PERGAMON

Neuromuscular Disorders 14 (2004) 107–116

www.elsevier.com/locate/nmd

Mitochondrial encephalomyopathies: gene mutation

Vol. 14 No. 1, January 2004

Disease	Mitochondrial DNA mutation	Gene location[a]	Mode of inheritance	Key references[b]
Mitochondrial encephalomyopathies associated with mitochondrial DNA mutations: defects of mitochondrial DNA				
KSS	Single large deletion		Sporadic	Holt et al. (1988) Zeviani et al. (1988)
	Large scale tandem duplication		Sporadic	Poulton et al. (1989)
Pearson's syndrome (±KSS)	Single large deletion		Sporadic	Rotig et al. (1989) McShane et al. (1991)
Pearson's s./multisystem	Deletion-duplication		Sporadic	Superti-Furga et al. (1993)
PEO	Single large deletion		Sporadic	Holt et al. (1988) Moraes et al. (1989)
	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Maternal	Moraes et al. (1993c)
	Point mutation nt-4274 T → C	tRNA-Ile	Sporadic (?)	Chinnerry et al. (1997a)
	Point mutation nt-4285 T → C	tRNA-Ile	Maternal	Silvestri et al. (1996)
	Point mutation nt-4309 G → A	tRNA-Ile	Sporadic (?)	Franceschina et al. (1998)
	Point mutation nt-5692 A → G	tRNA-Asn	Maternal	Seibel et al. (1994)
	Point mutation nt-5703 G → A	tRNA-Asn	Maternal	Moraes et al. (1993b)
	Point mutation nt-12311 T → C	tRNA-Leu(CUN)	Maternal	Hattori et al. (1994)
	Point mutation nt-12315-G → A	tRNA-Leu(CUN)	Sporadic	Fu et al. (1996)
PEO/myoclonus	Point mutation nt-8342 G → A	tRNA-Lys	Sporadic	Tiranti et al. (1999)
Multisystem/PEO	Point mutation nt-3256 C → T	tRNA-Leu(UUR)	Maternal	Moraes et al. (1993b)
PEO/multiple sclerosis	Point mutation nt-4298 G → A	tRNA-Ile	Sporadic (?)	Taylor et al. (1998)
PEO, myopathy, sudden death	Point mutation nt-3251 A → G	tRNA-Leu(UUR)	Maternal	Sweeney et al. (1993)
MELAS	Point mutation nt-583 G → A	tRNA-Phe	Sporadic (?)	Hanna et al. (1998a)
	Point mutation nt-1642 G → A	tRNA-Val	Maternal	Taylor et al. (1996)
	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Maternal	Goto et al. (1990) Kobayashi et al. (1990)
	Point mutation nt-3252 A → G	tRNA-Leu(UUR)	Maternal	Morten et al. (1993)
	Point mutation nt-3260 A → G	tRNA-Leu(UUR)	Maternal	Nishino et al. (1996a)
	Point mutation nt-3271 T → C	tRNA-Leu(UUR)	Maternal	Goto et al. (1991)
	Point mutation nt-3291 T → C	tRNA-Leu(UUR)	Maternal	Goto et al. (1994)
	Point mutation nt-5814 A → G	tRNA-Cys	Maternal	Manfredi et al. (1996)
	Point mutation nt-9957 T → C	COX III	Maternal	Manfredi et al. (1995a)

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Disease	Mitochondrial DNA mutation	Gene location[a]	Mode of inheritance	Key references[b]
	Point mutation nt-13513 G → A	ND5	Maternal	Santorelli et al. (1997a)
	Single large deletion		Sporadic	Campos et al. (1995)
MERRF	Point mutation nt-8344 A → G	tRNA-Lys	Maternal	Shoffner et al. (1990)
	Point mutation nt-8356 T → C	tRNA-Lys	Maternal	Silvestri et al. (1992)
	Point mutation nt-8363 G → A	tRNA-Lys	Maternal	Ozawa et al. (1997)
MERRF/MELAS	Point mutation nt-7512 T → C	tRNA-Ser(UCN)	Maternal	Nakamura et al. (1995)
	Point mutation nt-8356 T → C	tRNA-Lys	Maternal	Zeviani et al. (1993)
Parkinsonism/MELAS	4-bp deletion nt-14787	Cyt b	Sporadic	De Coo et al. (1999)
NARP	Point mutation nt-8993 T → G	ATPase 6	Maternal	Holt et al. (1990)
NARP/MILS	Point mutation nt-8993 T → C	ATPase 6	Maternal	De Vries et al. (1993)
	Point mutation nt-8993 T → G	ATPase 6	Maternal	Fryer et al. (1994)
	Point mutation nt-9176 T → C	ATPase 6	Maternal	Campos et al. (1997b)
MILS	Point mutation nt-8993 T → G	ATPase 6	Maternal	Tatuch et al. (1992) Shoffner et al. (1992)
	Point mutation nt-8993 T → C	ATPase 6	Maternal	Santorelli et al. (1994)
MILS adult-onset	Point mutation nt-1644 G → T	tRNA-Val	Maternal	Chalmers et al. (1997)
Spino-cerebellar/ Leigh syndrome	Point mutation nt-8344 A → G	tRNA-Lys	Maternal	Howell et al. (1996)
Bilateral striatal necrosis	Point mutation nt-8851 T → C	ATPase 6	Maternal	De Meirleir et al. (1995)
	Point mutation nt-9176 T → C	ATPase 6	Maternal	Thyagarajan et al. (1995)
Bilateral striatal necrosis/MELAS	Point mutation nt-3308 T → C	ND1	Maternal	Campos et al. (1997a)
Myopathy	Point mutation nt-618 T → C	tRNA-Phe	Maternal	Kleinle et al. (1998)
	Point mutation nt-3250 T → C	tRNA-Leu(UUR)	Maternal	Goto et al. (1992)
	Point mutation nt-3288 A → G	tRNA-Leu(UUR)	Maternal	Hadjigeorgiou et al. (1999)
	Point mutation nt-3302 A → G	tRNA-Leu(UUR)	Maternal	Bindoff et al. (1993)
	Point mutation nt-4409 T → C	tRNA-Met	Sporadic	Vissing et al. (1998)
	Point mutation nt-5521 G → A	tRNA-Trp	Maternal	Silvestri et al. (1998)
	Point mutation nt-12320 A → G	tRNA-Leu(CUN)	Sporadic	Weber et al. (1997)
	Point mutation nt-15762 G → A	Cyt b	Sporadic (?)	Andreu et al. (1998)
	Point mutation nt-15990 C → T	tRNA-Pro	Maternal	Moraes et al. (1993a)
	260-bp tandem duplication		Sporadic	Manfredi et al. (1995b)
Myopathy/painful stiffness	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Sporadic (?)	Deschauer et al. (1999)
Myopathy/neuropathy	Single large deletion		Sporadic	Molnar et al. (1996)
Myopathy/dystonia	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Maternal	Sudarsky et al. (1999)

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Disease	Mitochondrial DNA mutation	Gene location[a]	Mode of inheritance	Key references[b]
MlMyCa	Point mutation nt-3254 C → G	tRNA-Leu(UUR)	Maternal	Kawarai et al. (1997)
	Point mutation nt-3260 A → G	tRNA-Leu(UUR)	Maternal	Zeviani et al. (1991)
	Point mutation nt-3303 C → T	tRNA-Leu(UUR)	Maternal	Silvestri et al. (1994)
Hypertrophic cardiomyopathy	Point mutation nt-1555 A → G	12S rRNA	Maternal	Santorelli et al. (1999)
	Point mutation nt-4295 A → G	tRNA-Ile	Maternal	Merante et al. (1996)
	Point mutation nt-4300 A → G	tRNA-Ile	Maternal	Casali et al. (1995)
	Point mutation nt-8296 A → G	tRNA-Lys	Maternal	Akita et al. (2000)
	Point mutation nt-9997 T → C	tRNA-Gly	Maternal	Merante et al. (1994)
	Point mutation nt-15243 G → A	Cyt b	Sporadic	Valnot et al. (1999)
Multisystem cardiomyopathy	Point mutation nt-4269 A → G	tRNA-Ile	Maternal	Taniike et al. (1992)
	Point mutation nt-4320 C → T	tRNA-Ile	Maternal	Santorelli et al. (1995)
	Point mutation nt-8363 G → A	tRNA-Lys	Maternal	Santorelli et al. (1996a)
Fatal congenital multisystem disorder	Point mutation nt-15923 A → G	tRNA-Thr	Maternal	Yoon et al. (1991)
Sudden death multisystem disorder	Point mutation nt-10044 A → G	tRNA-Gly	Maternal	Santorelli et al. (1996b)
LHON	Point mutation nt-3394 T → C	NDI	Maternal	Brown et al. (1992a)
	Point mutation nt-3460 G → A	NDI	Maternal	Huoponen et al. (1991)
	Point mutation nt-4160 T → C	NDI	Maternal	Howell et al. (1991)
	Point mutation nt-4216 T → C	NDI	Maternal	Mackey and Howell (1992)
	Point mutation nt-4917 A → G	ND2	Maternal	Johns and Berman (1991)
	Point mutation nt-5244 G → A	ND2	Maternal	Brown et al. (1992b)
	Point mutation nt-7444 G → A	COX I	Maternal	Brown et al. (1992a)
	Point mutation nt-9101 T → C	ATPase 6	Maternal	Lamminen et al. (1995)
	Point mutation nt-9438 G → A	COX III	Maternal	Johns and Neufeld (1993)
	Point mutation nt-9804 G → A	COX III	Maternal	Johns and Neufeld (1993)
	#Point mutation nt-11778 G → A	ND4	Maternal	Wallace et al. (1988)
	Point mutation nt-13708 G → A	ND5	Maternal	Johns and Berman (1991)
	#Point mutation nt-14484 T → C	ND6	Maternal	Johns et al. (1992)
	Point mutation nt-15257 G → A	Cyt b	Maternal	Johns and Neufeld (1991)
	Point mutation nt-15812 G → A	Cyt b	Maternal	Johns and Neufeld (1991)
LHON/dystonia	Point mutation nt-11696 A → G	ND4	Maternal	De Vries et al. (1996)
	Point mutation nt-14459 G → A	ND6	Maternal	Jun et al. (1994)

Continued

Disease	Mitochondrial DNA mutation	Gene location[a]	Mode of inheritance	Key references[b]
	Point mutation nt-14596 T → A	ND6	Maternal	De Vries et al. (1996)
LHON/MELAS	Point mutation nt-13513 G → A	ND5	Maternal	Pulkes et al. (1999)
Dementia/chorea	Point mutation nt-5549 G → A	tRNA-Trp	Sporadic	Nelson et al. (1995)
Encephalomyopathy/ diabetes	Point mutation nt-14709 T → C	tRNA-Glu	Maternal	Hao et al. (1995) Hanna et al. (1995)
Diabetes/deafness	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Maternal	Van den Ouweland et al. (1992)
	Point mutation nt-8296 A → G	tRNA-Lys	Maternal	Kameoka et al. (1998)
	Large-scale tandem duplication		Maternal	Dunbar et al. (1993)
	Deletion-duplication		Maternal	Ballinger et al. (1994)
Diabetes, optic atrophy, deafness (Wolfram s.)	Single large deletion		Sporadic	Rotig et al. (1993)
Diabetes/deafness/ maculopathy/cataract	Single large deletion		Sporadic	Souied et al. (1998)
Diabetes/ataxia/PEO	Point mutation nt-3264 T → C	tRNA-Leu(UUR)	Maternal	Suzuki et al. (1998)
Tubulopathy/diabetes/ cerebellar ataxia	Large-scale tandem duplication		Maternal	Rotig et al. (1992)
Ataxia/leukodystrophy	Single large deletion		Sporadic	Nakai et al. (1994)
Hearing loss, ataxia, myoclonus	Single C insertion nt-7472	tRNA-Ser(UCN)	Maternal	Tiranti et al. (1995)
Mitochondrial encephalomyopathy	Point mutation nt-1606 G → A	tRNA-Val	Maternal	Tiranti et al. (1998a)
	Point mutation nt-3243 A → T	tRNA-Leu(UUR)	Sporadic	Shaag et al. (1997)
	ΔTnt-3271	tRNA-Leu(UUR)	Sporadic	Shoffner et al. (1995)
	Single T insertion nt-5537	tRNA-Trp	Maternal	Santorelli et al. (1997b)
	Point mutation nt-5540 G → A	tRNA-Trp	Sporadic	Silvestri et al. (2000)
	Point mutation nt-6930 G → A	COX I	Sporadic	Bruno et al. (1999)
	Point mutation nt-8328 G → A	tRNA-Lys	Sporadic	Houshmand et al. (1999)
	Point mutation nt-9952 G → A	COX III	Sporadic	Hanna et al. (1998b)
	Point mutation nt-15915 G → A	tRNA-Thr	Sporadic	Nishino et al. (1996b)
Infantile encephalopathy	Point mutation nt-3243 A → G	tRNA-Leu(UUR)	Maternal	Sue et al. (1999a)
	Point mutation nt-7543 G → A	tRNA-Asp	Maternal	Shtilbans et al. (1999)
Motor neuron disease-like	5-bp microdeletion	COX I	Sporadic	Comi et al. (1998)
Gastrointestinal s./ encephalonueropathy	Point mutation nt-8313 G → A	tRNA-Lys	Sporadic	Verma et al. (1997)
Chronic diarrhoea, villous atrophy/multisystem	Deletion-duplication		Sporadic	Cormier-Daire et al. (1994)
Exercise intolerance/ myoglobinuria	Point mutation nt-606 A → G	tRNA-Phe	Maternal	Chinnery et al. (1997b)
	15-bp microdeletion	Cox III	Sporadic	Keightley et al. (1996)
	Point mutation nt-11832 G → A	ND4	Sporadic	Andreu et al. (1999c)
	Point mutation nt-14846 G → A	Cyt b	Sporadic	Andreu et al. (1999b)
	Point mutation nt-15059 G → A	Cyt b	Sporadic	Andreu et al. (1999a)
	Point mutation nt-15084 G → A	Cyt b	Sporadic	Andreu et al. (1999b)

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Disease	Mitochondrial DNA mutation	Gene location[a]	Mode of inheritance	Key references[b]
	Point mutation nt-15168 G → A	Cyt b	Sporadic	Andreu et al. (1999b)
	24-bp deletion nt-15498 G → A	Cyt b	Sporadic	Andreu et al. (1999b)
	Point mutation nt-15615 G → A	Cyt b	Sporadic	Dumoulin et al. (1996)
	Point mutation nt-15723 G → A	Cyt b	Sporadic	Andreu et al. (1999b)
Aminoglycoside-induced and non-syndromic deafness	Point mutation nt-1555 A → G	12S rRNA	Maternal	Prezant et al. (1993)
Sensorineural deafness	Point mutation nt-7445 A → G	tRNA-Ser(UCN)	Maternal	Reid et al. (1994)
	Point mutation nt-7511 T → C	tRNA-Ser(UCN)	Maternal	Sue et al. (1999b)
Acquired idiopathic sideroblastic anemia	Point mutation nt-6721 T → C	COX I	Sporadic	Gattermann et al. (1997)
	Point mutation nt-6742 T → C	COX I	Sporadic	Gattermann et al. (1997)
	Point mutation nt-12301 G → A	tRNA-Leu(CUN)	Sporadic	Gattermann et al. (1996)
Mitochondrial encephalomyopathies associated with mitochondrial DNA mutations: mendelian-inherited mitochondrial DNA defects[c]				
PEO	Multiple deletions		Mendelian AD	Zeviani et al. (1989) Servidei et al. (1991)
		10q23.3–24.3		Suomalainen et al. (1995)
		3p14.1–21.2		Kaukonen et al. (1996)
		4q34-q35		Kaukonen et al. (1999)
Myopathy	Multiple deletions	Nuclear gene unknown	Mendelian AR	Yuzaki et al. (1989)
Sideroblastic anemia/myopathy	Multiple deletions	Nuclear gene unknown	Mendelian (AD?)	Casademont et al. (1994)
Progressive encephalomyopathy	Multiple deletions	Nuclear gene unknown	Mendelian AD	Cormier et al. (1991)
Familial recurrent myoglobinuria	Multiple deletions	Nuclear gene unknown	Mendelian (AR?)	Ohno et al. (1991)
MINGIE	Multiple deletions		Mendelian AR	Uncini et al. (1994)
		22q13.32-qter		Hirano et al. (1998)
		TP (*thymidine phosphorylase gene*)		Nishino et al. (1999)
Familial idiopathic cardiomyopathy	Multiple deletions	Nuclear gene unknown	Mendelian AD	Suomalainen et al. (1992)
PEO/cardiomyopathy	Multiple deletions	Nuclear gene unknown	Mendelian AR	Bohlega et al. (1996)
Sensory ataxic neuropathy/ dysarthria/PEO	Multiple deletions	Nuclear gene unknown	Sporadic	Fadic et al. (1997)
MERRF	Multiple deletions	Nuclear gene unknown	Sporadic	Blumenthal et al. (1998)
DIDMOAD (Wolfram syndrome)	Single large deletion	Nuclear gene unknown	Mendelian AR	Barrientos et al. (1996a)
	Multiple deletions	4p16	Mendelian AR	Barrientos et al. (1996b)
Fatal infantile myopathy	Severe depletion	Nuclear gene unknown	Mendelian	Moraes et al. (1991)
Myopathy of childhood	Partial depletion	Nuclear gene unknown	Mendelian	Tritschler et al. (1992)
Fatal infantile hepatopathy	Severe depletion	Nuclear gene unknown	Mendelian	Mazziotta et al. (1992)
Encephalopathy/myopathy	Depletion	Nuclear gene unknown	Sporadic	Kirches et al. (1998)
Encephalopathy/hepatopathy	Depletion	Nuclear gene unknown	Sporadic	Naviaux et al. (1999)

Mitochrondrial encephalomyopathies due to respiratory chain deficiency and nuclear gene mutations

Disease (OMIM)	Mode of inheritance[c]	Gene location[a]	Symbol (gene product)	Respiratory chain defect	Key references[b]
Leukodystrophy/myoclonic epilepsy (203540)	AR	11q13	NDUFV1 (*NADH-ubiquinone oxidoreductase flavoprotein 1*)	Complex I	Scheulke et al. (1999)
Fatal multisystem complex I deficiency (252010)	AR	5q11.1	NDUFS4 (*NADH-ubiquinone oxidoreductase FE-S protein 4)*	Complex I	Van den Heuvel et al. (1998)
Leigh syndrome (256000)	AR	19p13	NDUFS7 (*NADH-ubiquinone oxidoreductase FE-S protein 7*)	Complex I	Triepels et al. (1999)
	AR	11q13	NDUFS8 *(NADH-ubiquinone oxidoreductase FE-S protein 8*)	Complex I	Loeffen et al. (1998)
	AR	5p15	SDHA *(succinate dehydrogenase 2, flavoprotein subunit)*	Complex II	Bourgeron et al. (1995)
	AR	9q34	SURF-1	Complex IV	Tiranti et al. (1998b), Zhu et al. (1998)
Cardioencephalomyopathy (604377)	AR	22q13	SCO2	Complex IV	Papadopoulou et al. (1999)

Notes

KSS = Kearns-Sayres Syndrome (OMIM 530000); PEO = Progressive External Ophthalmoplegia (MIM 165130); MELAS = Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (OMIM 540000); MERRF = Myoclonic Epilepsy with Ragged Red Fibers (OMIM 545000); NARP = Neuropathy, Ataxia, Retinitis Pigmentosa (OMIM 551500); MILS = Maternally-Inherited Leigh's Syndrome (OMIM 516060); MiMyCa = Mitochondrial Myopathy and Cardiomyopathy; LHON = Leber's Hereditary Optic Neuropathy; # = mutations established primary (OMIM 535000); MNGIE = Myo-Neuro-GastroIntestinal Encephalopathy (OMIM 603041); DIDMOAD = Diabetes Insipida, Diabetes Mellitus, Optic Atrophy, Deafness (Wolfram syndrome, mitochondrial form OMIM 598500). [OMIM: Online Mendelian Inheritance in Man accessible via the Internet: http://www.ncbi.nlm.nih.gov/Omim/search-omim.html. OMIM is a database of human genes and genetic disorders edited by Victor A. McKusick and colleagues at John Hopkin's and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information].

[a] Mitochondrial DNA sequence according to Anderson [Anderson S, Bankier AT, Barrel BG, et al. Sequence and organisation of the human mitochondrial genome. Nature 1981;290:457–465].

[b] Key references: new key references are printed in bold in the table, and the full reference list is given below.

[c] Inheritance: AD, autosomal dominant; AR, autosomal recessive.

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