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Supplemental Data

Disease-Associated Genetic Variation in Human Mitochondrial Protein Import

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Supplemental Data

Supplemental Table 1: Human genes with reported variants associated with defective mitochondrial import and phenotype of knockout mice. Data for human diseases are reported with genes and phenotype entries in OMIM https://www.omim.org/ downloaded on 12/09/2018. When the OMIM annotations are not up to date with literature, relevant publications cited in the current study are added. The data for the phenotype of the knockout mice are from http://www.informatics.jax.org/ and presented with record IDs.

Supplemental Table 2: **Genes with variants associated with 3-MGA-uria. A.** as reported in OMIM phenotypic series [PS250950], https://www.omim.org/phenotypicSeries/PS250950 downloaded on 12/11/2018, **B.** additional genes reported in literature.

Supplemental References

1: to the main text

2: to Supplemental Table 1

3: to Supplemental Table 2

Supplemental Table 1

Import pathway component	Gene	Gene (MIM #)	Contribution last update	Last entry edit history	Map location	Disease phenotype	Phenotype (MIM #)	Inheritance	Knockout mouse phenotype (MGI #)
Transporter machinery	*AGK*	610345	20/06/2012	05/10/2016	7q34	Cataract 38 Sengers syndrome	614691 212350	AR AR	
	DNAJC19	608977	18/03/2014	02/08/2017	3q26.33	3-methylglutaconic aciduria, type V	610198	AR	
	OXA1L	601066	02/06/1999	06/04/2010	14q11.2	Not in OMIM. Supp. Ref 72 Thompson *et al.*			
	PAM16	614336	23/03/2015	14/04/2017	16p13.3	Spondylometaphyseal dysplasia, Megarbane-Dagher-Melike type	613320	AR	Embryonic or preweaning lethality (MGI:1913699)
	TIMM8A	300356	20/04/2016	20/04/2016	Xq22.1	Mohr-Tranebjaerg syndrome	304700	XLR	
	TIMM22	607251	10/30/2017	10/30/2017	17p13.3	Not in OMIM. Supp. Ref 73 Pacheu-Grau *et al.*			Embryonic or preweaning lethality (MGI:1929742)
	TIMM50	607381	03/10/2017	03/10/2017	19q13.2	3-methylglutaconic aciduria, type IX	617698	AR	Preweaning lethality (MGI:1913775)
MIA pathway	*CHCHD10*	615903	29/01/2015	25/10/2016	22q11.23	Myopathy, isolated mitochondrial Frontotemporal dementia and/or amyotrophic lateral sclerosis 2 Spinal muscular atrophy, Jokela type	616209 615911 615048	AD AD AD	Mild mitochondrial respiration, skeletal-muscle anomalies (MGI:2143558)
	GFER	600924	07/10/2009	09/10/2009	16p13.3	Myopathy, mitochondrial progressive, congenital cataract, hearing loss and developmental delay	613076		Embryonic lethality (MGI:107757)
Chaperone	*HSPD1*	118190	13/09/2018	19/09/2018	2q33.1	Leukodystrophy, hypomyelinating, 4 Spastic paraplegia 13	612233 605280	AR AD	Embryonic lethality (MGI:96242)
Client Processing	*AFG3L2*	604581	20/12/2016	05/01/2018	18p11.21	Spastic ataxia 5 Spinocerebellar ataxia 28	614487 610246	AR AD	Perinatal lethality (MGI:1916847)
	CLPB	616254	16/06/2015	02/08/2017	11q13.4	3-methylglutaconic aciduria, type VII, with cataracts, neurologic involvement and neutropenia	616271	AR	
	CLPP	601119	12/06/2018	13/06/2018	19p13.3	Perrault syndrome 3	614129	AR	Infertility and premature death (MGI:1858213)
	HTRA2	606441	03/01/2017	20/07/2017	2p13.1	3-methylglutaconic aciduria, type VIII	617248	AR	Parkinsonian symptoms, striatal neurons loss, spleen and thymus atrophy, failure to thrive, premature death (MGI:1928676)
	LONP1	605490	06/02/2015	09/02/2015	19p13.3	CODAS syndrome	600373	AR	Embryonic lethality (MGI:1921392)
	MIPEP	602241	30/11/2016	01/12/2016	13q12.12	Combined oxidative phosphorylation deficiency 31	617228	AR	
	PITRM1	618211	30/11/2018	30/11/2018	10p15.2	Not in OMIM. Supp. Ref 74 Brunetti *et al.*			Preweaning lethality (MGI:1916867)
	PMPCA	613036	03/02/2016	12/10/2016	9q34.3	Spinocerebellar ataxia, 2	213200	AR	
	PMPCB	603131	03/05/2018	29/08/2018	7q22.1	Multiple mitochondrial dysfunctions syndrome 6	617954	AR	Embryonic lethality (MGI:1920328)
	SPG7	602783	10/04/2013	22/07/2015	16q24.3	Spastic paraplegia 7	607259	AD, AR	Impaired motor skills (MGI:2385906)
	XPNPEP3	613553	08/09/2010	06/09/2013	22q13.2	Nephronophthisis-like nephropathy 1	613159	AR	
	YME1L1	607472	21/02/2018	21/02/2018	10p12.1	Optic atrophy 11	617302	AR	Embryonic lethality (MGI:1351651)
Lipid environment	*SERAC1*	614725	19/02/2018	23/02/2018	6q25.3	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	614739	AR	Mild neurological phenotype (MGI: 2447813)
	TMEM70	612418	01/07/2014	21/05/2015	8q21.11	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	614052	AR	Embryonic lethality (MGI:1915068)
	TAZ	300394	17/07/2012	13/07/2018	Xq28	Barth syndrome	302060	XLR	Male infertility (MGI:109626)

Supplemental Table 2

A

OMIM type	Gene/locus	Location	Gene/locus MIM number	Phenotype MIM number	Syndrome	Inheritance
I or MGA1	*AUH*	9q22.31	600529	250950		AR
II or MGCA2	*TAZ*	Xq28	300394	302060	Barth	XLR
III or MGCA3	*OPA3*	19q13.32	606580	258501	Costeff	AR
IV or MGCA4	*MGCA1*	not mapped				
V or MGCA5	*DNAJC19*	3q26.33	608977	610198	DCMA	AR
VI or MGCA6	*SERAC1*	6q25.3	614725	614739	MEGDEL	AR
VII or MGCA7	*CLPB*	11q13.4	616254	616271		AR
VIII or MGCA8	*HTRA2*	2p13.1	606441	617248		AR
IX or MGCA9	*TIMM50*	19q13.2	607381	617698		AR

B

	Gene/locus	Location	Gene/locus MIM number	Phenotype MIM number	Syndrome	Evidence for 3-MGA-uria
TIM22 component						
	AGK	7q34	610345	212350	Sengers	Supp. Ref 30 Mayr *et al.*
Complex V						
	ATPAF2	17p11.2	608918	604273		Supp. Ref 76 De Meirleir *et al.*
	ATP5F1D	19p13.3	603150	618120		Supp. Ref 77 Olahova *et al.*
	ATP5F1E	20q13.32	606153	614053		Supp. Ref 75 Mayr *et al.*
Complex V assembly factor gene						
	TMEM70	8q21.11	612418	614052		Supp. Ref 78 Spiegel *et al.*
Cristae junction organizing system						
	MICOS13	19p13.3	616658			Supp. Ref 79 Guarani *et al.*

Supplemental References

Additional references supporting the main text

The references were not included in the main text due to limit on number of allowed citations.

Introduction [1-5]

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