# The role of pharmacogenetics to prevent severe side effects

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# Individual Genetic Variability

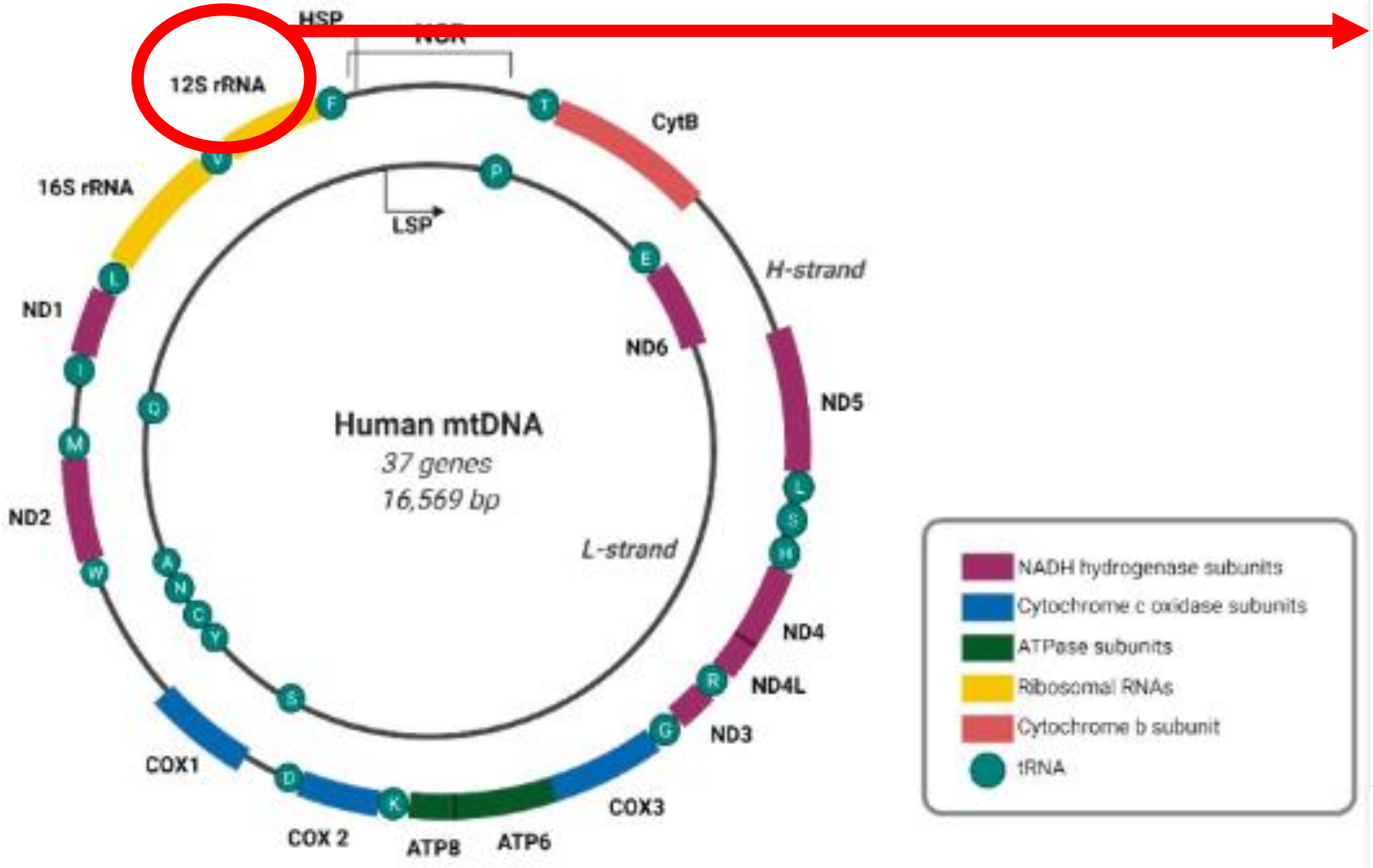
- Affect their responses to drugs
- ? Same efficacy
- Pgx allows to optimise drug dosage
  - for therapeutic effect
  - to reduce the incidence of side effects
- Pgx also can predict adverse reactions

→ available guidelines to help treatment guidance for dose recommendations or alternative options

# Some antimicrobials associated severe side effects due to genetics

| | |
|---|---|
| Abacavir → HLA-B*57:01 allele | • Pharmacogenetic testing for the HLA-B*57:01 allele before starting abacavir can prevent life-threatening hypersensitivity reactions. |
| Sulfamethoxazole → G6PD | • Patients with G6PD deficiency are at risk of haemolysis |
| Aminoglycosides → Variants in the MT-RNR1 gene | • Specific mitochondrial variants can cause hearing loss, eg m1555 a>g |

# Human mt DNA

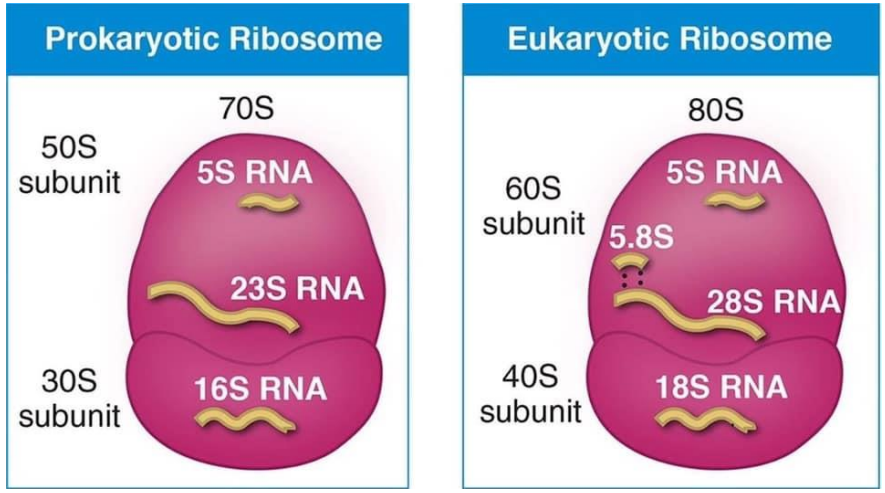



In humans, 12S rRNA is encoded by the MT-RNR1 gene and is 959 nucleotides long.

The transposition of one nucleotide for another one may have effects to the human being when given certain antibiotics.

Eg, m1555a>g variant
Prevalence 0.2

# MT-RNR1 gene




- The 12s rRNA subunit in humans is encoded by MT-RNR1 gene
- Is the homologue of the prokaryotic 16s rRNA
- Certain variants of the RNR1 gene cause a conformational changes in the eukaryote 12s rRNA subunit
- Aminoglycosides mechanism of action has an effect in certain individuals developing severe side effects eg AIO.
- Some MT-RNR1 variants (i.e., m.1095T>C; m.1494C>T; m.1555A>G)

Clinical Pharmacogenetics Implementation Consortium Guideline for the Use of Aminoglycosides Based on MT-RNR1 Genotype - McDermott - 2022 - Clinical Pharmacology & Therapeutics - Wiley Online Library

# MT-RNR1 variants

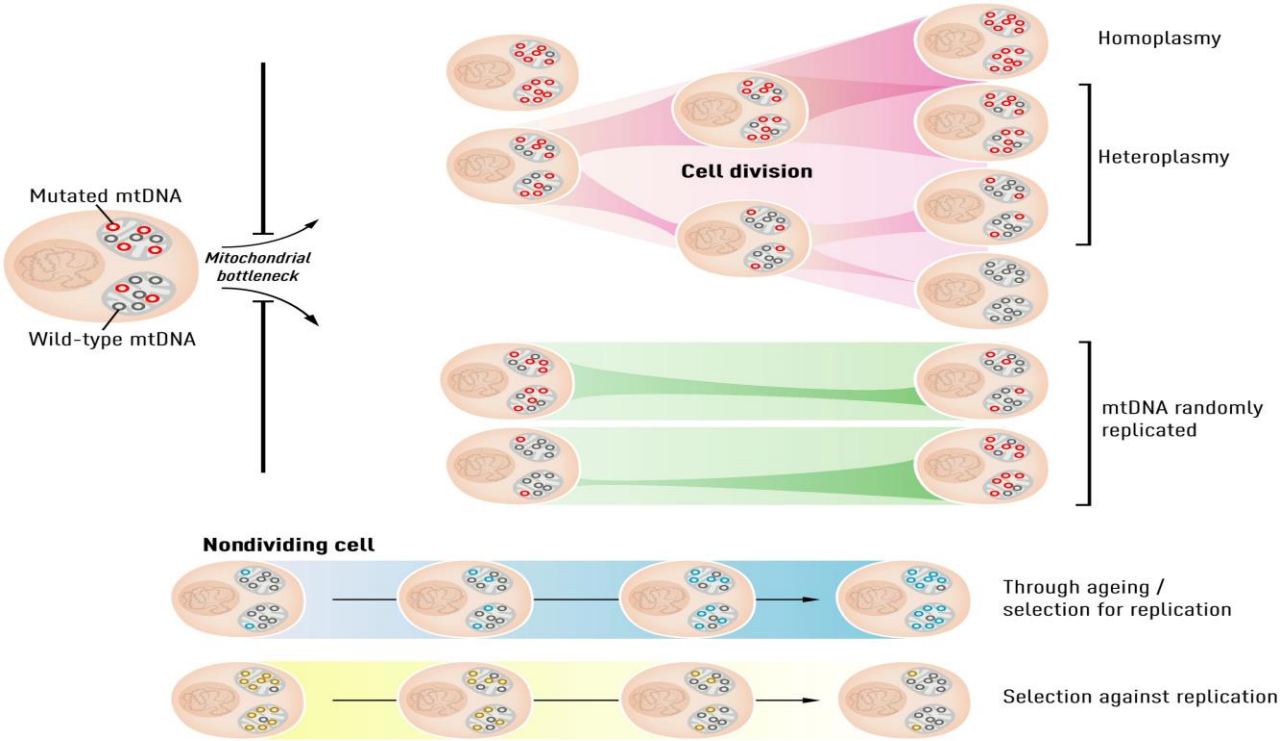
- A total of 75 variants have been identified, the most relevant ones from a clinical perspective identified so far:
  - m.1095T>C;
  - m.1494C>T;
  - m.1555A>G

- From a study on 169 hearing-impaired subjects, novel mutations appearing in MT-RNR1 (and other genes)
  - G786A
  - *T721C*
  - *T1119C*

1. List of variants in gene MT-RNR1 - ClinVar Miner (utah.edu)
2. *Association between idiopathic hearing loss and mitochondrial DNA mutations:*.
https://www.researchgate.net/publication/256085334_Association_between_idiopathic_hearing_loss_and_mitochondrial_DNA_mutations_A_study_on_169_hearing-impaired_subjects
[accessed Aug 02 2024].

# Mitochondrial DNA's inheritance

- Mother to child
- Genomic consideration: mt heteroplasmy




- Dynamic co-expression of inherited polymorphism and somatic mutations
- Different ratios of individual mt DNA

→ At replication: random distribution of variants and wild type DNA into daughter organells

→ Simply by chance the proportions of the mutant genomes may be different leading to different phenotypes

Patterns of Single-Gene Inheritance- Robert L. Nussbaum MD, FACP, FACMG, in Thompson & Thompson Genetics in Medicine, 2016
Wei, W., & Chinnery, P. F. (2020). Inheritance of mitochondrial DNA in humans: implications for rare and common diseases. *Journal of internal medicine*, *287*(6), 634–644.
McCormick EM, Muraresku CC, Falk MJ. Mitochondrial Genomics: A complex field now coming of age. Curr Genet Med Rep. 2018 Jun;6(2):52-61

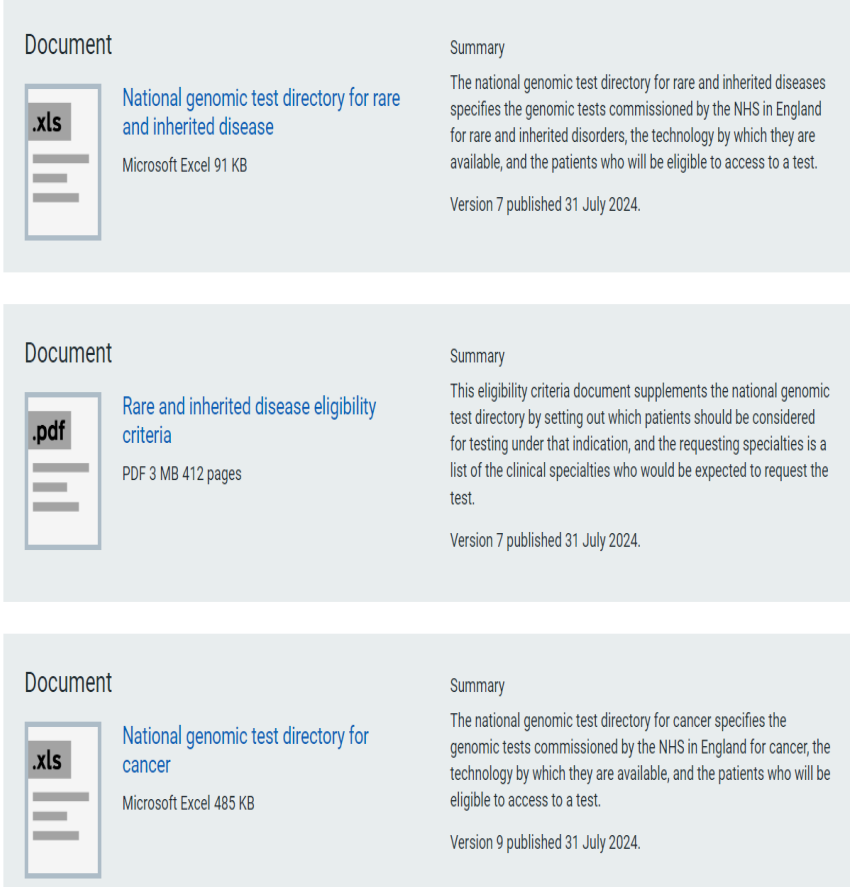
# NTD - Rare Disease Test Directory- RNR1 gene Inclusion Criteria

Testing criteria:

*1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders,*

*OR*

*2. individuals with hearing loss who have been exposed to aminoglycosides*



# Part IX. Audiology

## R65 Aminoglycoside exposure posing risk to hearing

### Testing Criteria

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders, OR
2. individuals with hearing loss who have been exposed to aminoglycosides

### Overlapping indications

- R67 Monogenic hearing loss should be used in individuals with unexplained hearing loss

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As appropriate

### Requesting Specialties

- Appropriate specialist referring clinician

### Specialist Service Group

- Core

### Associated Tests

| Code | Name | Optimal Family Structure | Scope(s) | Target Type | Target Name | Method |
|---|---|---|---|---|---|---|
| R65.1 | Aminoglycoside exposure posing risk to hearing | Singleton | Small variants | Single interval | MT-RNR1 m.1555A>G<br>m.1095T>C<br>m.1494C>T | Targeted variant testing |

# Case Studies

# Case study one

- 9 year old female patient presents to ED with ? Appendicitis
- Triage questions for Prophylactic antibiotics ask for any maternal history of deafness.
- Response from the mum: she (mum) was once exposed to a medication and had tinnitus with not relevant hearing loss BUT
  - her sister (aunty) is deaf bilateral after a traffic accident (not know if deafness was due to the crash or due to any medication she received during the 3 weeks of hospitalisation)
  - her eldest sister is partially deaf of the right ear after a viral infection. She was a teenager when this happened and does not know if she was ever exposed to any antibiotics during the viral infection but this was 30 years ago
  - Her mother (grandmother) became deaf after having had UTI and been in hospital, but she was already hard to hear. She lives in a nursing home and has dementia.

# Case study one

- 1st line prophylactic antibiotics for appendectomy in theatre:
  - Co-amox and Gentamicin
- Guidelines provide alternative abx for Penicillin allergy patients
  - Vancomycin and Gentamicin and Metronidazole

- Is it safe prescribe 1st line antibiotic therapy
- What are your options? Can you go to second line?
- Can you take a Pgx test and wait for the result?
- What if the result is positive? Can you communicate to the patient? How? what implications does this have?
- What is your governance process for this test? Record results?

# Discussion CS1

- **Implications of Findings**
  - Broader implications for patient care and personalised treatment.
  - Benefits of incorporating pharmacogenomic testing into routine clinical practice
  - Governance process
  - Female and potentially childbearing age
  - Mother has 2 sisters with children (grandma had 3 kids and is deaf after UTI episode with hospitalisation)
- **Challenges and Considerations**
  - Limitations of current pharmacogenomic testing
  - Ethical, legal, and social considerations
  - Quantification of the variant in the test not available
  - GP and sharing results with private entities
  - More research required and on going
  - Interoperability of systems- do they interface?

# Case study 2- Neonatal patient

- 32wk premature baby with IUGR born with 1.1kg admitted to NICU with a ? neonatal sepsis
- Mother G3P1, 35 yo, fit and well.

Your trust through charity has secured funding for implementation of a rapid POCT→ Currently one variant is rapidly detected in a POC, results within less than 30 min, which allow give abx fast

What are your considerations?

# Discussion CS2

Low threshold for antibiotics in neonates and Benpen and Agx are first line abx options in Neonatal sepsis

Agx SE can be life changing

Prevalence of variant tested is 0.2 (1 in 500)

Two variants not being tested

TAT for commissioned test depends on region

NICU admissions are overwhelming, when to provide info to parents for informed tx options or consent is test to be done

Cost of POCT as not commissioned

# More discussion