MT-TS1- mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside exposure- *Mitochondrial inheritance*

Classification Owner: Hearing Loss EP
Calculated classification: Definitive
Modified classification: None
Reason for modified classification: None
SOP: Gene Clinical Validity Standard Operating Procedures (SOP), Version 6

Classification status:
Date classification saved: 2018 Dec 20, 8:36 am
Replication Over Time: Yes
Contradictory Evidence? Proband: **No**, Experimental: **No**
Disease: mitochondrial non-syndromic sensorineural deafness with susceptibility to aminoglycoside exposure

Evidence Summary

MT-TS1 was first reported in relation to mitochondrial nonsyndromic hearing loss in 1993 (Prezant et al., 7689389). At least seven variants have been reported in humans (7445A>G, 7445A>C, 7445A>T, 7472insC, 7505T>C, 7510T>C, 7511T>C). Evidence supporting this gene-disease relationship includes case-level data, segregation data, and experimental data. Association is seen in at least 12 probands in 11 publications (PMIDs: 12461693, 8572257, 10094190, 10371545, 20153673, 27530448, 28320335, 15292920, 12471220, 18639500, 7581383). Variants in this gene segregated with disease in 92 additional family members. The gene-disease association is supported by in vitro functional assays (PMIDs: 18398437, 15694374, 15336535). Variants in this gene have been implicated in additional phenotypes including palmoplantar keratoderma with deafness, mitochondrial cytochrome c oxidase deficiency, exercise intolerance, MERRF/MELAS overlap syndrome and ptosis, hypotonia, seizures, and dilated cardiomyopathy. These are outside the scope of this assessment. In summary, MT-TS1 is definitively associated with mitochondrial nonsyndromic hearing loss. This has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time. This classification was approved by the ClinGen Hearing Loss Working Group on 7/17/2018.

Calculated Classification Matrix

Evidence Type						Count	Total Points	Points Counted
Genetic Evidence	Case-Level	Variant	Autosomal Dominant OR X-linked Disorder	Proband with other variant type with some evidence of gene impact		12	6	6
				Proband with predicted or proven null variant		0	0	0
				Variant is *de novo*		0	0	0
			Autosomal Recessive Disorder	Two variants (not predicted/proven null) with some evidence of gene		0	0	0
				Two variants in *trans* and at least one *de novo* or a predicted/proven		0	0	0
		Segregation			**Summed LOD**	**Family Count**	3	3
				Candidate gene sequencing				
				Exome/genome or all genes sequenced in linkage region	7.83	1		
				Total Summed LOD Score				
	Case-Control							
	Genetic Evidence Total:							**9**
Experimental Evidence	**Functional**			Biochemical Functions		0	0	0.5
				Protein Interactions		0	0	
				Expression		0.5	0	
	Functional Alternation			Patient Cells		0	0	1.5
				Non-patient cells		3	1.5	
	Models			Non-human model organism		0	0	0
				Cell culture model		0	0	
	Rescue			Rescue in human		0	0	
				Rescue in non-human model organism		0	0	
				Rescue in cell culture model		0	0	
				Rescue in patient cells		0	0	
	Experimental Evidence Total:							**2**
Total Points								**11**

Genetic Evidence: Case Level (variants, segregation)																		
Label	Variant type	Variant	Reference	Proband sex	Proband age	Proband ethnicity	Proband phenotypes	Segregations					Proband previous testing	Proband methods of detection	Score Status	Proband points (default points)	Reason for changed score
								# Aff	# Unaff	LOD score	Counted	Sequencing					
Family 1 Proband	Proband with other variant type with some evidence of gene impact	m.7511T>C	Chapiro E, et al., 2002, PMID: 12461693	Female	**Age of Report:** 23 Years		**HPO term(s):** Severe sensorineural hearing impairment	5	3	**Calculated:** 1.8	No			**Method 1:** PCR	0.5		Variant is absent from mtDB and MitoTIP in silico tool predicts likely pathogenic.
F-G Family 1 Proband	Proband with other variant type with some evidence of gene impact	m.7445A>G	Fischel-Ghodsian N, et al., 1995, PMID: 8572257	Female	**Age of Report:** 23 Years		**HPO term(s):** Progressive sensorineural hearing impairment Severe sensorineural hearing impairment Adult onset sensorineural hearing impairment	8	2	_	_			**Method 1:** PCR; **Method 2:** Sanger sequencing	0.5		Variant is absent from mtDB. In HmtDB, variant is absent from 'Normal' individuals and present in 0.03% 'Patient individuals. MitoTIP in silico tool does not have a prediction. Family is primarily homosplasmic.
Verhoeven Family 1 Proband	Proband with other variant type with some evidence of gene impact	m.7471_7472insC	Verhoeven K, et al., 1999, PMID: 10094190	Male	**Age of Report**: 68 Years		**HPO term(s):** Progressive sensorineural hearing impairment	27	3	**Calculated:** 7.83	Yes			**Method 1:** PCR	0.5		Variant is absent from mtDB and HmtDB. MitoTIP in silico tool does not have a prediction. Family is primarily homosplasmic.
Sue/Friedman Family Proband	Proband with other variant type with some evidence of gene impact	m.7511T>C	Sue CM, et al., 1999, PMID: 10371545	Female		Not Hispanic or Latino	**HPO term(s):** Bilateral sensorineural hearing impairment Progressive sensorineural hearing impairment **free text**: variable onset HL, COX deficiency in muscles	16	4	_	_		10340654; Friedman et al. 1999	**Method 1:** PCR	0.5		Variant is absent from mtDB and MitoTIP in silico tool predicts likely pathogenic.

Hutchin Family 1 Proband	Proband with other variant type with some evidence of gene impact	m.7510T>C	Hutchin TP, et al., 2000, PMID: 10978361	Male	**Age of Diagnosis:** 15 Months	Not Hispanic or Latino	**HPO term(s):** Profound sensorineural hearing impairment **free text:** asymmetric hearing loss	3	–	–	–			**Method 1:** PCR	0		not scored because of unspecified/heteroplasmy
Tang Family Proband	Proband with other variant type with some evidence of gene impact	NC_012920.1:m.7505T>C	Tang X, et al., 2010, PMID: 20153673	Male	**Age of Onset:** 3 Years	Not Hispanic or Latino	**HPO term(s):** Bilateral sensorineural hearing impairment Severe sensorineural hearing impairment	7	2	**Calculated:** 1.8	No			**Method 1:** Genotyping; **Method 2:** Sanger sequencing	0.5		Variant is absent from mtDB and HmtDB. MitoTIP in silico tool predicts possibly pathogenic.
TCR26	Proband with other variant type with some evidence of gene impact	m.7444G>A	Subathra M, et al., 2016, PMID: 27530448	Female		Not Hispanic or Latino	**HPO term(s):** Severe sensorineural hearing impairment Prelingual sensorineural hearing impairment Global developmental delay	–	–	–	–			**Method 1**: Sanger sequencing	0		not scored because this variant is present in a high number of control individuals.
AJ7	Proband with other variant type with some evidence of gene impact	m.7471_7472insC	Subathra M, et al., 2016, PMID: 27530448	Female	**Age of Report**: 28 Years		**HPO term(s):** Profound sensorineural hearing impairment Prelingual sensorineural hearing impairment	–	–	–	–			**Method 1**: Sanger sequencing	0.5		Variant is absent from mtDB and HmtDB. MitoTIP in silico tool does not have a prediction. Family is primarily homosplasmic.
BJ303-III-1	Proband with other variant type with some evidence of gene impact	m.7445A>T	Chen J, et al., 2008, PMID: 18639500	Female	**Age of Onset:** 1 Years		**HPO terms(s):** Severe sensorineural hearing impairment	–	–	–	–			**Method 1:** Sanger sequencing	0.5		Variant is absent from mtDB and HmtDB. Found in 3 of 65 (3.08%) F4b haplogroup in Mitobank.
Mutai Family Proband	Proband with other variant type with some evidence of gene impact	m.7511T>C	Mutai H, et al., 2017, PMID: 28320335	Unknown			**HPO term(s):** Moderate sensorineural hearing impairment	5	8	**Calculated:** 1.2	No			**Method 1:** Sanger sequencing **Description of genotyping method:** mtDNA analysis on 2 rRNA and 22 tRNA genes	0.5		Variant is absent from mtDB and MitoTIP in silico tool predicts likely pathogenic.

Jacobs proband	Proband with other variant type with some evidence of gene impact	m.7445A>G	Jacobs HT, et al., 2005, PMID: 15292920	Unknown				_	_	_	_			**Method 1:** PCR	0.5		Variant is absent from mtDB. In HmtDB, variant is absent from 'Normal' individuals and present in 0.03% 'Patient individuals. MitoTIP in silico tool does not have a prediction.
BJ304-III-4	Proband with other variant type with some evidence of gene impact	m.7445A>C	Chen J, et al., 2008, PMID: 18639500	Male	**Age of Report**: 19 Years		**HPO term(s):** Profound sensorineural hearing impairment	_	_	_	_			**Method 1**: Sanger sequencing	0.5		Variant is absent from mtDB. In HmtDB, variant is present in 0.06% of 'Normal' individuals and 0% in 'Patient" individuals. MitoTIP in silico tool does not have a prediction.
de Castillo Proband	Proband with other variant type with some evidence of gene impact	m.7510T>C	del Castillo FJ, et al., 2002, PMID: 12471220	Female			**HPO term(s):** Postlingual sensorineural hearing impairment Moderate sensorineural hearing impairment Moderate sensorineural hearing impairment	21	_	_	_			**Description of genotyping method**: 148 Spanish families with maternal NSHL inheritence pattern tested for m.1555A>G, m.1095T>C and m.7510T>C variants.	0.5		The variant is absent from mtDB and HmtDB. MitoTIP on silico tool predicts possibly pathogenic. The variant is observed in 21 individuals with maternal pattern inheritance of nonsyndromic hearing loss.
Tiranti Proband	Proband with other variant type with some evidence of gene impact	m.7471_7472insC	Tiranti V, et al., 1995, PMID: 7581383	Male	**Age of Onset**: 25 Years		**HPO term(s):** Progressive sensorineural hearing impairment Tinnitus Gait ataxia Dysarthria Generalized hypotonia Reduced tendon reflexes **free text:** hypodiadochokinesia	8	_	_	_				0.5		Variant is absent from mtDB and HmtDB. MitoTIP in silico tool does not have a prediction.
														Total Points:	**6**		

Genetic Evidence: Case Level (family segregation information without proband data or scored proband data)						
No segregation evidence for a Family without a proband was found.						
Genetic Evidence: Case-Control						
No scored Case-Control evidence was found						
Experimental Evidence						
Label	**Experimental category**	**Reference**	**Explanation**	**Score status**	**Points (default points)**	**Reason for changed score**
Swalwell Expression	**Expression** B	Swalwell H, et al., 2008, PMID: 18398437	As the level of m.7472insC increases, the steady-state level of mt-tRNA^ser(UCN) decreases. Cells harboring >50% m.7472insC variant exhibit barely detectable transcript levels. Suggests that both m.7472insC and m.7473A>C mutations act synergistically in vitro, with the suppressive effect of the m.7472A>C variant regulated at the level of transcription by the m.7472insC variant amount.	Score	**0.5** (0.5)	
Swalwell Non-Patient Cells	**Functional Alteration:** Non-patient cells	Swalwell H, et al., 2008, PMID: 18398437	clones with the m.7472A>C variant alone had marked respiratory deficiency, whereas clones with both mutations respired at rates comparable to controls	Score	**0.5** (0.5)	
Li Non-Patient Cells	**Functional Alteration:** Non-patient cells	Li X, et al., 2005, PMID: 15694374	The amount of tRNA(Ser(UCN)) in mutant cells decreased compared to control cells. Aminoacylation capability test show a 22% reduction in efficiency of charging in mutated tRNA(Ser(UCN)) compared to controls.	Score	**0.5** (0.5)	
Toompuu Non-Patient Cells	**Functional Alteration:** Non-patient cells	Toompuu M, et al., 2004, PMID: 15336535	extracted and deacetylated RNA from the cell cybrids and found over 11% of all tRNA(Ser(UCN)) molecules from 7472insC cells had incorrect 5' and/or 3' termini. Most commonly, one extra 5' terminal nucleotide (U) added. Errors on the 3' side were more diverse. Authors further found that the incorrect 5' and 3' termini lead to improper tRNA processing	Score	**0.5** (0.5)	
				Total points:	**2.00**	