VitaSIRO *solo*™

MT-RNR1 SNP Assay

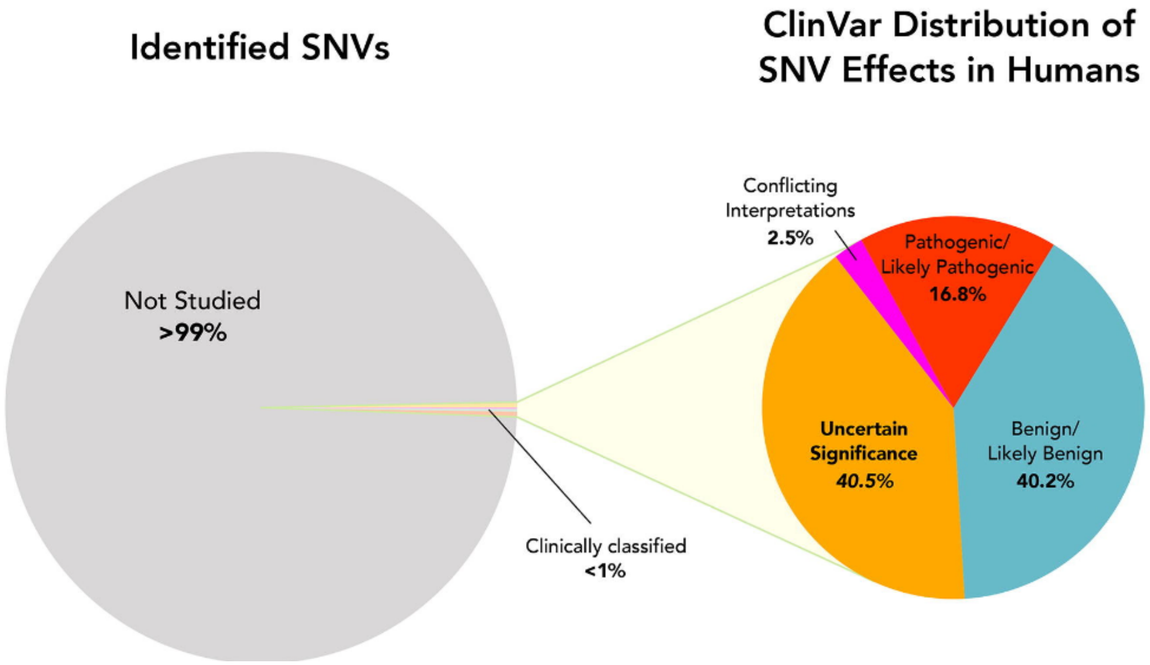
Avoid Aminoglycoside-Induced Ototoxicity in Neonates

credo™ DIAGNOSTICS

Knowledge Empowering People

una health

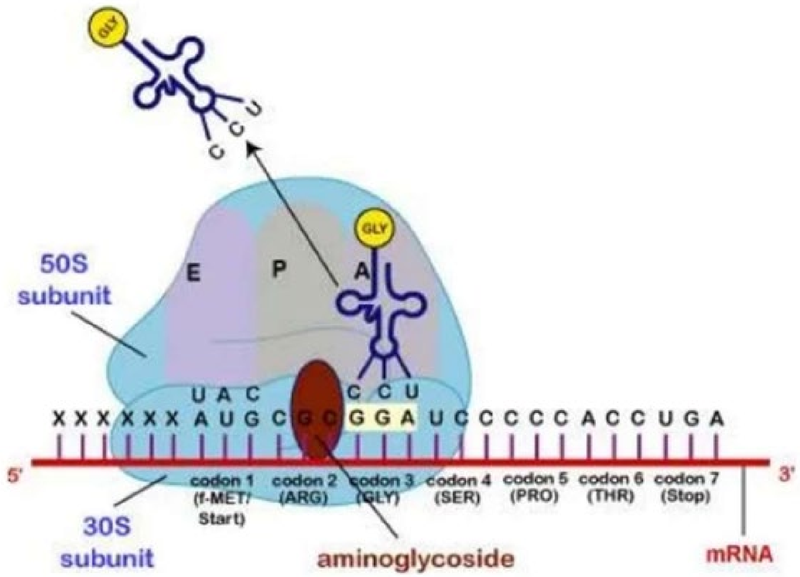
Single Nucleotide Variants



- Single nucleotide variants (SNVs) are the most common type of polymorphism in the human genome.
- With the average individual carrying approximately 3–4 million SNVs.
- Around 16.8% are classified as pathogenic or likely pathogenic, 40.2% as benign or likely benign, while the largest fraction (40.5%) remains of uncertain significance.

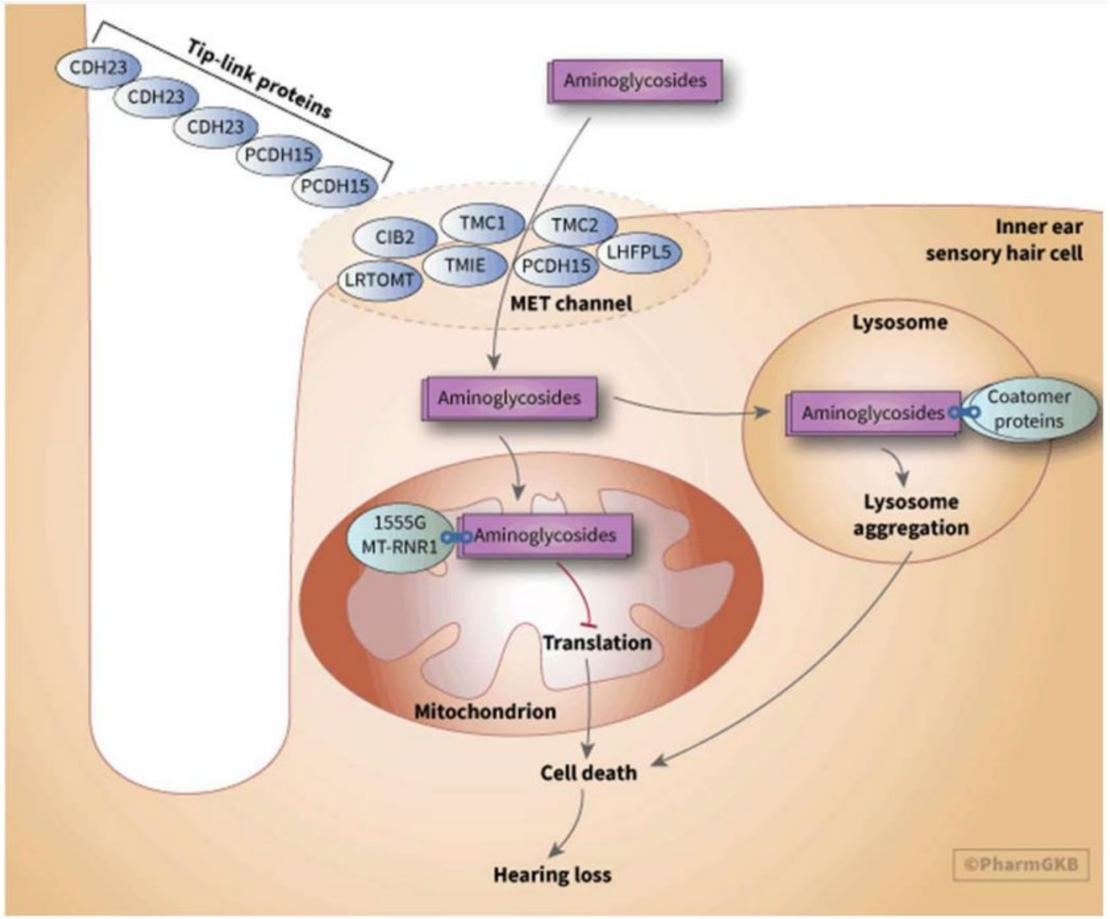
Background: Aminoglycosides

- Newborns are particularly susceptible to bacterial infections for various reasons.
- Aminoglycosides are potent, broad-spectrum antibiotics effective against both **Gram-positive** and **Gram-negative** bacterial infections.
- The work by inhibiting the translation of mRNA through binding to the 30S subunit of the ribosome.



Background: Ototoxicity

- The human 12S ribosome RNA is encoded by the **MT-RNR1** gene.
- When the **m.1555A>G** mutation occurs on this gene, it increases the binding affinity between aminoglycosides and the 12S RNA in human cells.
- The interaction can lead to the death of sensory hair cells in the inner ear, ultimately resulting in hearing loss.



MT-RNR1 Mutation

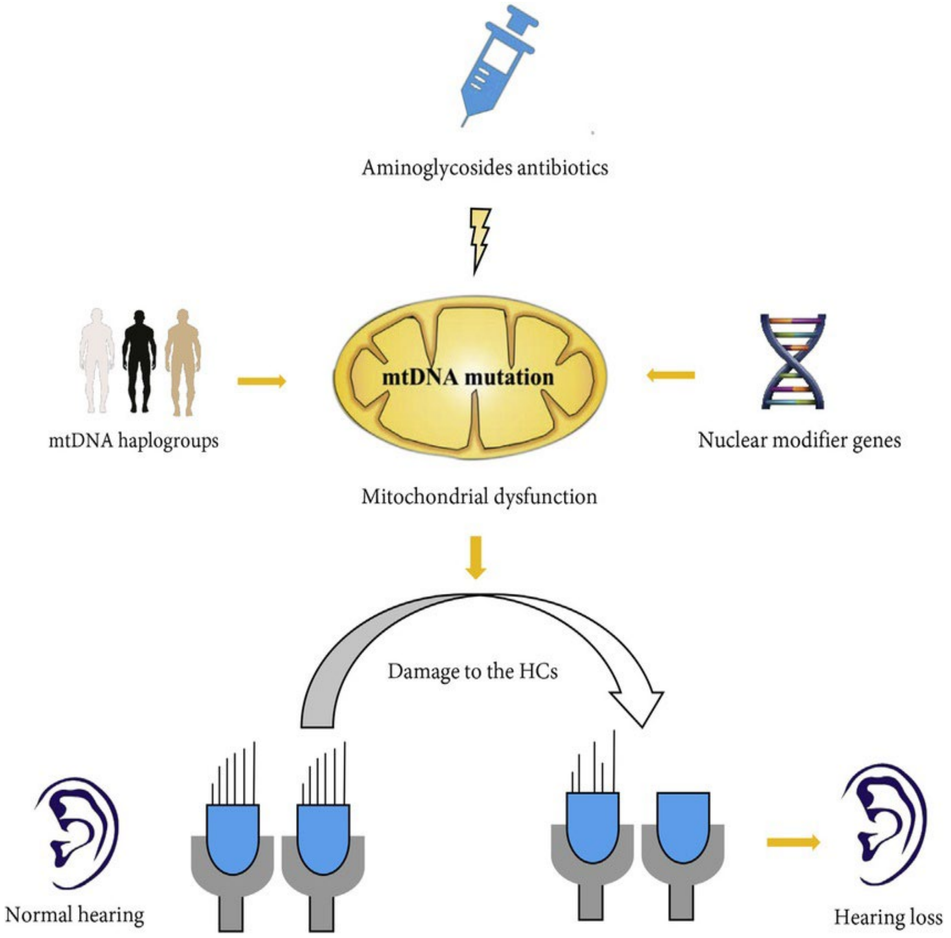
Genetic variations within the mitochondrial gene *MT-RNR1* (12s rRNA) have been strongly linked with the development of hearing loss following treatment of aminoglycoside antibiotics.

Mitochondrial Nonsyndromic Hearing Loss

Gene (OMIM)	Key Gene References (PubMed)
MT-RNR1 (see note 1)	Prezant et al., 1993
MT-CO1 (see note 1, note 2)	Reid et al., 1994
MT-TS1 (see note 1)	Reid et al., 1994
MT-ND1	Lévêque et al., 2007
MT-TS2	Lévêque et al., 2007
MT-TH	Yan et al., 2011
MT-TI	Gutiérrez Cortés et al., 2012
MT-TL1	Mori et al., 2016
MT-TK	Mori et al., 2016

Hereditary Hearing Loss Homepage (hereditaryhearingloss.org/mitochondrial)

Pathways Leading to Hearing Loss



Journal of Otology 12(1) February 2017

Epidemiology

The prevalence of the deafness-associated MT-RNR1 variants is varied by population

➔ m.1555A>G : 0.2% in the general population

➔ m.1494C>T :0.07% to 0.03% by different population

Population	Percentage of m. 1494 C>T	Prevalence
Japan	0.7% HL	1/140
	0% general population	0/1683
United States	0.07% general population	1/1473
China	~0.38% NSHL	~21/5589
	0.45% HL	2/440
	~0.02% Neonates	~14/69621

Population	Percentage of m. 1555 A>G	Prevalence
Japan	3.45% HL	11/319
	0.06% general population	1/1683
Indonesia	5.3% deafness	4/75
Greece	0.42% NSHL	2/478
China	~4.21% NSHL	~217/5155
	~6.55% HL	~39/595
	~0.17% Neonates	~117/68440
	~0.34% Newborns	~7/2046
Spain	17% deafness	9/54
United States	0.2% general population	3/1473
Europe	0.19% ALSPAC	18/9371
Australia	0.21% general population > age 49	6/2856
Germany	0.2% newborns	12/7056
South Africa	0.5% general population	1/204
Taiwan	0.1% newborns	1/1017

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE, Diagnostics Assessment Programme*
**HL hearing loss, NSHL nonsyndromic hearing loss, ALSPAC Avon Longitudinal Study of Patients and Children*

Epidemiology_ New Zealand

Brian J. Scrimshaw · Jim M. Faed · Warren P. Tate
Kankatsu Yun

Rapid identification of an A1555G mutation in human mitochondrial DNA implicated in aminoglycoside-induced ototoxicity

Abstract This article describes a multiplex allele-specific PCR (AS-PCR) approach for detection of an A to G mutation occurring in the human mitochondrial 12s RNA gene at nucleotide 1555. Possession of this mutation has been shown to be associated with irreversible hearing loss following administration of aminoglycoside antibiotics, and in some families is associated with profound sensorineural deafness in the absence of aminoglycoside antibiotics. We screened 206 unrelated individuals from the province of Otago, New Zealand, and found one who possessed the mitochondrial 1555 A to G mutation (0.48%; 95% confidence interval, 0.01–2.75).

J Hum Genet (1999) 44:388–390

Clinical Value

- Benzylpenicillin with gentamicin is recommended for infants suspected of early-onset infections and should be administered as soon as possible, always within 1 hour of the decision to treat.
- The MT-RNR1 mutation significantly increases the risk of profound deafness when infants are treated with aminoglycosides.
- Currently, available lab testing cannot provide results within the necessary time frame.

Market Restrictions

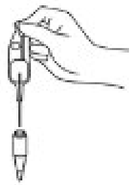
- **Sampling:**
  Invasive sample collection that is difficult to obtain from infant. *Reference
- **Turnaround Time:**
  The report is available within 5-10 working days after the test request (blood test). *Reference
- **POC Test/NPT Availability:**
  Only one commercially available assay is classified as NPT. *Reference
- **Cost:**
  The cost of NGS/sequencing is high.
- **Complexity:**
  The operation of NGS/sequencing is highly complicated.

Our Solution

Diagnostic Procedure in 4 Steps:

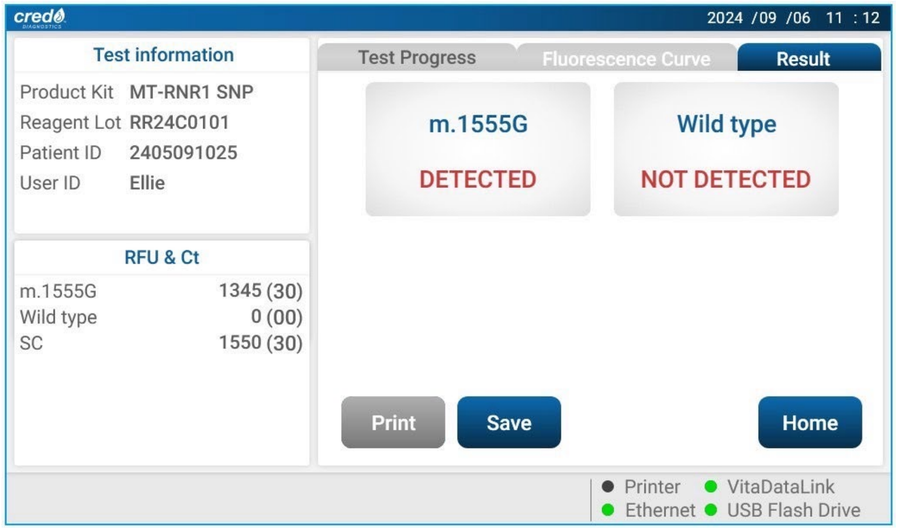
Collect

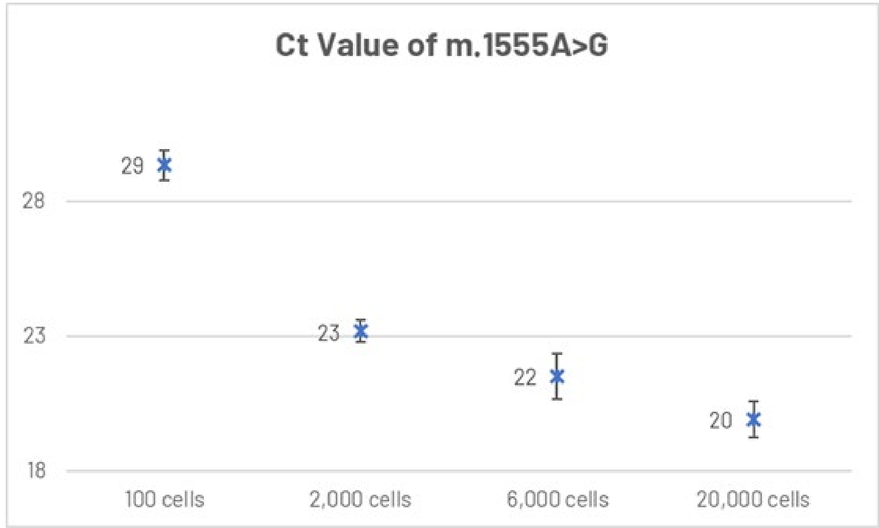
Lyse



Transfer

Start Run

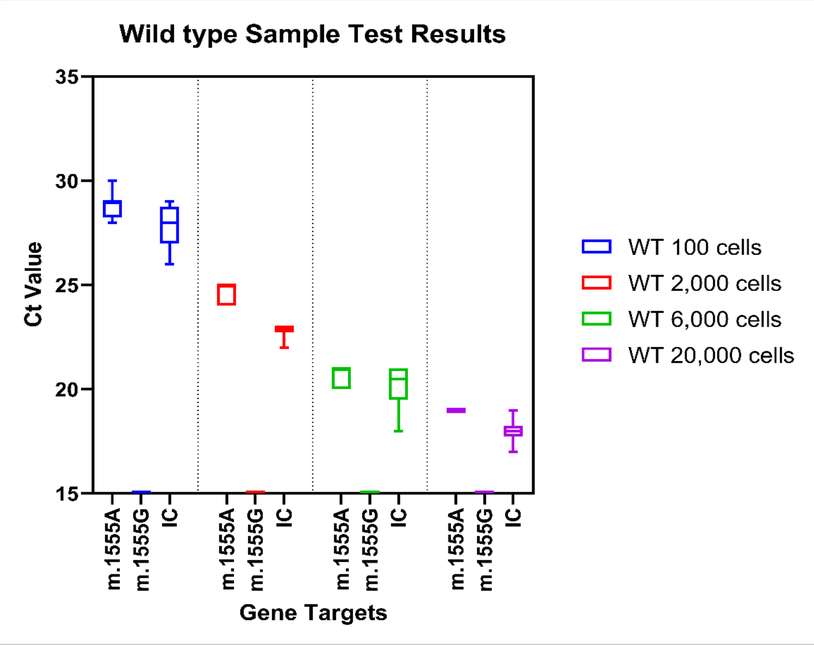


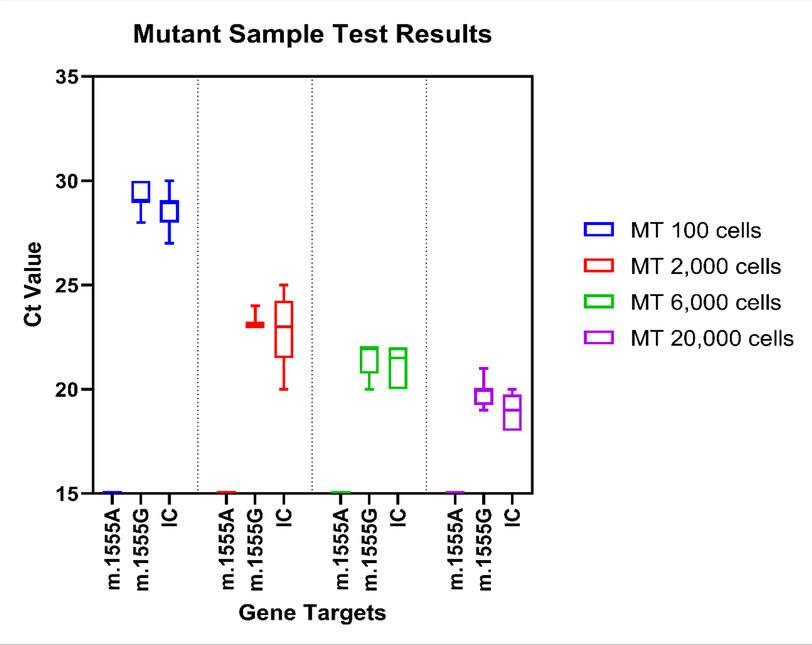


* The assay was validated with EMQN MT-RNR1 POCT Device Verification Sample.

Performance

Analytical sensitivity





(1). EMQN MT-RNR1 POCT Device Verification Sample was used as reference material

Interference testing

Interference	conc./swab (ug/ul)	m. 1555A (N=9)		sample control (N=9)	
		Ct	RFU	Ct	RFU
m. 1555A sample	-	17	2220	16	3633
Hemoglobin	1.44	16	2147	15	2754
Mucin	2.27	17	2220	16	3633
Urea	4.05	15	2174.67	15	2761
Tetracycline	0.00009	16	2367.89	15	2892.44

** The data presented above is the preliminary test result, and the analytical study will be conducted subsequently.*

Unique Selling Points

Non-Invasive Sampling

Easier and faster buccal swab specimen collection

Turnaround Time

Real time PCR results within **20 minutes**

POC Test/NPT Availability

Small footprint and **easy to use** with better performance

Cost

Targeting the most common mutation, 1555A>G, to be **cost-effective**

Complexity

Less than 3 minutes of hands-on time with **minimum training**

Product Specification

VitaSIRO *solo*™ Instrument

Dimensions	23.1 x 20.0 x 27.0 cm (H x W x D)
Weight	3.6 kg
Power Supply	12V, 5A
Color Touch Screen	7” capacitive touch LCD display
Fluorescence Detection	450 to 750 mm
Fluorescence Channel	6+1 (Internal Control)
Storage Environment	15-40°C
Operating Environment	19-38°C, 10-80%RH
Power Adaptor	INPUT: AC 100-240V~2.0A Max, 50-60 Hz OUTPUT: DC 12V-5A

VitaSIRO *solo*™ MT-RNR1 SNP assay

Applied Platform	VitaSIRO *solo*™
Target Gene	MT-RNR1 m.1555 A>G
Targeted Disease	aminoglycoside induced hearing loss (AIHL)
Specimens	buccal swab
Method	Direct lysis + real time-PCR
Internal control	Mitochondria specific gene
Turnaround Time	20 minute
Limit of Detection	< 100 cells per swab
Availability	**2025, Jan (RUO version)**

Without music, life would be a blank to me.

— Jane Austen, Emma

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