*Macedonian pharmaceutical bulletin, 68 (Suppl 1) 411 - 412 (2022)*
*Online ISSN 1857 - 8969*
*DOI:10.33320/maced.pharm.bull.2022.68.03.198*
*Short communication*

# Mitochondrial DNA mutations and the risk for aminoglycoside-induced deafness

Emilija Shukarova Stefanovska[1*], Marina Davceva Chakar[2], Gjorgji Bozhinovski[1]

*[1]Research Center for Genetic Engineering and Biotechnology "Georgi D.Efremov", Macedonian Academy of Sciences and Arts, Av. Krste Misirkov 2, 1000 Skopje, R.N.Macedonia*
*[2]University Clinic of Otorhinolaryngology, Faculty of Medicine, Ss. Cyril and Methodius University, Vodnjanska 17, 1000 Skopje, Republic of North Macedonia*

## Introduction

Aminoglycosides are widely used for efficient treatment of gram-negative bacterial infections. However, even since the discovery of streptomycin, it is known that the major side effect of aminoglycosides is irreversible ototoxicity (Nguyen and Jeyakumar, 2019). Aminoglycosides have variable cochlea-toxicity leading to permanent hearing loss and vestibulotoxicity resulting in dizziness and ataxia (Gao et al., 2017). Significant progress has been made in understanding aminoglycoside ototoxicity, which seems to be mediated by the disruption of mitochondrial protein synthesis, the overexpression of NMDA receptors (N-methyl-D-aspartate), and the formation of free radicals. Understanding the mechanism of ototoxicity induced by aminoglycosides will be helpful for developing new therapeutic methods to protect hearing (Fu et al., 2021).

As previously reported, individuals bearing mitochondrial DNA mutations in the 12S rRNA gene, are more prone to aminoglycoside-induced ototoxicity. It is speculated that these mutations cause human mitochondrial ribosomes to more closely resemble bacterial ribosomes and enable a stronger aminoglycoside interaction (Foster and Tekin, 2017). Hot spot regions for deafness mutations are the *MTRNR1* gene, encoding the 12S rRNA and the *MTTS1* gene, encoding the tRNA for Ser(UCN). Nucleotide changes are observed with a variable frequency among different populations of deaf persons. Among them, homoplasmic m.1555A>G and m.1494C>T mutations at the highly conserved decoding region of the 12S rRNA have been the most commonly reported variants identified among cases of aminoglycoside ototoxicity and late-onset hearing loss (Maeda et al., 2020).

## Aim of the study

The aim of this study was to determine the presence and frequency of the mtDNA mutations as a cause of deafness among 150 Macedonian patients with nonsyndromic hearing loss.

## Materials and methods

A total of 150 Macedonian individuals diagnosed with non-syndromic sensorineural hearing impairment at the Othorinolarynology clinic, Medical faculty, Skopje, participated in this investigation. A comprehensive history and physical examination were performed.

In order to determine the five most common mitochondrial mutations associated with deafness: (NC_012920.1:m.827A>G (rs28358569); NC_012920.1:m.961delinsCn (rs1556422499); NC_012920.1:m.1095T>C (rs267606618); NC_012920.1:m.1494C>T (rs267606619) and NC_012920.1:m.1555A>G (rs267606617)) a SNaPshot method was designed.

Additionally, among 10 patients with only one *GJB2* mutation, the most common cause of congenital non-

*emilija@manu.edu.mk

syndromic hearing loss, the *MTRNR1* gene was sequenced, in order to detect other variants that as a modifier could influence to the pathologic effect of the *GJB2* mutation. For analysis of *MTRNR1* gene direct Sanger Sequencing method using BigDye Termination Sequencing kit v1.1 (Thermo Fisher Scientific) was performed on ABI 3500 Genetic Analyzer.

## Results and discussion

The mutational screening revealed that the two most commonly reported deafness-associated mutations, m.1555A>G and m.1494C>T were not found among analyzed patients. The presence of one potentially pathogenic substitution m.T961G in one patient and the m.G709A polymorphism in two patients were detected. An unpublished variant NC_012920.1:m1303G>A was found in one patient with only one *GJB2* mutation and the pathological effect of this variant should be further analyzed.

## Conclusion

In conclusion, our result suggests that mitochondrial DNA mutations do not represent a substantial risk factor for aminoglycoside-induced deafness in the Macedonian population.

## References

Foster, J., Tekin, M., 2016. Aminoglycoside induced ototoxicity associated with mitochondrial DNA mutations, Egypt. J. Med. Hum. Gen., 17(3), 287-293. https://doi.org/10.1016/j.ejmhg.2016.06.001

Fu, X., Wan, P., Li, P., Wang, J., Guo, S., Zhang, Y., An, Y., Ye, C., Liu, Z., Gao, J., Yang, J., Fan, J., Chai, R., 2021. Mechanism and Prevention of Ototoxicity Induced by Aminoglycosides. Front Cell. Neurosci. 15(15), 692762. https://doi.org/10.3389/fncel.2021.692762

Gao, Z., Chen, Y., Guan, M.X., 2017. Mitochondrial DNA mutations associated with aminoglycoside induced ototoxicity. J Otol. 12(1), 1-8. https://doi.org/10.1016/j.joto.2017.02.001

Maeda, Y., Sasaki, A., Kasai, S., Goto, S., Nishio, S.Y., Sawada, K., Tokuda, I., Itoh, K., Usami, S.I., Matsubara, A., 2020. Prevalence of the mitochondrial 1555 A>G and 1494 C>T mutations in a community-dwelling population in Japan. Hum Genome Var. 18, 7-27. https://doi.org/10.1038/s41439-020-00115-9

Nguyen, T., Jeyakumar, A., 2019. Genetic susceptibility to aminoglycoside ototoxicity. Int. J. Pediatr. Otorhinolaryngol. 120, 15-19. https://doi.org/10.1016/j.ijporl.2019.02.002