

Frequency of *MT-RNR1* Variants Identified Through Pharmacogenetic Testing in a Large Adult Cohort

Driver M¹, Marcath L¹, Rigobello R¹, Chibuk J¹, Walsh M¹, Gallegos M¹, Zhou Y¹, Wang Y^{1,2}

1. Baylor Genetics, Houston, TX, USA
2. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, US

2026PA-0000000163

Introduction

- Pathogenic variants in *MT-RNR1*, including m.1555A>G, m.1095T>C, and m.1494C>T, are associated with an increased risk of aminoglycoside-induced hearing loss (AIHL).¹
- Due to this risk, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends avoiding the use of aminoglycoside antibiotics in individuals with these *MT-RNR1* variants.¹
- Testing for these variants has been incorporated into some pharmacogenetic (PGx) panels.
- However, availability of *MT-RNR1* testing for these findings is more limited in typical PGx panel testing due to capture and reporting needs for mitochondrial genome assessment such as detection of plasmid levels.
- The frequency of *MT-RNR1* variants in an unselected adult cohort undergoing PGx testing is limited.

Methods

- We conducted a retrospective review of consecutive PGx cases at our clinical diagnostic laboratory.
- Our PGx capture includes CPIC-recommended *MT-RNR1* variants m.1555A>G, m.1095T>C, and m.1494C>T and plasmid level detection.
- Cases were excluded if the individual was less than 18 years old at the time of testing or sex was unknown or unspecified.
- Sequencing data were reviewed to determine whether homoplasmic or heteroplasmic m.1555A>G, m.1095T>C, or m.1494C>T variants were identified in *MT-RNR1*.
- Population frequencies of these variants were reviewed in the Genome Aggregation Database (gnomAD).²

Results

Figure 1. Demographic characteristics for the cohort of adults undergoing PGx testing.



Figure 3. Approximately 1 in 385 adults with PGx testing had an increased risk of AIHL due to the detection of relevant *MT-RNR1* variants.

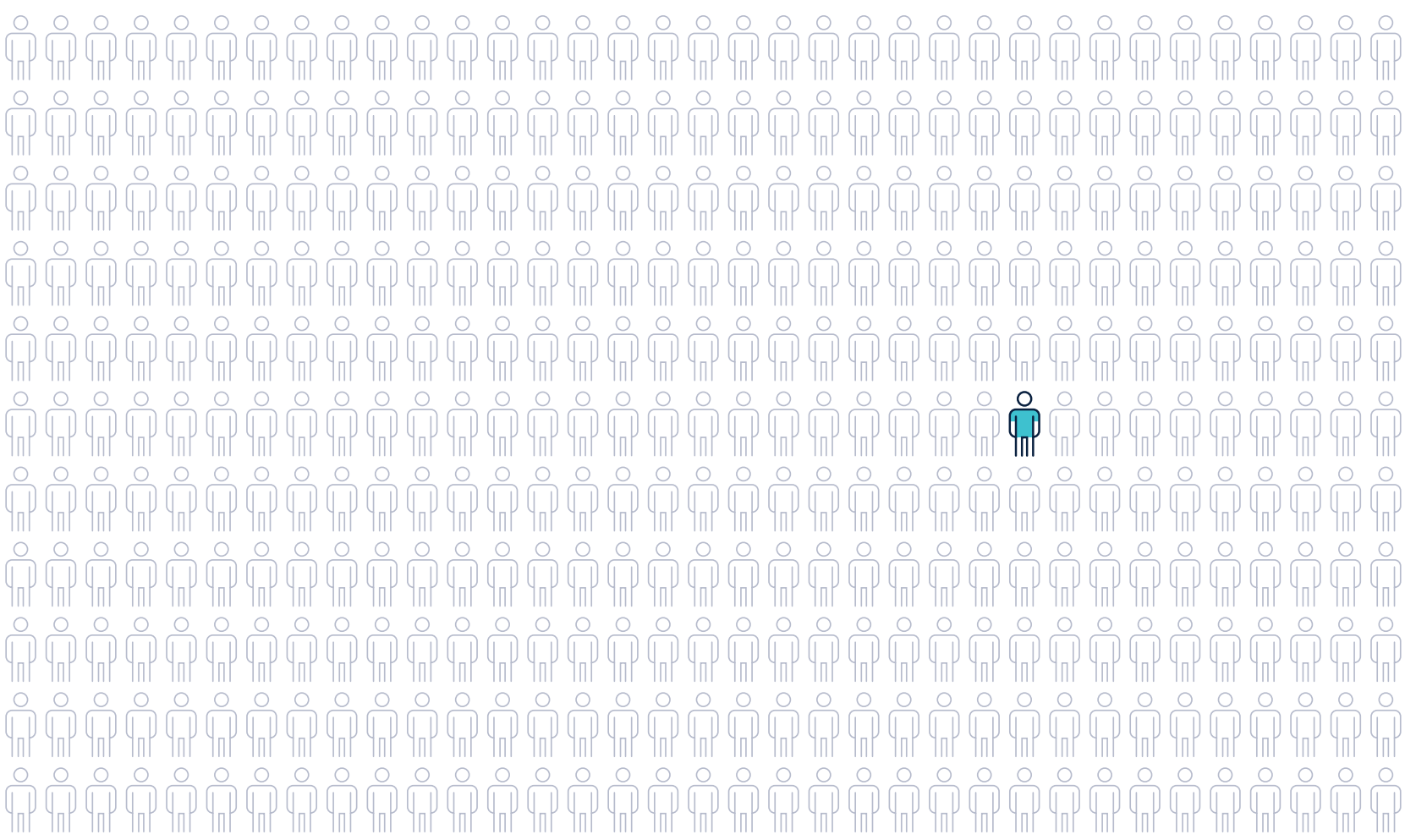


Figure 2. Number of cases with *MT-RNR1* variants stratified by variant and sex. Two m.1555A>G variants were heteroplasmic (35.5% and 73.6% heteroplasmy). All other variants were homoplasmic.

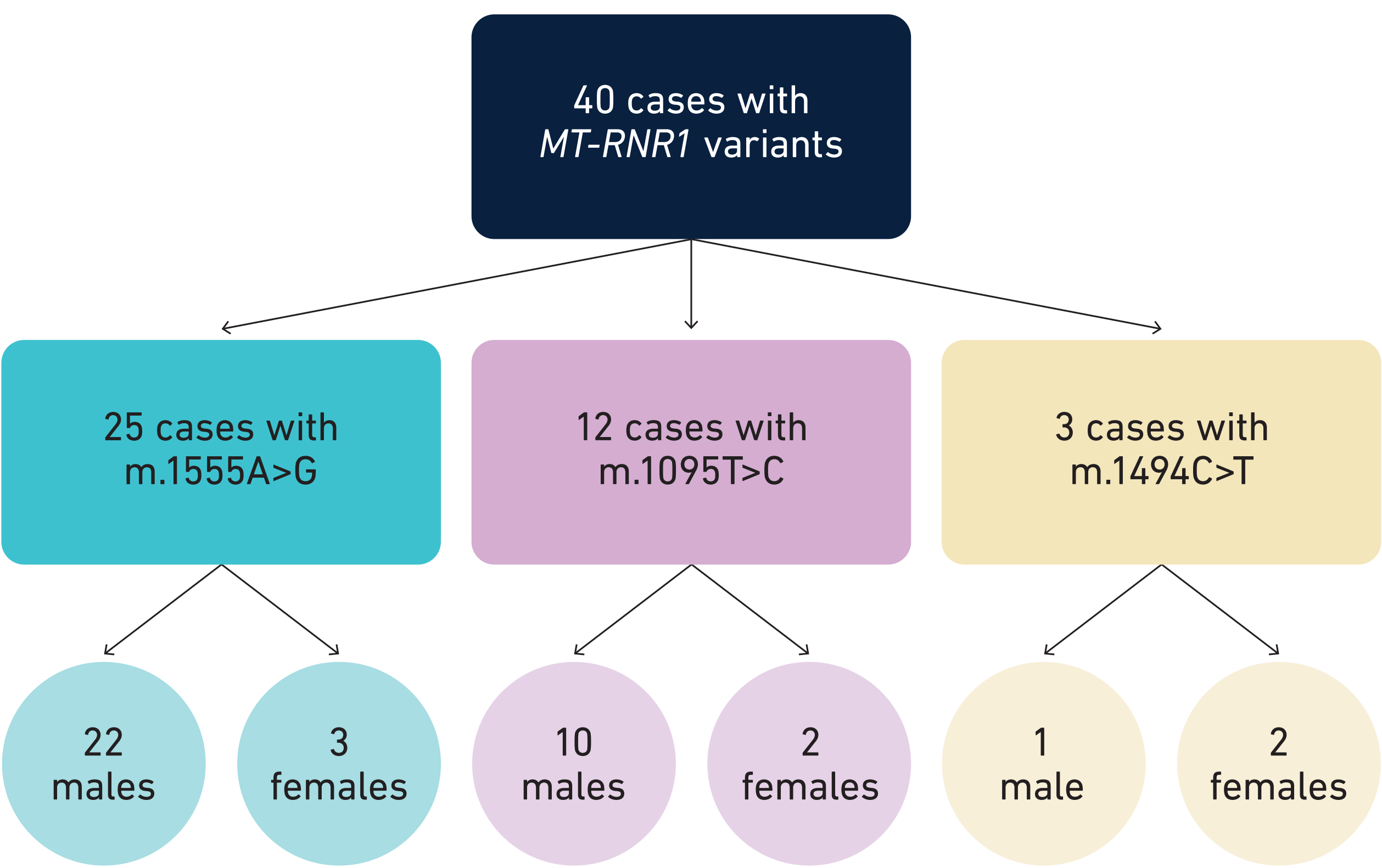
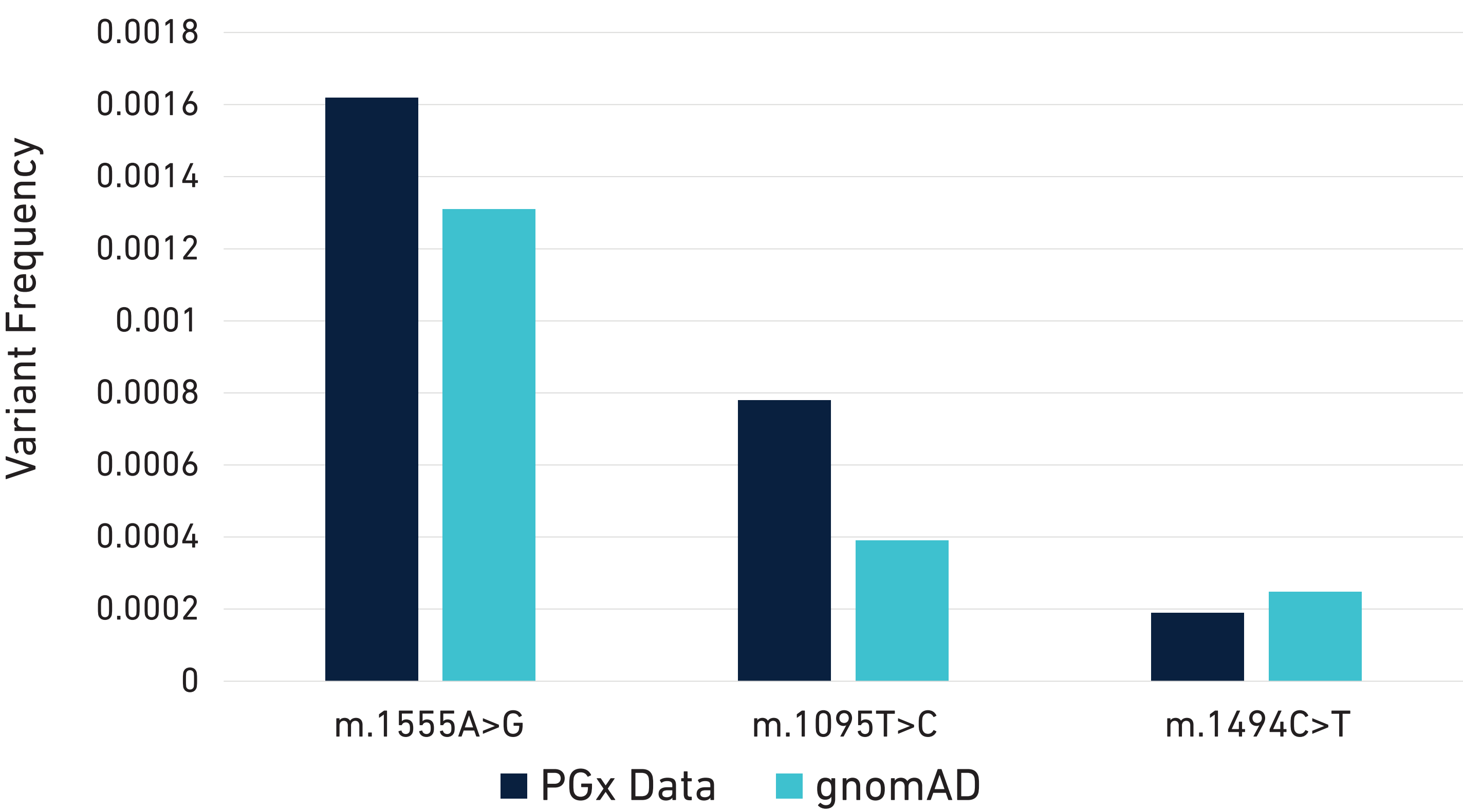


Figure 4. Frequency of *MT-RNR1* variants in our PGx cohort compared to gnomAD.



Conclusion

- Findings from this study demonstrate that approximately 1 in 385 adults have an increased risk of AIHL due to the detection of relevant *MT-RNR1* variants.
- Variant-level data suggests that the frequency of *MT-RNR1* variants, specifically m.1555A>G and m.1095T>C, appear to differ from currently available data.
- Due to the maternal inheritance of mitochondrial DNA variants, cascade testing should be considered for maternal relatives of all individuals with a relevant *MT-RNR1* variant, as well as for all children of females with these identified variants.
- Aminoglycosides are often reserved for more severe infections due to their toxicity profile making the inclusion of *MT-RNR1* variants on PGx panels, and appropriate cascade testing for relatives, important to ensure this information would be available at the time of use to avoid AIHL.