NHS Central & South Genomic Laboratory Hub

NHS Central and South Genomic Medicine Service Alliance

# Information and pathway summary

# MT-RNR1 testing for risk of aminoglycoside-induced ototoxicity (Test R65.1 in National Genomic Test Directory)

## Background

Aminoglycoside antibiotics (amikacin, gentamicin, tobramycin, neomycin, and streptomycin) can cause ototoxicity, which can be permanent[1,2]. Single nucleotide variants have been identified in the human mitochondrial gene *MT-RNR1* that are associated with increased risk of aminoglycoside induced hearing loss, even when the drug is used within normal therapeutic levels[2]. The most common *MT-RNR1* variant associated with increased risk is m.1555A>G, which has an estimated prevalence of 1 in 500 (0.2%) in the general population[2].

## Commissioning Criteria and testing populations

*MT-RNR1* testing for the m.1555A>G variant is commissioned for use in England via the National Genomic Test Directory, in the following patient groups[3]:

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

**Note that as testing may take up to six weeks, it is only appropriate to be used pre-emptively, rather than at the point of antibiotic prescribing**

**Regardless of *MT-RNR1* status, all patients receiving aminoglycosides should continue to be monitored for toxicity and drug levels in accordance with existing local and national guidelines**

## Testing Pathway via Genomic Laboratory Hub

- Prioritise patients for testing where necessary
- Provide patient/carer information and obtain verbal consent
- Inform patient/carer that even if a normal *MT-RNR1* test result is obtained, aminoglycoside ototoxicity may still occur
- Annotate medical records to indicate testing requested
- Send an EDTA blood sample (1-2ml for neonates, 2-5ml for children/adults) and rare disease request form** via the local pathology laboratory to your regional genetics laboratory for rare disease testing**, ensuring that the request form states test code 'R65.1'
- It is possible that the laboratory may have stored DNA available for R65.1 testing; if a previous genetic test has been sent, please contact the relevant laboratory by email to to confirm (contact details for the three rare disease testing laboratories within the Central and South Genomics Laboratory Hub are provided below)***. Additionally, patients newly diagnosed with Cystic Fibrosis via R184 testing will have R65.1 testing initiated by the genetics laboratory.

**Request forms for each of the three rare disease genetic testing laboratories within the Central & South Genomic Laboratory Hub can be obtained from the respective websites:

West Midlands Regional Genetics Laboratory referral form
Oxford Genetics Laboratories referral form
Wessex Regional Genetics Laboratory referral form

***email addresses to contact laboratories:

West Midlands Regional Genetics Laboratory – bwc.rgldna.others@nhs.net
Oxford Genetics Laboratories – orh-tr.dutyscientist.oxfordgen@nhs.net
Wessex Regional Genetics Laboratory – shc-tr.wrgldutyscientist@nhs.net

## Consent and patient information

Only verbal consent will be required as this is considered as a safety test, however you may decide to obtain written consent for your patient cohort. Please follow your internal consent governance procedures. You may wish to develop a patient information leaflet to explain why the test has been taken and what it will mean for them and family members if m.1555A>G is detected.

- If an individual with an *MT-RNR1* variant has previously received aminoglycosides and not developed hearing loss, this does not exclude them from developing it with subsequent doses.
- A normal test result does not eliminate the risk of aminoglycoside induced hearing loss. This is because there are other, more common, mechanisms in which aminoglycosides cause hearing loss. Other risk factors include

prematurity, renal impairment, severe inflammatory response syndrome, prolonged exposure, and high plasma concentrations.
- Patients only require this test to be carried out once, as the results remain applicable to subsequent treatment with aminoglycosides.

## Results and communication

- Inform patient or carer of result
- Upload result to electronic patient record, highlight within clinic letters & annual review template where applicable (e.g. in Cystic Fibrosis) & communicate to patient's GP
- Use SNOMED code to record test result in patient records:
    - 702781009 Mitochondrial 1555 A to G mutation negative
    - 702782002 Mitochondrial 1555 A to G mutation positive

## For patients with *MT-RNR1* m.1555A>G variant

- In addition to steps above, record the result on the patient's drug allergy status as a relative contraindication
- Discuss with the Trust Microbiology team to establish if an antibiotic treatment plan is required
- Avoid aminoglycoside antibiotics unless the risk of hearing loss is outweighed by the severity of infection and there is a lack of alternative treatments
- Consider referral to clinical genetics to allow identification of other family members with the *MT-RNR1* variant

## Actioning *MT-RNR1* results

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidance for the use of aminoglycosides based on *MT-RNR1* genotype in 2021[4].
- Each Trust should have a policy outlining the responsibility of all healthcare professionals in checking whether the *MT-RNR1* results are available before aminoglycoside treatment is administered to the patient.
- In the rare scenario that aminoglycosides are required in the presence of an *MT-RNR1* variant, they should be used for the shortest possible period, under supervision of an infectious disease or microbiology specialist, with therapeutic drug monitoring, and audio vestibular assessment during and after treatment. Patients and carers should be counselled and consented to the increased risk of aminoglycoside induced ototoxicity.
- Prophylaxis with oral N-acetylcysteine (NAC) to prevent aminoglycoside induced ototoxicity can be considered. The majority of evidence for prophylaxis is in renal patients, but other high risk patient groups may also benefit[5]

## Contact details for further advice

- For clinical eligibility and laboratory queries, please contact the Oxford Genetics Laboratories (oxford.mitogenetics@nhs.net). If further clinical advice is required when an *MT-RNR1* variant is detected, please contact Dr Victoria Nesbitt (NHS Highly Specialised Services for Rare Mitochondrial Disorders, Oxford Centre; mitohelp@ouh.nhs.uk; tel 01865 225899).

## Future developments

- Currently the R65 test only tests for one variant, m.1555A>G. In the future other variants may be added as more evidence is obtained. The GMSA will provide support and guidance should this occur.
- Point of care testing: A point of care testing system for m.1555A>G has been trialled within the neonatal setting and reviewed by the NICE Diagnostics Assessment Programme Early Value Assessment programme[6]; please note this is not a full technology assessment and the test is not currently commissioned by the NHS. Institutions wishing to implement point of care testing should contact Central and South GMSA for guidance, and collect data to support further assessment of the technology. Please see further guidance on the NICE website: https://www.nice.org.uk/guidance/hte6/chapter/4-Evidence-generation-recommendations
- Local Trusts developing guidance which may cover commissioned populations should consider inclusion of R65 testing – the GMSA can provide further guidance.

# Example test report – variant detected

UKAS MEDICAL 8694

Oxford Regional Genetics Laboratories
Churchill Hospital
Old Road, Headington
Oxford OX3 7LE
www.ouh.nhs.uk/geneticslab

NHS
Oxford University Hospitals
NHS Foundation Trust
Director of Laboratory: Carolyn Campbell, FRCPath
orh-tr.dutyscientist.oxfordgen@nhs.net ☎ +44 (0)1865 226001

## GENOMIC LABORATORY REPORT

<TOPERSON>

<TOJOBTITLE>
<TOADDRESS>

| | |
|---|---|
| Patient Name: | <Patientfirstname> <PATIENTSURNAME> |
| Date of Birth: | <DATEOFBIRTH> |
| Sex: | <Gender> |
| NHS No: | <NHSNUMBER> |
| Your Ref: | <HOSPITALNO> |
| Family No: | <INTERNALFAMILYNO> |

cc: <COPYTOADDRESS>

### ANALYSIS FOR AMINOGLYCOSIDE OTOTOXICITY

**Reason for testing**

<Patientfirstname> has <specify condition – e.g. cystic fibrosis>. Molecular genetic analysis for the m.1555A>G pathogenic *MT-RNR1* mitochondrial DNA variant is requested as <Patientfirstname> may require treatment with aminoglycosides and this variant predisposes to aminoglycoside ototoxicity.

**Result summary:** This individual is at high risk of aminoglycoside ototoxicity, and should not be treated with aminoglycosides.

**Result**

This individual is homoplasmic for the m.1555A>G pathogenic *MT-RNR1* mitochondrial DNA variant.

**Implications of result**

This individual is at high risk of aminoglycoside ototoxicity, and should not be treated with aminoglycosides. This individual is also at increased risk of developing hearing loss independent of aminoglycoside exposure.
*If female* This has implications for recurrence in any offspring.
*If male* This individual is not at risk of transmitting m.1555A>G to any offspring.

**Recommended action**

Referral to a specialist mitochondrial disease clinic may be appropriate.
This result also has implications for other maternal relatives who may wish to consider molecular testing (via referral to a clinical genetics department or specialist mitochondrial disease service). Relatives at risk of having this variant should avoid aminoglycosides and noise exposure.
A copy of this report has been sent to Dr Victoria Nesbitt from whom further advice is available (01865 225899).

Written by: <WRITER> <WRITERJOBD> Authorised: <AUTHORISER> <AUTHORISERJOBD> Date issued: <AUTHORISEDDATE>

**Variant details**

| Gene | Heteroplasmy / Homoplasmy | Sample type | HGVS description | [a]Classification |
|---|---|---|---|---|
| *MT-RNR1* | Homoplasmic | Blood / Urine / Muscle | NC_012920.1: m.1555A>G | Pathogenic |

Please note that the methodology used cannot distinguish homoplasmy from greater than approximately 95% heteroplasmy.

**Test methodology**

Aminoglycoside antibiotics can cause dose related ototoxicity (hearing impairment due to drug/chemical exposure). The most common known predisposing variant is the pathogenic m.1555A>G mitochondrial DNA variant in the mitochondrial ribosomal RNA (*MT-RNR1* gene)[1]. m.1555A>G is usually homoplasmic and maternally inherited. The m.1555A>G mitochondrial DNA variant is analysed by pyrosequencing.
This is Test ID R65.1 in the NHS England National Genomic Test Directory for Rare and Inherited Disease.
Clinical sensitivity: the proportion of cases of aminoglycoside ototoxicity due to m.1555A>G is unknown. The prevalence of m.1555A>G in populations of European origin is estimated to be 1 in 500[2,3]. Prevalence in other populations is not known.
Analytical sensitivity: this is expected to be >99% for the variant tested, when present at >10% heteroplasmy; the lower limit of heteroplasmy which can be detected is approximately 5-10%.
[a]Variants are classified using an in-house approach based on the ACMG/AMP guidelines (Richards et al., 2015 Genet Med 17(5):405-24), the Association for Clinical Genomic Science (ACGS) 2020 guidelines (www.acgs.uk.com/quality/best-practice-guidelines) and the ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_ntDNA (https://clinicalgenome.org/site/assets/files/4953/clingen_mito_disease_acmg_specifications_v1-1.pdf).
References: [1] Bitner-Glindzicz & Rahman, 2007, BMJ, 335, 784-785; [2] Bitner-Glindzicz et al., 2009, N Eng J Med, 360 (6), 640-642; [3] Vandebona et al., 2009, N Eng J Med, 360 (6), 642-644.



**Sample Details:**

**Laboratory No:** <SAMPLEID> **Sample Received:** <RECEIPTDATE> **Sample Type:** DNA from peripheral blood

## Example test report – variant not detected

UKAS MEDICAL 8694

Oxford Regional Genetics Laboratories
Churchill Hospital
Old Road, Headington
Oxford OX3 7LE
www.ouh.nhs.uk/geneticslab

NHS
Oxford University Hospitals
NHS Foundation Trust
Director of Laboratory: Carolyn Campbell, FRCPath
orh-tr.dutyscientist.oxfordgen@nhs.net ☎ +44 (0)1865 226001

# GENOMIC LABORATORY REPORT

<TOPERSON>
<TOJOBTITLE>
<TOADDRESS>

| | |
|---|---|
| Patient Name: | <Patientfirstname> <PATIENTSURNAME> |
| Date of Birth: | <DATEOFBIRTH> |
| Sex: | <Gender> |
| NHS No: | <NHSNUMBER> |
| Your Ref: | <HOSPITALNO> |
| Family No: | <INTERNALFAMILYNO> |

cc: <COPYTOADDRESS>

## ANALYSIS FOR AMINOGLYCOSIDE OTOTOXICITY

**Reason for testing**

<Patientfirstname> has <specify condition – e.g. cystic fibrosis>. Molecular genetic analysis for the pathogenic m.1555A>G mitochondrial DNA variant is requested as <Patientfirstname> may require treatment with aminoglycosides and this variant predisposes to aminoglycoside ototoxicity.

**Result summary**

**This individual's risk of aminoglycoside ototoxicity is reduced.**

**Result**

The pathogenic m.1555A>G mitochondrial DNA variant was not detected in this individual.
This individual's risk of aminoglycoside ototoxicity is reduced.

Written by: <WRITER> <WRITERJOBD>
Authorised: <AUTHORISER> <AUTHORISERJOBD>
Date issued: <AUTHORISEDDATE>

**Test methodology**

Aminoglycoside antibiotics can cause dose related ototoxicity (hearing impairment due to drug/chemical exposure). The most common known predisposing variant is the pathogenic m.1555A>G mitochondrial DNA variant in the mitochondrial ribosomal RNA (*MT-RNR1* gene)[2]. m.1555A>G is usually homoplasmic and is maternally inherited. The m.1555A>G mitochondrial DNA variant is analysed by pyrosequencing.

This is Test ID R65.1 in the NHS England National Genomic Test Directory for Rare and Inherited Disease.

Clinical sensitivity: the proportion of cases of aminoglycoside ototoxicity due to m.1555A>G is unknown. The prevalence of m.1555A>G in populations of European origin is estimated to be 1 in 500[2,3]. Prevalence in other populations is not known.

Analytical sensitivity: this is expected to be >99% for the variant tested, when present at >10% heteroplasmy; the lower limit of heteroplasmy which can be detected is approximately 5-10%.

MtDNA GenBank Accession: NC_012920.1

References: [1] Bitner-Glindzicz & Rahman, 2007, BMJ, 335, 784-785; [2] Bitner-Glindzicz et al., 2009, N Eng J Med, 360 (6), 640-642; [3] Vandebona et al., 2009, N Eng J Med, 360 (6), 642-644.



**Sample Details:**

**Laboratory No:** <SAMPLEID> **Sample Received:** <RECEIPTDATE> **Sample Type:** DNA from peripheral blood

## Acknowledgements

This information and pathway summary contains information adapted from a briefing document developed by the R65 Task and Finish Group, led by Aris Saoulidis (NHSE Genomics Unit/ East GMSA), Vicky Chaplin (NHSE Genomics Unit), and Paul Selby (East GMSA), and from MT-RNR1 exemplar and best practice guidelines from SW GMSA (team led by Rachel Palmer and Kate North) and North Thames GMSA (Dharmisha Chauhan and Veronica Chorro-Mari).

## References

1. British National Formulary. Aminoglycosides Treatment Summary. Aminoglycosides | Treatment summaries | BNF | NICE. Accessed 21st July 2023.
2. Medicines and Healthcare products Regulatory Agency. Drug Safety Alert. https://www.gov.uk/drug-safety-update/aminoglycosides-gentamicin-amikacin-tobramycin-and-neomycin-increased-risk-of-deafness-in-patients-with-mitochondrial-mutations Accessed 21st July 2023
3. NHS England. National Genomic test directory. NHS England » National genomic test directory. Accessed 21st July 2023
4. Clinical Pharmacogenetics Implementation Consortium. Guideline for the use of Aminoglycosides based on NT-RNR1 genotype. Available from: Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of aminoglycosides based on MT-RNR1 genotype (cpicpgx.org). Accessed 21st July 2023
5. Kranzer K et al. 2015. A systematic review and meta-analysis of the efficiency and safety of N-Acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multi-resistant TB. Thorax [Online]. Available from: A systematic review and meta-analysis of the efficacy and safety of N-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB - PubMed (nih.gov). Accessed 13th September 2023.
6. NICE. Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment https://www.nice.org.uk/guidance/hte6 Accessed 21st July 2023

## Authors

Hayley Wickens (consultant pharmacist GMSA), Carl Fratter (consultant clinical scientist GLH) with thanks to the authors named above.

Reviewed by C&S Pharmacogenomics Group

Approved by Central and South Genomic Medicine Service Operational Board September 2023

September 2023, review date September 2025