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ATYPICAL CASES OF HEARING LOSS IN PATIENTS WITH A MITOCHONDRIAL VARIANT m.1555A>G OF THE *MT-RNR1* GENE IN THE REPUBLIC OF BURYATIA

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In a previous study, we found a high prevalence of the m.1555A>G variant of the *MT-RNR1* gene, which causes mitochondrial hearing loss (OMIM 561000) among deaf patients living in the Baikal Lake region. In this regard, in the present study, a genotype-phenotypic analysis of the hearing function in individuals with the m.1555A>G variant was carried out in the discovered Siberian region. Clinical and audiological analysis was performed in 48 people with this mitochondrial variant, whose average age was 51.3±15.5 years. The obtained genotype-phenotypic data are consistent with previously conducted studies of the features of the auditory function in individuals with m.1555A>G, which note incomplete penetrance of the manifestation of the pathological phenotype. Of particular interest in our cohort are three cases of mixed hearing loss, including both sensorineural (inner ear defect) and conductive (middle ear defect) components. The detected conductive component, which is atypical for this mitochondrial form of the disease, may be associated with idiopathic non-infectious foci of the pathological process in the middle ear. We do not exclude the possibility that the detected clinical signs may be a consequence of systemic damage to the hearing organ in this mitochondrial variant. On the other hand, the detected cases may be related to a cross-pathological effect caused by another form of a less common or rare disease. The obtained results require further genotype-phenotypic studies.

Keywords: mitochondrial hearing loss, m.1555A>G variant, *MT-RNR1* gene, genotype-phenotypic analysis, Buryatia

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Introduction. Mitochondria are intracellular organelles responsible for the production of adenosine triphosphate (ATP) through a process called oxidative phosphorylation [20]. In this process, energy is released by breaking down glucose and fatty acids via the mitochondrial respiratory chain [31]. Mutations in mitochondrial DNA have been described primarily in various rare syndromes, but are also found in more common diseases such as sensorineural hearing loss. One such mitochondrial mutation leading to isolated hearing loss is m.1555A>G in the *MT-RNR1* gene (OMIM 561000). There are several hypotheses regarding the pathogenetic mechanism of m.1555A>G in the *MT-RNR1* gene. In general, researchers believe that the m.1555A>G variant of the *MT-RNR1* gene is one of the “mild” ones compared to other pathogenic variants in mitochondrial DNA, since it does not lead to systemic disorders and does not always lead to hearing loss, and the manifestation of the pathogenic effect of

this mutation requires the participation of modulating factors [12, 22, 24]. Some of these modulators are probably aminoglycoside antibiotics, the principle of action of which is based on their ability to bind to the A-site of the 16S subunit of the bacterial ribosome and thus selectively disrupt the synthesis of prokaryotic proteins without affecting the ribosomes of eukaryotes, due to structural differences [12, 25]. The A>G substitution at position 1555 of human 12S rRNA results in a new C-G pairing, resulting in similarity with the A-site of bacterial 16S rRNA, which is a target for aminoglycoside antibiotics [13]. However, another hypothesis suggests that the m.1555A>G variant of the *MT-RNR1* gene can exhibit a pathogenic effect without the influence of external modulators [10, 12, 13, 16, 23, 25, 30]. Since the substitution of adenine for guanine at position 1555 of the *MT-RNR1* gene results in a change in the conserved A-site (aminoacyl-tRNA acceptor site) of 12S rRNA, this may lead to reading errors during the synthesis of oxidative phosphorylation proteins [23]. In a previous study, we found a high prevalence of the m.1555A>G variant of the *MT-RNR1* gene among patients with hearing impairments living in the Lake Baikal region [15]. With an average worldwide prevalence of the m.1555A>G variant of 1.8% (863/47328), the overall contribution among patients with hearing impairments in the Republic of Buryatia was 12.7% (21/165), and among Buryat patients 20.2% (15/74) [15]. The obtained results indicate that Eastern Siberia is the second largest region of accumulation of the mitochondrial form of hearing loss in the world, after the southern European territory of the Iberian Peninsula, where the overall contribution of this form of hearing loss varies from 17% to 41% [6, 34]. Analysis of the complete mitochondrial genome in 14 unrelated Buryat families carrying the m.1555A>G variant revealed a mitochondrial lineage common to the vast majority of examined individuals, associated with subhaplogroup A5b (92.9%). Considering that more than 90% of Buryat families with the m.1555A>G variant belonged to the same maternal line, it was suggested that the high prevalence of this pathogenic variant in the Lake Baikal region is due to the founder effect [Borisova et al., 2024]. In this regard, in the present work, a genotype-phenotypic analysis of the state of auditory function in patients with the m.1555A>G variant in the *MT-RNR1* gene was carried out in the discovered Siberian focus of accumulation of this mitochondrial disease.

Materials and methods. Study sample. In the Republic of Buryatia, 48 people with the pathogenic variant m.1555A>G of the *MT-RNR1* gene were studied, the average age at the time of the study was 51.3±15.5 years. By nationality, the study sample consisted of: Buryats - 97.9% (47/48), Russians - 2.1% (1/48).

Clinical and audiological analysis. Audiological examination of the hearing state was carried out using pure tone threshold audiometry using an "AA222" audiometer (Interacoustics, Denmark). The degree of hearing loss was assessed by the hearing thresholds of the better hearing ear in the speech frequency range of 0.5, 1.0, 2.0, 4.0 kHz according to the international classification, according to which the first degree of hearing loss corresponds to 26-40 dB, the second degree - 41-55 dB, the third degree - 56-70 dB, the fourth degree - 71-90 dB, deafness >90 dB. For a detailed audiological analysis, we used the clinically important speech frequency range ($PTA_{0.5,1,0.2,0,4.0kHz}$). Audiograms with breaks were normalized by introducing the maximum values (120.0 dB) at frequencies to which the patient did not respond. Sensorineural hearing loss was diagnosed in cases of increased bone and air conduction thresholds on audiograms, mixed - with an increase in bone and air conduction thresholds with an interval exceeding 20.0 dB in total in the $PTA_{0.5,1,0.2,0,4.0kHz.}$ Hearing loss was considered asymmetric if the interaural difference in hearing thresholds at the PTA frequencies of 0.5, 1, 0.2, 0.4.0 kHz was more than 15.0 dB.

Detection of the m.1555A>G variant in the *MT-RNR1* gene. Genomic DNA was extracted from venous blood using the phenol-chloroform method. Detection of the m.1555A>G variant in the *MT-RNR1* gene was performed by PCR-RFLP analysis using the previously described sequence of oligonucleotide primers, with a modified reverse primer, which allows the creation of an artificial recognition site for the restriction endonuclease *Hae*III [10]. As a result, after 12-hour treatment of the amplification product at 37°C with the *Hae*III enzyme: normally (1555A) two restriction fragments are formed (216 and 123 bp), with the substitution (1555G) three restriction fragments (216, 93 and 30 bp). Verification of the presence of m.1555A>G in the *MT-RNR1* gene was carried out by Sanger sequencing using the original sequence of oligonucleotide primers: F - AAACGCTTAGCCTAGCCACA, R - GCTACACTCTGGTTCGTCCA, selected using the Primer-BLAST program [29].

Ethical approval. The studies provided for in this work were carried out after informed written consent of the participants. The research work was approved by the local committee on biomedical ethics at the Yakut Scientific Center of Complex Medical Problems in 2019 (Yakutsk, protocol No. 7 dated August 27, 2019).

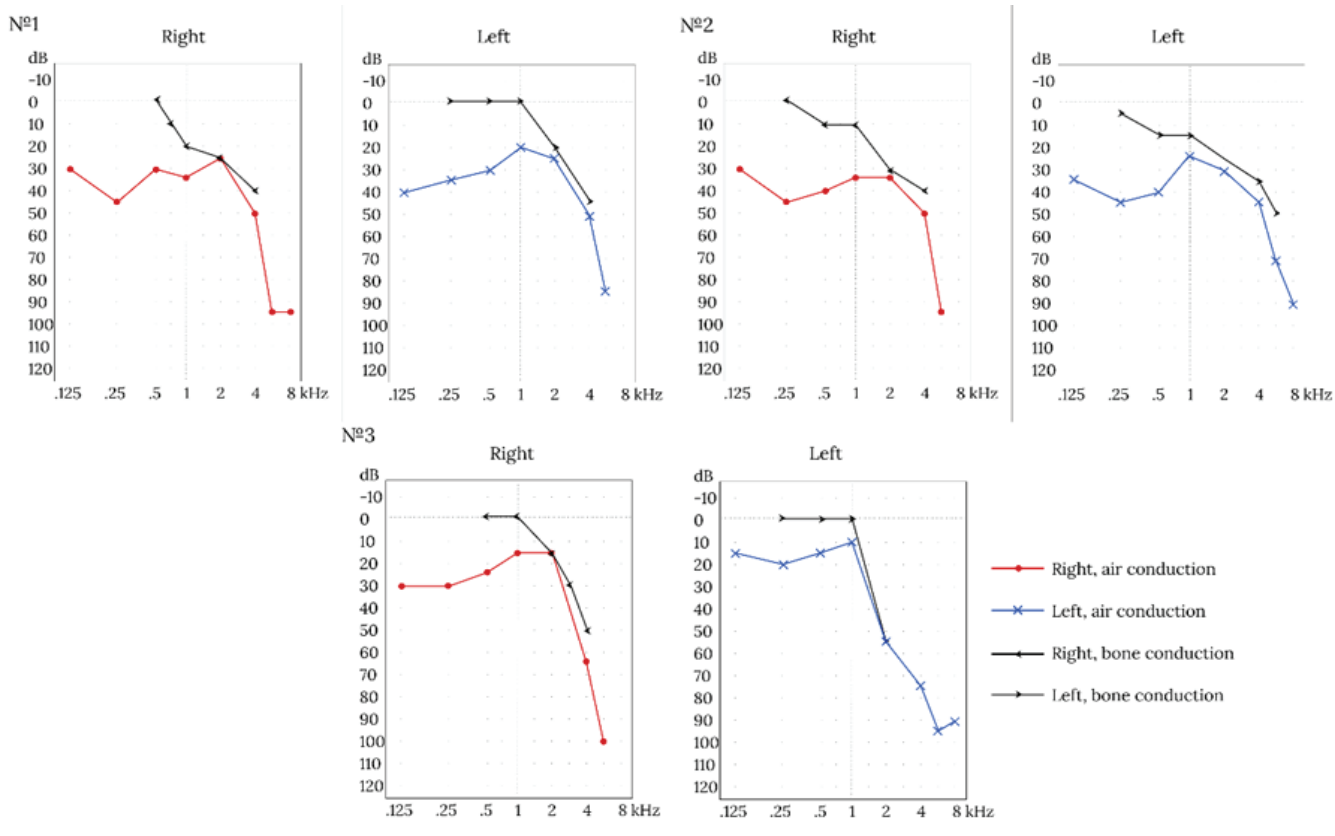
Results and discussion. In this work, a clinical and audiological analysis of the hearing function was performed in 48 individuals with the mitochondrial variant m.1555A>G in the *MT-RNR1* gene (mean age 51.3 years) living in the Republic of Buryatia. As a result, audiological profiles of the state of the hearing function were obtained for all study participants. The characteristics of individuals with m.1555A>G in the *MT-RNR1* gene are presented in Table.

In 27.1% of individuals with the m.1555A>G variant of the *MT-RNR1* gene, hearing in the $PTA_{0.5,1,0.2,0,4.0kHz}$ frequency range was within normal values. In 64.6% of the examined subjects, the type of hearing loss was sensorineural, of varying severity from I–II degree of hearing loss to profound (Table). In 8.4% of patients with the m.1555A>G variant of the *MT-RNR1* gene, a mixed form of hearing loss was detected, including both sensorineural (inner ear pathology) and conductive components (middle ear pathology) (Table). One patient with a mixed type of hearing loss was found to have

The auditory function in individuals with m.1555A>G in the *MT-RNR1* gene

Type and degree of the hearing loss	n	%
Normal hearing	13	27.1
Sensorineural hearing loss (n=31. 64.6%)		
- I-II degree	2	4.1
- III-IV degree	9	18.7
- Profound	20	41.6
Mixed hearing loss (n=4. 48.4%)		
- I-II degree	4	8.4
Total	48	100

Note: n - is the number of individuals with m. 1555A>G in the *MT-RNR1* gene.



Audiograms of patients with mixed hearing loss with the mitochondrial variant m.1555A>G in the *MT-RNR1* gene

a perforation of the eardrum, indicating inflammatory processes caused by otitis media. In three of the four patients, signs associated with developmental abnormalities or otitis media were not detected. The age at the time of the examination of these three patients was 54, 68 and 69 years, respectively. All three patients - one man and two women - came from unrelated Buryat families and lived in the same region of the Republic of Buryatia. It should be noted that before the examination, these patients did not complain about their hearing, but according to the clinical and audiological examination, hearing loss in the speech frequency range ($PTA_{0.5,1,0.2,0,4.0kHz}$) corresponded to the first degree of mixed hearing loss. Audiograms of patients with a mixed form of hearing loss with the m.1555A> G variant in the *MT-RNR1* gene are shown in Figure.

The genotype-phenotypic data obtained by us are consistent with previously conducted studies of the characteristics of the hearing function in patients with the m.1555A>G variant in the *MT-RNR1* gene, which note incomplete penetrance of the manifestation of the pathological phenotype in affected families [10, 12, 13, 16, 23, 25, 30, 32]. In other words, not all carriers of m.1555A>G may have clinically significant hearing loss. It is believed that the age of onset, as well as the degree of hearing loss in individuals with m.1555A>G in the *MT-RNR1* gene, can vary widely - from normal hearing to deafness. The manifestation of signs of hearing loss in carriers of the m.1555A>G variant in some families positively correlated with treatment with aminoglycoside antibiotics [10, 12, 13, 16, 23, 25, 30], as well as with the age of patients [42]. However, not all registered cases of mitochondrial hearing loss can be explained by the ototoxic effect of drugs and progression with age. In this regard, many researchers believe that there are other factors, including genetic ones (mitochondrial environment and/or variants in the nuclear genome), modulating the pathological "manifestation" of the m.1555A>G variant [7, 10, 12, 13, 14, 18, 23, 25, 27, 32]. Since we did not find any references in the literature about conductive or mixed type of hearing loss in patients with m.1555A>G in the *MT-RNR1* gene, and the pathogenetic mechanism of mitochondrial hearing loss is associated with damage to cochlear cells, the type of hearing loss should be exclusively sensorineural. In this regard, three cases of mixed type of hearing loss in patients with m.1555A>G in the *MT-RNR1* gene are of particular interest in our cohort of examined individuals. We do not exclude the possibility that the detected clinical signs may be a consequence of previously undescribed systemic damage to the hearing organ in the mitochondrial variant m.1555A>G. Since, despite the fact that the m.1555A>G variant of the *MT-RNR1* gene is generally considered to be a non-syndromic sensorineural type of hearing loss, there is an alternative opinion that this pathogenic variant is capable of having not only local, but even multi-organ damage potential, which requires a broader clinical study of this form of the disease, since multi-system manifestations can be barely noticeable or even subclinical (short stature, osteoporosis, arterial hypertension and recurrent headache) [11].

On the other hand, our three cases of mixed hearing loss in patients with m.1555A>G in the *MT-RNR1* gene in the Republic of Buryatia may be associated with a cross-over pathological effect caused by another form of a less common or rare disease. Due to the absence of other clinical manifestations in the patients examined by us, as well as their age (54, 68, and 69 years) and gender (one man and two women), it is unlikely that the identified cases are associated with a cross-over effect of an

X-linked recessive form of hearing loss (DFNX2, OMIM 304400). In addition, we cannot completely exclude the version of an atypical manifestation (incomplete penetrance of clinical signs) of one of the rare syndromes in which a mixed type of hearing loss can be observed: branchio-oto-renal syndrome (OMIM 113650), Stickler syndrome (OMIM 108300), Marfan syndrome (OMIM 154700), Treacher Collins syndrome (OMIM 154500), Axenfeld-Rieger syndrome (OMIM 602482) and many others. However, in our opinion, the most likely cause may be an idiopathic non-infectious focus of the pathological process in the middle ear, caused by otosclerosis. The otosclerotic process is based on focal lesions of the bony capsule of the otic labyrinth, with healthy bone being replaced by newly formed porous, spongy, vascular-rich bone tissue during growth, which is why the early stages of otosclerosis are sometimes called otospongiosis. The prevalence of otosclerosis worldwide varies from 1 in 330 in Europe, 1 in 3,300 in Africa, to 1 in 33,000 in Asia [35]. Patients typically have conductive hearing loss, primarily affecting low and mid frequencies, which often progresses to mixed hearing loss. The disease typically manifests in the second, third, or fourth decade and is generally successfully corrected with a combination of surgery and hearing aids [28]. Although both environmental and genetic risk factors have now been identified, the etiology of sporadic cases of otosclerosis remains unknown [5]. An exception are rare familial forms of otosclerosis, segregating according to the autosomal dominant type of inheritance, for some of which genetic loci linked to this disease have been mapped [1, 2, 4, 8, 17, 19, 36, 37]. Despite some success in mapping loci linked to otosclerosis, pathogenic variants in any genes have not been identified to date. However, in 2022, a 15-nucleotide heterozygous deletion in the coding region of the *FOXL1* gene was identified in families with otosclerosis from the Canadian province of Newfoundland and Labrador [3], the product of which is presumably involved in bone remodeling processes in the auditory capsule [26], which was described as casuative for the autosomal dominant form of otosclerosis type 11 (OMIM 620576) [3].

Conclusions. Taking into account the atypical for the mitochondrial form of hearing loss - a mixed type of hearing loss in three Buryat patients with m.1555A>G in the *MT-RNR1* gene, which was not associated with otitis media, the detected clinical signs may be a consequence of a previously undescribed systemic lesion in this mitochondrial variant. On the other hand, the detected clinical signs may be caused by a cross-pathological effect due to another unspecified form of the disease. In our opinion, the most likely cause of the atypical picture of hearing loss in patients with m.1555A>G may be a cross-pathological effect caused by otosclerosis or another rare disease in which a mixed type of hearing loss can be observed (branchio-oto-renal syndrome, Stickler syndrome, Marfan syndrome, Treacher Collins syndrome, Axenfeld-Rieger syndrome and many other syndromes). Given the wide range of nosological forms associated with mixed type of hearing loss, the obtained results require further molecular genetic studies using high-throughput sequencing methods.

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DIAGNOSTIC AND TREATMENT METHODS

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SACRUM WITH FIVE PAIRS OF SACRAL OPENINGS, AS A PATHOGNOMONIC SYMPTOM OF LUMBOSACRAL TRANSITIONAL VERTEBRAE

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Introduction. Clinical experience shows that during radiological examination of the pelvis, patients are often diagnosed with a sacrum with five pairs of sacral openings, while normally there should be four. Purpose: To which form of dysplasia should cases of diagnosis of the sacrum with five pairs of sacral openings be attributed. Material and methods. The clinical material for the study was the results of computed tomography of the lower lumbar spine and pelvic bones in 78 patients who were diagnosed with a sacrum with five pairs of sacral openings. The CT examination of the patients was carried out on a 128-slice «General Electric» device. Results. The study established that the analyzed group of 78 patients was heterogeneous and consisted of two subgroups. Patients of the first subgroup (52 (66.7%) patients) had fused upper sacral vertebrae by transverse processes to the left and right of the sacral crest. Patients of the second subgroup (26 (33.3%) patients) had similar bone fusion of two upper sacral vertebrae on one side, there was no such concrescence on the contralateral side, and synchondrosis was clearly defined. Discussion. The sacrum with five pairs of sacral openings should be attributed to such a congenital pathology of the lumbosacral junction as lumbosacral vertebrae. It is known that this disease is divided, according to the classification of A.E. Castellvi et al. (1984), into 7 different types. Those clinical observations that were diagnosed in patients of the studied cohort should be attributed to types IIIb (first subgroup, 52 patients) and IV (second subgroup, 26 patients) of the disease. In the clinical picture of each of the types of pathology, vertebrogenic pain syndrome of lumbosacral localization prevails. Conclusion. The presence of such a bright radial symptom of sacral pathology as five pairs of sacral openings allows for timely diagnosis of cases of transitional lumbosacral vertebrae, informing patients about the nature of the disease, and, if necessary, prescribing therapy adequate to the severity of the condition.

Keywords: sacrum, cranial sacral vertebrae, sacral openings, lumbosacral transitional vertebrae.

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Introduction. In clinical practice, there are often situations when, during a radiological examination of the pelvis, patients are diagnosed with a sacrum with five pairs of sacral openings [9]. In these cases, the question arises: is this radiological picture normal or is it a variant of pathology [11]. There is no direct answer to this question in modern literary sources [3].

Purpose: To establish which form of dysplasia should be attributed to cases of diagnosis of a sacrum with five pairs of sacral openings.

Material and methods. The clinical material for the study was the results of computed tomography (CT) of 252 patients aged 12 to 86 years with injuries and diseases of the lower lumbar spine and pelvis, in whom images of the sacrum were "obtained" during the radiological diagnostics. In total, out of 252 patients

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