

# Variant m.1555A>G in *MT-RNR1* causes hearing loss and multiorgan mitochondrial disorder

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## Abstract

**Background:** Mitochondrial disorders (MIDs) are usually multisystem disorders, affecting not only a single organ/tissue but also progressively more than one.

**Methods:** Letter to the Editor.

**Results:** Though phenotypic manifestations of the m.1555A>G mutation are usually mono-organic, there are indications that short stature, osteoporosis, arterial hypertension, and recurrent headache can be also a manifestation of this variant.

MID patients with apparently single organ involvement need to be prospectively investigated for multisystem disease, as multisystem manifestations can be subtle or even subclinical.

Concerning the phenotypic expression of the m.1555A>G variant it is crucial to know the heteroplasmy rates in various tissues, as they may strongly contribute to the phenotypic expression of the disease. Maternal transmission can be confirmed by running a basic local alignment search tool.

**Conclusions:** The m.1555A>G variant is not only associated with hearing loss but with a number of other multiorgan manifestations. Heteroplasmy rate are required for establishing a genotype/phenotype correlation.

**Abbreviations:** BLAST = basic local alignment search tool, MID = mitochondrial disorder, MIMODS = mitochondrial multiorgan disorder syndrome, mtDNA = mitochondrial DNA, PCR = polymerase chain reaction.

**Keywords:** cardiac involvement, deletion, mitochondrial, mtDNA, multisystem

## 1. Introduction

In a recent article, Ou et al reported about a 50-year-old female with impaired hearing starting in her twenties.<sup>[1]</sup> Since, two of her sons also suffered from hypoacusis, a maternal trait of inheritance was suspected. Work-up for mitochondrial DNA (mtDNA) mutations indeed revealed the variant m.1555A>G in the 12S rRNA gene.<sup>[1]</sup>

**Diagnosis:** Patients with hereditary hearing loss following a maternal trait of inheritance require work-up for mutation in the mtDNA. The mtDNA mutation most frequently associated with hereditary hearing loss is the variant m.1555A>G in 12S rRNA (*MT-RNR1*).

## 2. Intervention and outcome

We disagree with the notion that the m.1555A>G variant only caused hearing loss in the patient described by Ou et al.<sup>[1]</sup> The patient also had a history of short stature osteoporosis, arterial hypertension, and cyclic headache, all typical phenotypic features of a mitochondrial disorder (MID).<sup>[2]</sup> These phenotypic features suggest that the m.1555A>G variant causes not only hypoacusis but also mitochondrial multiorgan disorder syndrome (MIM-ODS).<sup>[2]</sup>

Another shortcoming of the study is that clinically affected and unaffected first degree family members were not prospectively investigated for multisystem disease. We should know if the two sons only suffered from hypoacusis or from other abnormalities as well and if supposedly unaffected first degree family members in fact had subclinical or mildly manifesting MID.

A further shortcoming is that the index case was not prospectively investigated for MIMODS. We should be informed if short stature was attributable to pituitary insufficiency, and if there was ocular, cardiac, pulmonary, gastrointestinal, renal, hematological, immunological, dermal, or orthopedic involvement. Recording of an electrocardiogram is not sufficient to exclude cardiac disease. At least an echocardiographic investigation and a cerebral MRI should be carried out to confirm or exclude cardiomyopathy or cerebral involvement.

Missing in the study is the heteroplasmy rate of the m.1555A>G variant. Since, heteroplasmy rates have frequently a strong impact on the phenotypic expression of mtDNA variants,<sup>[3]</sup> it is crucial to determine heteroplasmy rates in hair follicles, skin fibroblasts, muscle, buccal mucosal cells, lymphocytes, or urinary epithelial cells. Another factor influencing the

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phenotype is the mtDNA copy number within a mitochondrion. If the copy number variation is high, it may also determine the phenotype.<sup>[4]</sup>

Furthermore, we do not agree with the interpretation of the pedigree as showing a maternal trait if inheritance. Since only two generations are shown with only three clinically affected patients, the trait could be also interpreted as autosomal dominant or even X-linked with a manifesting female carrier. To further substantiate maternal transmission, information about more than two generations should be provided.

In this regard, it is worthwhile to explain why the authors used the restriction enzyme BsmAI to cut the target gene and polymerase chain reaction (PCR) to amplify the DNA fragments. Why not running a basic local alignment search tool (BLAST) to identify the PCR sequencing information? BLAST may reveal if the mutation was transmitted via a maternal, an autosomal dominant, or an X-linked trait of inheritance.

### 3. Conclusions

In summary, the study would profit from prospective investigations for multisystem disease in the index case and all first degree relatives. The study lacks determination of the hetero-

plasmid rates and mtDNA copy number in different tissues, lacks genetic studies of affected and unaffected first degree relatives, and lacks demonstration of an unambiguous maternal trait of inheritance.

### Author contributions

**Conceptualization:** Josef Finsterer.

**Writing – original draft:** Josef Finsterer.

**Writing – review & editing:** Josef Finsterer.

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