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Mitonuclear epistasis and mitochondrial disease

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Wang et al. (2015) report the joint effect of genetic variants in both the nuclear and mitochondrial DNA (mtDNA) on the occurrence of Kallmann syndrome in a large Han Chinese family. The nuclear variant (*KAL1* c.146G > T, p.Cys49Phe) is not expected to cause changes to protein structure or function. Although the pathogenicity of the mitochondrial variant ($tRNA^{cys}$, m.5800A > G) has been predicted (Bannwarth et al., 2013), there is no empirical evidence to support that prediction and it was not found to depress cellular oxidative phosphorylation (Wang et al., 2015). Their interpretation is that the two point mutations act synergistically, causing abnormal migration of gonadotropin-releasing hormone neurons, which is thought to be the underlying mechanism for this developmental disorder. Since mutations in both genomes are required for manifestation of the phenotype, their results challenge how mitochondrial disease may be defined. We suggest that this two-locus/genome model of mitochondrial disease phenotypes may apply more broadly than is currently appreciated. Although the action of genetic background or modifiers have been implicated in altering the penetrance of primary pathological mutations underlying mitochondrial disease, reviews of this evidence have focused on specific disease sub-types (Bénit et al., 2010). Here, a review of the published evidence from the medical literature suggest that mitonuclear epistatic interactions are widespread and make a significant contribution to the variability in disease penetrance, which is a widely reported feature of mitochondrial pathologies (Limongelli et al., 2004). We have identified 15 loci in mtDNA where the pathogenic effect (spanning a number of different mitochondrial diseases) is dependent upon the nuclear background, specific nuclear polymorphic sites, or expression levels of nuclear genes (Table 1). In most cases, the defect in the mtDNA can be modified by multiple different nuclear loci, although some 'master modifiers' appear capable of influencing multiple mtDNA mutations (e.g. *VARS2*, *LARS2*). A further 11 nuclear loci have been identified where mitochondrial haplotype (or variants) have modified the pathogenic phenotype, which includes type II diabetes, Parkinson's and Alzheimer's disease as well as classical mitochondrial diseases. Only 6 of these loci co-localize to mitochondria. In one example, the deleterious effect of the m.5703G > A mutation in human cell lines disappeared after a period of time in culture (Hao et al., 1999). However, replacement of the nuclear background (using cybrids) re-introduced the deleterious phenotype. These data support a compensatory model of evolution within the nuclear genome in response to the presence of deleterious mutations within the mitochondrial genome. Together these studies highlight the potential role of mitonuclear epistasis in the expression and penetrance of human mitochondrial disease.

We declare no competing interests.

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Table 1
List of primary pathogenic loci in the mitochondrial and nuclear genomes (and their associated diseases), with evidence for modification at loci in the complementary genome (* nuclear genes that are not co-localized to the mitochondria). The primary pathogenic loci are defined as loci with published scientific evidence for their pathogenicity. Readers are directed to the MitoMap (http://www.mitomap.org/MITOMAP) or OMIM (https://www.omim.org/) databases for associated citations. Studies providing evidence for modifier effects usually post-date that for primary pathogenic loci.

	Primary pathogenic locus	Disease (OMIM identifier)	Modifier
Mitochondrial			
1	12S rRNA; 1491A > G or 1409C > T	Non-syndromic sensorineural deafness (500008), aminoglycoside-induced deafness (580000)	*MTO2* (Yan et al., 2005)
2	12S rRNA; 1494C > T	Non-syndromic sensorineural deafness (500008), aminoglycoside-induced deafness (580000)	Nuclear background (Zhao et al., 2005), *MRPS12* (Emperador et al., 2015), *GJB2* (Kokotas et al., 2010), *SLC26A4* (Huang et al., 2013)
3	12S rRNA; 1555A > G	Non-syndromic sensorineural deafness (500008), aminoglycoside-induced deafness (580000)	8p23.1 region, *MRPS18CP2* variants, *DEFA3* loss (Ballana et al., 2007), *MRPS12* (Emperador et al., 2015), *MTO1*, *GTPBP3* (Y. Bykhovskaya et al., 2004a, 2004b; Bykhovskaya et al., 2009), *TFB1M* (Bykhovskaya et al., 2009; Yelena Bykhovskaya et al., 2004a, 2004b), *TMRU* (Bykhovskaya et al., 2009; Guan et al., 2006)
4	$tRNA^{Val}$; 1624C > T	Leigh syndrome (256000)	*VARS2L* (McFarland et al., 2002; Rorbach et al., 2008), *VARS2*, *LARS2* expression (Hornig-Do et al., 2014)
5	$tRNA^{Leu(UUR)}$; 3243A > G	MELAS (540000), maternally inherited diabetes and deafness (MIDD; 590050),	*LARS2* (Munakata et al., 2005; Park et al., 2008), *PGC-1α*, *PGC-1β* (Srivastava et al., 2009), *LARS2* expression (Perli et al., 2014), *GTPBP3*, *MTO1* and *TRMU* expression regulated by microRNA-9/9* expression (Meseguer et al., 2015)
6	ND1; 3460A > G	LHON (535000)	Nuclear background (Cock et al., 1998), X chromosome region (Hudson et al., 2005)
7	$tRNA^{Ile}$ 4277T > C	Hypertrophic cardiomyopathy	*IARS2*, *LARS2* (Perli et al., 2012), *VARS2*, expression (Perli et al., 2014)
8	$tRNA^{Ile}$ 4290T > C	Familial progressive necrotising encephalopathy (590045.0005)	Nuclear background (Limongelli et al., 2004)
9	$tRNA^{Ile}$ 4300A > G	Primary familial hypertrophic cardiomyopathy (590045.0006)	Nuclear background (Davidson et al., 2009), *IARS2*, *VARS2*, *LARS2* expression (Perli et al., 2014)
10	$tRNA^{Asn}$; 5703G > A	Isolated ophthalmoplegia (590010.0001)	Nuclear background (Hao et al., 1999)
11	$tRNA^{Cys}$; 5800A > G	Kallmann syndrome (147950)	*KAL1* variants (Wang et al., 2015)
12	$tRNA^{Lys}$; 8344A > G	Myoclonus epilepsy associated with ragged-red fibers (MERRF; 545000)	*GTPBP3*, *MTO1* and *TRMU* expression regulated by microRNA-9/9* expression (Meseguer et al., 2015)
13	$tRNA^{Gly}$ 10003T > C	Maternally inherited type 2 diabetes (125853)	Nuclear background (Liu et al., 2015)
14	ND4; 11778G > A	Leber's optic atrophy (516003.0001)	Nuclear background (Zhou et al., 2010), *PARL* (Phasukkijwatana et al., 2010), *YARS2* (Jiang et al., 2015)
15	$tRNA^{Glu}$ 14674T > C	Mitochondrial myopathy, infantile, transient (590025.0002)	Nuclear background (Horvath et al., 2009)
Nuclear			
1	*NDUFA1*	Mitochondrial complex I deficiency (252010)	mtDNA background (Potluri et al., 2009)
2	*ANT1*	Myopathy, cardiomyopathy	mtDNA haplotype H protective relative to U (Strauss et al., 2013)
3	*MTO1*	Hypertrophic cardiomyopathy and lactic acidosis (614702)	$tRNA^{Phe}$ 593T > G (Charif et al., 2015)
4	*TFAM rs2306604*	Parkinson's disease (168600)	HV mtDNA haplotype cluster higher risk than non-HV cluster (Gaweda-Walerych et al., 2010)
5	*NDUFC2*	Type 2 diabetes (222100)	mtDNA haplotype (Gershoni et al., 2014)
6	*YARS2*	Myopathy, lactic acidosis, sideroblastic anaemia (MLASA; 600462)	mtDNA haplotype (Riley et al., 2013)
7	*HNF1α**	Maturity-onset diabetes of the young (606391), maternally inherited diabetes and deafness (MIDD; 590050)	$tRNA^{Leu(UUR)}$; 3243A > G (Cervin et al., 2004)
8	*beta MHC**	Beta myosin heavy chain linked hypertrophic cardiomyopathy (160760.0002)	mtDNA mutations (Arbustini et al., 1998)
9	*POLG*	MELAS (540000), sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO; 607459), Alpers syndrome (203700)	mtDNA haplotype (Neeve et al., 2012; Rajakulendran et al., 2016)
10	*TTR**	Transthyretin familial amyloid polyneuropathy (105210)	mtDNA haplotype (Bonaiti et al., 2010)
11	*APOE**	Alzheimer disease (104300)	mtDNA haplotype (Carrieri et al., 2001)

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