gropman A. A cystic fibrosis patient with two novel mutations in mitochondrial DNA: mild disease led to delayed diagnosis of both disorders. Am J Med Genet 2002; 113: 59-64.

51) Matam K, Shaik NA, Aggarwal S, Diwale S, Banaganapalli B, Al-Aama JY, Elango R, Rao P, Hasan Q. Evidence for the presence of somatic mitochondrial DNA mutations in right atrial appendage tissues of coronary artery disease patients. Mol Genet Genomics 2014; 289: 533-540.

52) Orcesi S, Gorni K, Termine C, Uggetti C, Veggiotti P, Carrara F, Zeviani M, Berardinelli A, Lanzi G. Bilateral putaminal necrosis associated with the mitochondrial DNA A8344G myoclonus epilepsy with ragged red fibers (MERRF) mutation: an infantile case. J Child Neurol 2006; 21: 79-82.

53) Oldfors A, Holme E, Tulinius M, Larsson NG. Tissue distribution and disease manifestations of the tRNA(Lys) A-->G(8344) mitochondrial DNA mutation in a case of myoclonus epilepsy and ragged red fibres. Acta Neuropathol 1995; 90: 328-333.

54) Helm M, Florentz C, Chomyn A, Attardi G. Search for differences in post-transcriptional modification patterns of mitochondrial DNA-encoded wild-type and mutant human tRNALys and tRNALeu(UUR). Nucleic Acids Res 1999; 27: 756-763.

55) Sissler M, Helm M, Frugier M, Giege R, Florentz C. Aminoacylation properties of pathology-related human mitochondrial tRNA(Lys) variants. RNA 2004; 10: 841-853.

56) Enriquez JA, Chomyn A, Attardi G. MtDNA mutation in MERRF syndrome causes defective aminoacylation of tRNA(Lys) and premature translation termination. Nat Genet 1995; 10: 47-55.

57) Fu K, Hartlen R, Johns T, Genge A, Karpati G, Shoubridge EA. A novel heteroplasmic tRNAleu(CUN) mtDNA point mutation in a sporadic patient with mitochondrial encephalomyopathy segregates rapidly in skeletal muscle and suggests an approach to therapy. Hum Mol Genet 1996; 5: 1835-1840.

58) Sazonova MA, Ryzhkova AI, Sinyov VV, Galitsyna EV, Melnichenko AA, Demakova NA, Sobenin IA, Shkurat TP, Orekhov AN. Mitochondrial genome mutations associated with myocardial infarction. Dis Markers 2018; 2018: 9749457.

59) Paris Z, Alfonzo JD. How the intracellular partitioning of tRNA and tRNA modification enzymes affects mitochondrial function. IUBMB Life 2018; 70: 1207-1213.

60) Tzen CY, Thajeb P, Wu TY, Chen SC. Melas with point mutations involving tRNALeu (A3243G) and tRNAGlu(A14693g). Muscle Nerve 2003; 28: 575-581.

61) Ding Y, Li Y, You J, Yang L, Chen B, Lu J, Guan MX. Mitochondrial tRNA(Glu) A14693G variant may modulate the phenotypic manifestation of deafness-associated 12S rRNA A1555G mutation in a Han Chinese family. J Genet Genomics 2009; 36: 241-250.

62) Qin Y, Xue L, Jiang P, Xu M, He Y, Shi S, Huang Y, He J, Mo JQ, Guan MX. Mitochondrial tRNA variants in Chinese subjects with coronary heart disease. J Am Heart Assoc 2014; 3: e000437.

63) Jia Z, Zhang Y, Li Q, Ye Z, Liu Y, Fu C, Cang X, Wang M, Guan MX. A coronary artery disease-associated tRNAThr mutation altered mitochondrial function, apoptosis and angiogenesis. Nucleic Acids Res 2019; 47: 2056-2074.

64) Jia Z, Wang X, Qin Y, Xue L, Jiang P, Meng Y, Shi S, Wang Y, Qin Mo J, Guan MX. Coronary heart disease is associated with a mutation in mitochondrial tRNA. Hum Mol Genet 2013; 22: 4064-4073.