Molecular diagnostics of hearing loss due to mutations in the *SLC26A4* gene in indigenous peoples of Southern Siberia (Russia)

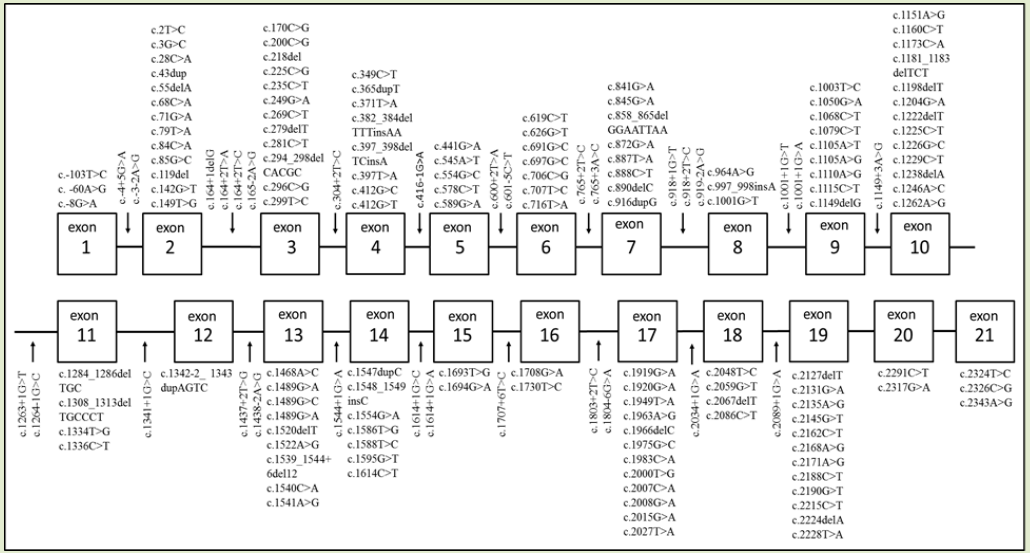
V.Y. Danilchenko[1], M.V. Zytsar[1], M.S. Bady-Khoo[2], E.A. Maslova[1,3], O.L. Posukh[1,3]

1 - Federal Research Center Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia
2 - Perinatal Center of the Republic of Tyva, Kyzyl, Russia
3 - Novosibirsk State University, Novosibirsk, Russia

Mutations in gene *SLC26A4* (7q22-q31, 21 exons) are a common cause of hearing loss in many populations.

SLC26A4 encodes transmembrane protein pendrin - a multifunctional anionic transporter that is expressed in inner ear, thyroid, and kidneys.

Mutations in *SLC26A4* lead to recessively inherited deafness (DFNB4) usually accompanied by the abnormalities in inner ear structures, and some forms of Pendred syndrome. More than 500 pathogenic *SLC26A4*-variants associated with hearing impairments are currently revealed in patients in different populations worldwide but there are still many regions where the *SLC26A4* contribution to deafness remains unknown.



The structure of the *SLC26A4* gene with mutations associated with hearing loss.

The authors declare that they have no competing interests

Mutational spectrum and pathogenic contribution of the *SLC26A4* gene in deafness in the indigenous peoples of Southern Siberia (Russia)

We analyzed all 21 exons and flanking regions of the *SLC26A4* gene in Tuvinian and Altaian patients with deafness of unknown etiology. Significantly higher pathogenic contribution of the *SLC26A4* gene in deafness was found in Tuvinian patients (28.2%) in contrast to Altaian patients (4.3%) ($p<0.05$) (Table 1.)

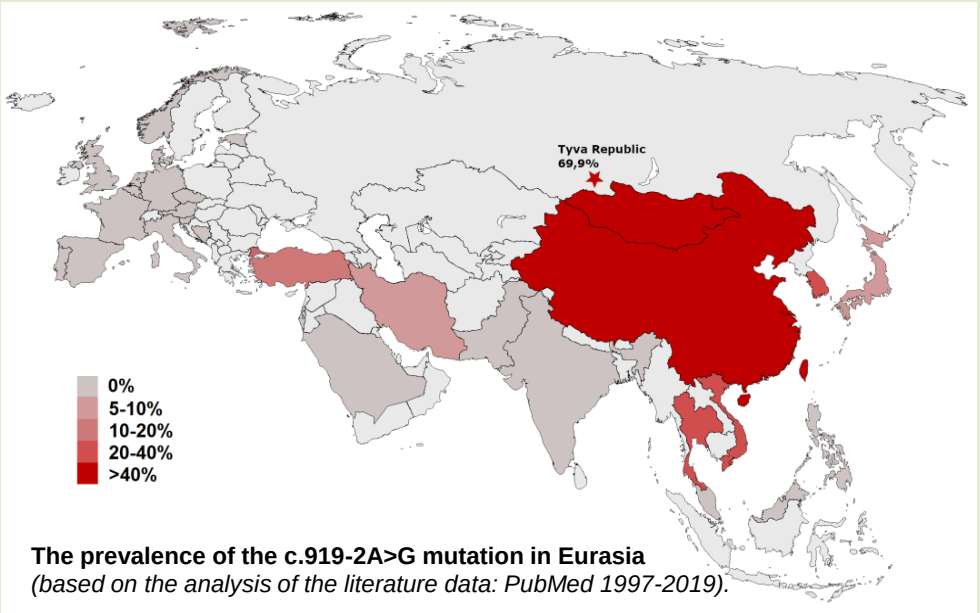
Both known c.170C>A, c.919-2A>G, c.2027T>A, c.2034+1G>A, c.2168A>G and novel c.1545T>G, c.1717G>T pathogenic recessive variants as well as a wide range of benign variants were found in the *SLC26A4* sequences of patients.

High frequency of mutation c.919-2A>G in Tuvinians (69.9% of all mutant alleles detected in patients and carrier frequency reaching to 5.1% in Tuvinian control sample) is probably due to the founder effect.

Table 1. The *SLC26A4* genotypes in examined patients.

SLC26A4 genotypes	Tuvinian patients (n=220)	Altaian patients (n=93)
Homozygous and compound heterozygous *SLC26A4* genotypes		
c.[919-2A>G];[919-2A>G]	30	-
c.[2027T>A];[2027T>A]	4	-
c.[2168A>G];[2168A>G]	-	2
c.[170C>A];[170C>A]	1	-
c.[919-2A>G];[2027T>A]	14	2
c.[919-2A>G];[1545T>G*]	8	-
c.[170C>A];[919-2A>G]	3	-
c.[919-2A>G];[2034+1G>A]	1	-
c.[1545T>G*];[2027T>A]	1	-
Total	62 (28.2%)	4 (4.3%)
Heterozygous *SLC26A4* genotypes		
c.[919-2A>G];[?]	9	-
c.[170C>A];[?]	1	-
c.[1545T>G*];[?]	1	-
c.[2027T>A];[?]	1	1
c.[1717G>T*];[?]	-	1
Total	12	2

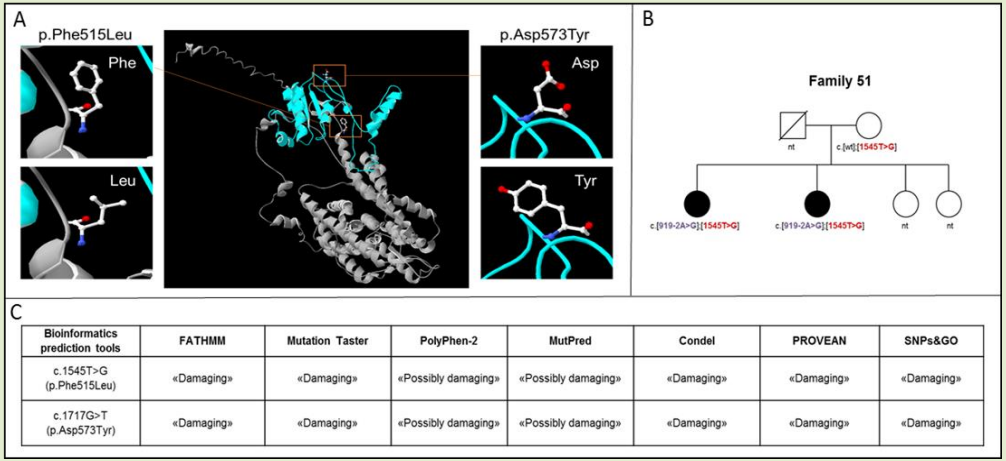
*** - novel variant.**



The prevalence of the c.919-2A>G mutation in Eurasia
(based on the analysis of the literature data: PubMed 1997-2019).

Mutational spectrum and pathogenic contribution of the *SLC26A4* gene in deafness in the indigenous peoples of Southern Siberia (Russia)

Probable pathogenicity of novel c.1545T>G and c.1717G>T *SLC26A4* variants was established by the bioinformatics prediction tools, and for variant c.1545T>G was confirmed by its segregation with hearing loss revealed by the analysis of patient's pedigrees.



Bioinformatics prediction tools	FATHMM	Mutation Taster	PolyPhen-2	MutPred	Condel	PROVEAN	SNPs&GO
c.1545T>G (p.Phe515Leu)	«Damaging»	«Damaging»	«Possibly damaging»	«Possibly damaging»	«Damaging»	«Damaging»	«Damaging»
c.1717G>T (p.Asp573Tyr)	«Damaging»	«Damaging»	«Possibly damaging»	«Possibly damaging»	«Damaging»	«Damaging»	«Damaging»

A. The 3D structure of the pendrin protein (*I-Tasser*) with novel c.1545T>G (p.Phe515Leu) and c.1717G>T (p.Asp573Tyr) mutations (*Swiss-PdbViewer*). *STAS–domain is shown by blue.*
B. Pedigree of family with novel *SLC26A4* mutation c.1545T>G (p.Phe515Leu).
C. The results of the bioinformatics prediction tools.

Conclusion:

This is the first study to address the *SLC26A4* mutations contribution in deafness in indigenous populations of Southern Siberia.

Contrast differences in the proportion of deafness caused by the *SLC26A4* mutations were revealed in Tuvinians (28.2%) and Altaians (4.3%) despite of their related ethnicity and close residence of these indigenous peoples of Southern Siberia.

Novel data on spectrum and prevalence of pathogenic and benign variants of gene *SLC26A4* in Siberian populations significantly contribute to the *SLC26A4* allelic diversity worldwide.

Study was supported by the Projects #0259-2019-0010-C-01, #0324-2019-0041-C-01, and the RFBR grant #17-29-06016_ofi-m.