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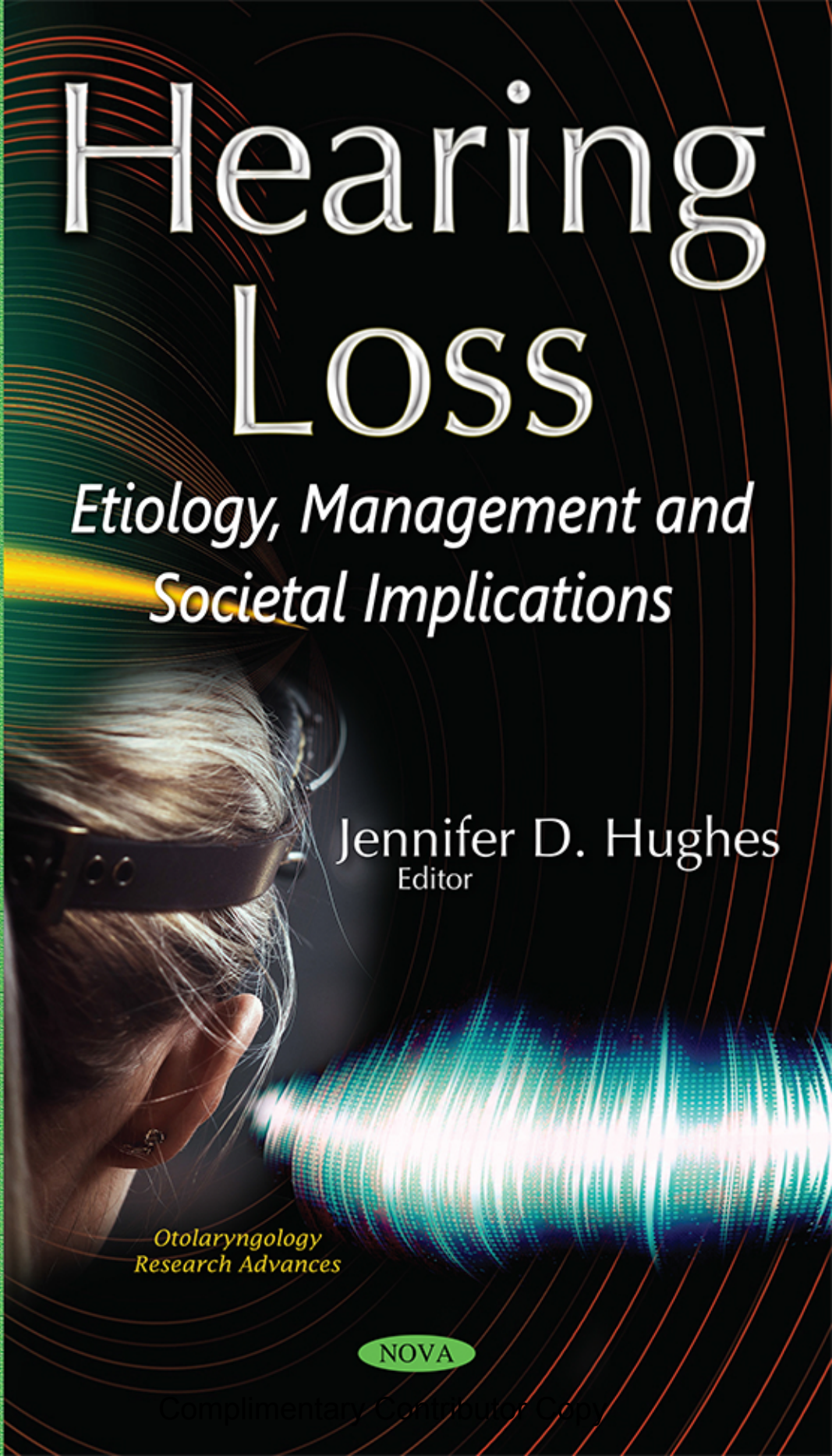

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HEARING LOSS

ETIOLOGY, MANAGEMENT AND SOCIETAL IMPLICATIONS

JENNIFER D. HUGHES
EDITOR

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Chapter 8

HEARING LOSS OF VOLGA-URAL REGION IN RUSSIA

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ABSTRACT

We studied the molecular basis of NSHL in Volga-Ural region. The Volga–Ural region of Russia is of particular interest, because its ethnic populations mostly belong to the Turkic, Finno-Ugric, and Slavonic linguistic groups and have complex ethno genesis and combine the Caucasian and Mongoloid components in various proportions. The data on the prevalence of hereditary non-syndromic sensorineural hearing loss in the Volga-Ural region was received. It was 5.7 per 100000 (1:17543) of the population. The heterozygous carrier frequency of c.35delG, c.167delT and c.235delC mutations of the GJB2 gene in 17 populations of Eurasia was revealed. The analysis of the spectrum and frequency of mutations in genes GJB2, GJB6, GJB3, 12SrRNA, tRNASer (UCN), SLC26A4 and SLC26A5 in patients with non-syndromic sensorineural hearing loss from Bashkortostan Republic was performed. The mechanism of accumulation of non-syndromic sensorineural hearing loss caused by c.35delG mutation in Volga-Ural region is analyzed on the basis of haplotype analysis. The age of c.35delG mutation in the GJB2 gene in populations of the Volga-Ural region was defined. New approaches are developed to prevent hereditary sensorineural hearing loss and to improve medical and genetic consulting for patients with the inherited form of hearing impairment in Volga-Ural region.

Keywords: hearing loss, genes GJB2, GJB6, GJB3, 12SrRNA, tRNASer(UCN), SLC26A4 and SLC26A5

According to various sources, congenital deafness is found in 0,05% - 0,1% of the children; what is more, the majority of sick children (92%) suffer from sensorineural deafness (NSD). In most cases (about 90%) they are children of hearing parents and their families had no cases of hearing-impaired relatives. Depending on the nature of its cause, deafness is usually divided into two large groups: hereditary and acquired. Acquired hearing loss occurs due to the influence of various adverse environmental factors on a fetus, an infant or an older child. Depending on the nature of deafness, they distinguish between conductive and sensorineural types, meanwhile intermediate and mixed forms are frequently observed. Mixed hearing loss is characterized by the presence of both types of impairments: conductive and sensorineural. The cause of conductive hearing loss is a damage of the outer and middle ear and nasopharynx. Anomalies of the pinna and ear canal (atresias, microtias, development abnormalities of the auditory ossicles or otostapes fixation, etc.) can be attributed to the pathology of the external ear. If we talk about the

abnormalities of the outer and middle ear, it is obvious that these types of pathologies are congenital; with age conductive type of hearing loss develops mainly due to otosclerosis (Duman et al., 2013).

Sensorineural deafness may be determined by the damage in different parts of the inner ear: the cochlea (the organ of Corti), the vestibulocochlear nerve, the pathways or the relevant structures of the brain. Sensorineural hearing loss is usually divided into cochlear (it occurs when hair cells in the organ of Corti are damaged) and retrocochlear in which cochlear neuritis is diagnosed (Tavartkiladze et al., 1996; Altman et al., 2003). A number of anomalies in the structure of the inner ear have been described in the result of pathomorphological studies of temporal bones in deaf individuals. It was found that congenital deafness may be determined by primary changes in the cochlea itself (Fishman et al., 1996).

Until 1995, clinical researchers had to face significant difficulties in the study of NSD, as before the methods of molecular genetic analysis of hereditary forms of hearing loss and deafness had been introduced into medical practice, scientific literature mainly had the descriptions of genealogy with the hypothetic types of inheritance and the attempts of segregation analysis. It was impossible to prove the hereditary nature of hearing loss in the families with sporadic cases. (Fishman et al., 1996). Assortative marriages and intermarriages between the hearing-impaired and deaf individuals should be specifically noted, as they play an important role in the spread of certain forms of deafness and hearing loss, having complex etiology, pathogenetic and epidemiologic mechanisms. Thus, molecular analysis is the only way of non-syndromic deafness adequate diagnosis, especially in the absence of genealogic pedigree data.

The most common form of hereditary deafness is the so-called nonsyndromic or isolated form, characterized by hearing loss only. In some forms of hereditary deafness there is a combination of hearing loss and abnormalities of other organs or systems. They are usually denoted as syndromic forms. In some syndromes, besides hearing impairment, there are also observed vision, thyroid, pigmentation disorders or kidney pathologies, etc. (Everett et al., 1999). One of the most world common forms of syndromic deafness, that can be found in 3-6% of all congenital deafness cases, is Usher syndrome (Nance, 2003; Duman et al., 2013). Usher syndrome, in its various forms, is a combination of hearing loss and vision impairment. Waardenburg syndrome is the cause of hearing loss in about 2 - 5% of congenital deafness cases (Ouyang et al., 2002; Morton, 2006). This syndrome is characterized by skin and hair pigmentation abnormalities combined with minor facial

anomalies in addition to hearing loss. At the present moment, there are more than 400 syndromes combined with hearing loss pathology (OMIM 2013).

Clinical polymorphism of many syndromic and nonsyndromic hereditary forms of hearing loss and deafness is primarily determined by genetic heterogeneity of this pathology.

The number of patients with hearing impairments in Russian Federation exceeds 13 million people; more than 1 million of them are children. Total deafness is recorded in 1 per 1000 newborns. Moreover, during the first 2-3 years of life, 2-3 children lose hearing. 14% of people aged from 45 to 64 and 30% of people aged over 65 have hearing impairment. According to WHO, over 30% of the world population will suffer from hearing impairment in 2020 (Tavartkiladze et al. 2010).

During the targeted screening of the child population for the hearing impairment in several countries (England, Germany, Italy, Spain, Sweden, Finland, USA), averagely, deafness was detected in 1 per 650 newborns. The screening was carried out on the basis of complete audiological examination (Snoeckx et al., 2005). According to the data of various authors, it is noted that in the US at least 1 per 1000 live newborns is born with moderate or severe bilateral NSD, including 4 completely deaf children per 10,000. It is three times more than Down's syndrome, six times more than spina bifida and 50 times more than phenylketonuria (Petersen et al., 2006).

The analysis of children's age characteristics at the time of diagnosis in surdologopaedic offices of Russian regions showed that the diagnosis of hearing loss and deafness was untimely: children under 1 make only 5% of the total number of the examined; aged from 1 to 3 - 14%; about a third of children (28%) is placed in the dispensary registration list at the age of 3-7; 30% of children had hearing impairment detected at the age of 7-14 and 23% at the age of 14-18 (Tavartkiladze et al., 2010).

It is quite a difficult task - to get a complete picture about the frequency of hearing impairment among children, since numerous criteria must be taken into account: the nature of pathology, age of onset, degree of hearing loss, the child's age, family history, and character of the various complications during mother's pregnancy and labor, past illnesses, place of study, and others. Children with severe hearing loss initially fall into a specific group and they are available to account for the prevalence registration of deafness due to the possibility of studying in specialized correctional institutions. While children with mild and moderate degrees of NSD often do not get under audiologists' supervision, because they can study at an elementary school and not complain about hearing loss during medical examinations. It requires specific diagnostic

and screening programs, including genetic testing, to identify such forms of children's hearing loss that mainly develop during the first year of life.

In practice, it is often quite difficult to differentiate congenital hearing loss from hearing impairment occurring postpartum during the first year of life, especially if the degree of sound perception impairment is slight and the progression of the process is slow (Cryns et al., 2004; Tavartkiladze et al., 2010).

The data on the prevalence of prelingual non-syndromic sensorineural deafness in the world literature is quite scarce. Thus according to The Gallaudet Encyclopedia of Deaf People and Deafness (1986) and The Encyclopedia of Deafness and Hearing Disorders (2004), the prevalence of congenital deafness is 50 per 100 000 in the US, 47 per 100 000 in France and 46 per 100 000 in the UK. In Europe, the incidence of congenital autosomal recessive deafness is averagely in 1 per 5000 newborns, autosomal dominant in 1 per 10000, X-linked in 1 per 100 000 boys (Alvarez et al., 2010; Duman et al., 2013). According to the register of British Columbia (Canada), the frequency of the dominant deafness is 0,19 and recessive is 0,25 per 10,000 newborns (Petersen at al., 2006; Alvarez et al., 2010).

Diagnostic screening programs for assessing the frequency of congenital hearing loss in newborns are carried out in a number of European and Asian countries, as well as in the United States (Tsukada et al., 2010; Duman et al., 2013).

In the former CIS countries in the period from 1983 to 1989, a study on the prevalence, etiology and clinical features of sensorineural hearing impairment in children of the Republic of Uzbekistan was carried out (Agzamhodzhaev SS, 1989). It was shown that NSD occurred in 9,7 per 10000 children on the territory of the Republic of Uzbekistan. The hereditary nature of the disease is established in 44% of cases. Isolated hearing impairments were detected in 94,8% of children and syndromal hearing impairments in 5,2% of cases.

Research on the epidemiology of hereditary deafness forms was carried out in a number of regions of the Russian Federation in the framework of integrated health and population-genetic survey of a region, providing a wide range of hereditary diseases detection (including different forms of hearing loss), together with the study of the genetic structure peculiarities. That made it possible to explain the basic mechanism behind the dissemination of hereditary deafness in region's districts. In these studies it was shown that spatial differences in the frequencies of hearing loss in different regions were determined by the peculiarities of the genetic structure of the populations

studied, in particular, the level of genetic subdivision and the influence of genetic drift (Shokarev R.A. et al., 2002; Panakhian V.M. 2004, Markova et al., 2005; Zinchenko R.A. et al., 2007; Shokarev R.A. et al., 2005; Zinchenko et al., 2012; 2013; Bessonova et al., 2012).

Numerous studies point to a significant contribution of genetic factors in the process of sound perception impairment (Cryns et al., 2004; Smith et al., 2005; Petersen et al., 2006; Duman et al., 2013). Almost all inheritance types are observed in the inherited forms of hearing impairment, including X-linked and mitochondrial forms. Different loci of numerous nonsyndromic forms of deafness are denoted by letters DFN, taken from the English word deafness and they are numbered in chronological order as they had been discovered. Autosomal dominant loci are denoted as DFNA, autosomal recessive as DFNB and X-linked as DFN. The most common form of hereditary hearing loss is nonsyndromic deafness. It is characterized by clinical polymorphism and genetic heterogeneity (Petit et al., 2001; Morton, 2006; Petersen et al., 2006). This form of the disease occurs most frequently among the patients with hereditary nonsyndromic deafness (from 30 to 75% of all cases) (Denoyelle et al., 1997; Estivill et al., 1998; Antoniadi et al., 1999; Loffler et al., 2001; Morton, 2006; Petersen et al., 2006; Tekin et al., 2010). Approximately 70-77% of all non-syndromic deafness cases occur in autosomal recessive forms, 20-25% in autosomal dominant and all other cases in X-linked and mitochondrial forms of deafness (Morton et al., 2006).

Genetic heterogeneity of hereditary sensorineural deafness forms is determined by the fact that more than 60 genes take part in the process of embryonic development of the organ of Corti (Duman et al., 2013). Most of the mutations that cause sound perception impairment are identified in the genes encoding connexins GJB2, GJB6, GJB3, GJA1, GJB1. Besides, the mutations that lead to hearing loss were also found in the genes of other proteins that are widely expressed in the inner ear tissues: collagen, actins, tectorines and others. Using the method of linkage analysis more than 110 loci for hereditary nonsyndromic sensorineural hearing loss and deafness were mapped. At the present time, more than 65 genes where mutations are responsible for the occurrence of human deafness were identified. It is noteworthy that the search for genes in which mutations are responsible for the development of many hereditary defects, including hereditary deafness, got intensified with the end of major international research – the project of the human genome sequencing (Human Genome Project) (http://www.gdb.org/) and haplotype mapping (Haplotype Mapping Project) (http://www.hapmap.org/). These research programs were actually catalysts

for the development of more effective and rapid technologies of decryption, generating and interpreting a large array of genetic databases (http://www.gdb.org/).

It was found that more than 50% of congenital nonsyndromic NSD is caused by mutations in the gene GJB2 (connexin 26 gene) (Smith et al., 2005). The contribution of this gene to the development of some nonsyndromic and syndromic forms is 4-80% (Petersen et al., 2006; Vivero et al., 2010).

Protein connexin 26 (Cx26) is involved in the formation of gap junction intercellular contacts necessary to move ions and small molecules in the tissues of the cochlea. Six connexins are joined together forming a connexon penetrating the cell membrane, which forms a channel together with the connexon of the neighboring cell.

At the present time it is observed that in some ethnic groups there is a high frequency of heterozygous carriers of the most frequent mutations the gene GJB2. The most common of these are deletions of: guanine at position 35 - c.35delG, cytosine at position 235 - c.235delC, thymine at position 167 - c.167delT and replacements - p.Trp24X and p.Arg143Trp. Moreover, the mutation c.35delG occurs mainly in populations of Europe, the Middle East and North America (Rabionet et al, 2000; Mustapha et al., 2001; Najmabadi et al., 2002; Tekin et al., 2003, 2010). The mutation c.235delC is major for the Mongoloid populations and occurs mainly in East Asia among the Japanese, Chinese and Koreans. It is also recorded among the Mongols and the Altaians (Yan et al., 2003; Posukh et al., 2005).

Mutation c.167delT is widespread mainly among the Ashkenazi Jewish groups, but there are some peoples of the Mediterranean, Eastern Europe and sporadically throughout Eurasia (Morell et al., 1998; Lerer et al., 2001; Gasparini et al., 2000; Bors et al., 2004). p.Trp24X mutation is most common in India and Slovakia (Mukherjee et al., 2003; Minarik et al., 2003; Ramchander et al., 2005) and p.Arg143Trp is a major mutations in Ghana (Africa) (Brobby et al., 1998; Hamelmann et al., 2001; Nagla et al., 2004).

Currently there are more than 130 different dominant and recessive mutations in the gene GJB2 (Connexin-Deafness Homepage). Dominant effect of many connexin gene 26 mutations is mainly being associated with the mutation location in the domains of connexin 26. It was previously shown that some mutations located in specific regions of the gene GJB2 may affect the assembly of various classes of homologous and heterologous connexons (Bicego et al., 2006).

In order to estimate the prevalence of hereditary forms of non-syndromic sensorineural hearing loss in the Volga-Ural region, without differentiation

into types, we used the materials of a complex entire health and population-genetic examination of the population in seven districts of the Republic of Bashkortostan (RB), carried out in the period from 2005 to 2008 in collaboration with Research Center of Medical Genetics (RCMG) of the Russian Academy of Medical Sciences (RAMS) (Moscow), the information on all known patients with congenital deafness, living on RB territory was obtained from the database of the National Surdologic Center where the majority of families with hereditary hearing loss is registered, the examination records in special schools of RB for hearing-impaired and deaf, documents on medical and social expertise on inspection of hearing-impaired and deaf between the years of 2000 and 2012 years. The obtained information was specified at the moment of the study through a targeted request to the central city and regional hospitals, special schools and correctional kindergartens, as well as during expedition trips in 2000 - 2012, performed together with the staff of the Republican Surdologic Center aimed at additional clinical examination of patients and their families, as well as blood sampling for DNA analysis.

In order to carry out clinical and epidemiological research, the data on each patient that has been living on the territory of the Republic of Bashkortostan during the study period from 1 January 2000 to 1 January 2011 were collected. The criterion for inclusion in the study was the diagnosis of "hereditary sensorineural hearing loss / deafness» (G11 according to ICD-10) established on the basis of clinical, laboratory and instrumental and molecular genetic research methods in accordance with current diagnostic criteria proposed by The National Institute on Deafness and Other Communication Disorders (Omaha, USA) and recommended in 2003 by European Thematic Network on Genetics Deafness GENDEAF (Mazzoli et al., 2003).

During the study the data on the patients' ethnicity was specified through interviewing and finding out the parents' nationality up to the third generation. Particular attention was paid to the establishment of the place of birth of the probands, their parents and grandparents; intermarriages revealing in the families of the examined patients. According to the initial data analysis and, based on the diagnostic criteria for NSD, nonsyndromic sensorineural hearing impairments with a burdened family history of sound perception violations were distinguished out of the total number of isolated hearing loss/deafness cases. Thus, 246 families of patients with NSD from RB were included in the study. According to the degree of hearing loss in probands, the families were distinguished as follows: I degree of hearing loss was reported in 4 families, II

degree of hearing loss - in 17 families, III degree of hearing loss - in 31 family, IV degree of hearing loss - in 62 families and deafness - in 132 families.

The ethnic composition of the examined families using molecular-genetic methods was as follows: Russians - 98 families, Tatars - 58 families, Bashkirs - 37 families, Mari - 5 families, Ukrainians - 3 families, Armenians - 3 families, mixed ethnicity - 42 families. In order to analyze the frequencies and spectrum of mutations in the genes of mitochondrial DNA, the unrelated individuals from 999 families (520 healthy donors and 479 patients with impaired auditory function) from different regions of the Russian Federation were analyzed (Table. 1).

Table 1. Number and ethnicity of patients and control groups to analyze the frequencies and spectrum of mutations in the genes of the mitochondrial DNA

Ethnicity	Regions								
	The Republic of Bashkortostan		Saint-Petersburg			The Sakha (Yakutia) Republic		The Altai Republic	
			Patients						
	Patients	Control	ASD	NSD	Control	Patients	Control	Patients	Control
Russians	98	50	71	46	100	10	0	10*	-
Tatars	45	50	-	-	-	-	-	-	-
Bashkirs	30	48	-	-	-	-	-	-	-
Yakuts	-	-	-	-	-	48	120	-	-
Altains	-	-	-	-	-	-	-	64*	150
Kazakhs	-	-	-	-	-	-	-	12*	-
Mestizos	22	-	-	-	-	-	-	-	-
Other nationalities	9	2	-	5	-	7	-	2	-
Total	204	150	71	51	100	65	120	88	150

* - Also included individuals of mixed ethnicity, maternally related to Russians, Altaians, Kazakhs, respectively. ASND is a group of patients with acute sensorineural; NSSND is a group of patients with non-syndromic sensorineural deafness/hearing loss.

The population sample group consisted of 2 078 DNA samples obtained from healthy unrelated individuals. The ethnic composition of the studied samples was as follows: Russians (N = 92), Belarusians (N = 97), Ukrainians (N = 90), Abkhazians (N = 80), Avars (N = 60), Cherkessians (N = 80), Ingushes (N = 80), Kazakhs (N = 240), Uighurs (N = 116), Uzbeks (N = 60), Bashkirs (N = 400), Tatars (N = 96), Chuvashs (N = 100), Udmurts (N = 80), Komi-Permyaks (N = 80), Mordvins (N = 80) and Yakuts (N = 247).

The clinical material collected in RB was analyzed by segregation analysis, aimed at checking the conformity of the distribution of patients and healthy ones in revealed nuclear families according to a certain pattern of inheritance - autosomal dominant or autosomal recessive. The segregation analysis was performed in order to get the share of sporadic cases using the method of maximum probability, taking into account the possibility of registration in accordance with the algorithm of complex segregation analysis, developed by Morton (Lalouel et al., 1983).

Molecular genetic studies were performed using standard methods: DNA extraction; polymerase chain reaction of DNA synthesis (PCR); amplified fragment length polymorphism (AFLP), restriction fragment length polymorphism (RFLP), hybridization on (HHL) chips (Asper Biothech Ltd); single-strand conformation polymorphism (SSCP) and resequencing.

The prevalence of hereditary nonsyndromic deafness in RB ranged from 15 to 30,11 per 10^5 people and is one of the most common hereditary diseases among the population in some areas of RB (Zinchenko et al., 2009). The results of our research indicate that NSD is distributed unevenly on the territory of RB. Its distribution in the regions of RB is shown in Figure 1.

The NSD prevalence in RB, totally, was 5,7 per 10^5 (1: 17,543) inhabitants. The disease was registered in 35 (out of 54) administrative districts of the Republic. Analysis of the data shows wide variation of NSD prevalence: from 0,39 to 39,67 per 100 000 people. There are no registered cases of the disease in 19 districts of the Republic: Alsheyevsky, Bakalinsky, Belokataysky, Bizhbulyaksky, Blagovarsky, Duvansky, Dyurtyulinsky, Yermekeyevsky, Zilairsky, Kaltasinsky, Kuyurgazinsky, Mechetlinsky, Miyakinsky, Nurimanovsky, Sterlibashevsky, Tatyshlinsky, Fyodorovsky, Chekmagushevsky, Sharansky. Minimum prevalence of the disease was detected in Ilishevsky, Belebeyevsky, Beloretsky, Meleuzovsky, Gafuriysky, Ishimbaysky, Krasnokamsky districts and was less than 3 per 10^5 people. The highest rate of 39,67 per 10^5 was registered in the Arkhangelsky region, second place was taken by Salavatsky district and the third one by Baltachevsky (38,57 and 32,39 per 100000 people, respectively). When

determining the causes of the increased disease prevalence in some areas (more than 15 per 10^5) it was found that the highest values of this indicator may be associated with territorial dislocation of the correctional schools. This fact can be explained by the special lifestyle features of the deaf and hearing-impaired individuals.

When comparing the NSD prevalence maps on the territory of RB and maps of correctional schools for the deaf / hearing-impaired, the correspondence of high NSD prevalence rates and geographic location of this or that correctional school.

These conclusions are supported by a number of European studies of hereditary forms of hearing loss. The introduction of sign language in Europe and the creation of schools for the deaf and hearing-impaired more than 300 years ago helped to break a social isolation caused by communication defect, and, thusly, helped to increase chances of deaf and hearing-impaired individuals to marry, which, in its turn, led to increase of the number of assortative marriages and birth rate increase in this population group (Tekin et al., 2007; 2010).

Mutation c.35delG (p.Gly12Valfsx1) of the GJB2 gene is the most common for populations of Western Europe where its frequency is 20% of all hereditary isolated hearing impairments and every 33rd resident is a heterozygous carrier (Mahdieh et al., 2009).

During the first phase of research 390 patients from 204 unrelated families of RB underwent screening for c.35delG mutations in the gene connexin 26 (GJB2). This deletion was detected in the homozygous state in 66 patients (58 unrelated). In 67 (56 unrelated) patients c.35delG mutation was identified in the heterozygous state and in 45 (39 unrelated) patients it was in the compound heterozygous state with other mutations in the GJB2. Thus, mutation c.35delG was discovered in 153 unrelated families, which is 75% of all surveyed families with NSD.

Taking into account the number ratio in families in the probands of which c.35delG mutation was identified in homo-, hetero- and compound heterozygous state, we performed the evaluation of the deletions frequency in patients, which amounted to 34% in the studied samples of patients. This result is consistent with the literature data on the high prevalence of this mutation in different ethnic groups. Basically, this mutation is recorded with a high frequency among patients with hereditary deafness in Europe, North. America and Eurasia (Man et al., 2007).

The frequency of c.35delG mutation on patients' chromosomes of Russian ethnicity was 43%, among the Tatars with NSD - 27%, among the Bashkirs

with NSD - 13% (χ^2 = 10,644; p <0,05; df = 2). Therefore, there are statistically significant differences between the groups of patients (Bashkirs, Tatars and Russian)s in the frequency of c.35delG mutation in the gene GJB2. In the group of mestizos the c.35delG frequency was 34%. The small number of representatives of other ethnic groups in the patients' samples made impossible to carry out statistical analysis and calculate the c.35delG frequency in the gene GJB2. These results confirm the data on prevalence of this deletion among the patients from Europe and its lower prevalence among patients with NSD from Asia (Dai et al., 2009).

The cause of hearing loss can be considered established in 66 patients from 54 unrelated families on both chromosomes of which c.35delG mutation was identified. Both differential diagnosis of hereditary disease etiology and prospective medical and genetic counseling, including the possibility of prenatal molecular genetic diagnosis, are possible in these families. Taking into account high frequency of assortative marriages between deaf individuals (45% of RB patients), it is easy enough to explain the relative prevalence of homozygous c.35delG mutations in the gene GJB2 (28%) among the patients with NSD.

22 mutations were identified in the result of molecular-genetic analysis of the genes GJB2, GJB3, GJB6, SLC26A4, SLC26A5 and MYO7A. The spectrum and frequency of mutations found in RB patients with NSD have expressed ethnic heterogeneity. Thus, the most common mutation identified with a frequency of 42.8% on chromosomes of Russian ethnicity carriers was c.35delG deletion in the gene GJB2. The following mutations had frequency higher than 1%: c.314_327del14 (2,5%), c.167delT (1,5%), g.-3179G> A (1,02%) and c.224G> A (1,02%). The frequency of other mutations does not exceed 0,5%.

Following mutations were identified on chromosomes of patients with NSD, having Tatar ethnicity: c.35delG (27,8%), c.314_327del14 (6,67%), c.167delT (3,33%), g.-3179G> A (3,33%), c.235delC (2,22%), c.358_360delGAG (2,22%), c.333_334delAA (2,22%), c.310_325del14 (2,22%), c. 35dupG (1,11%); and two polymorphic variants: c.79G> A (6,67%) and c.457G> A (1,1%) in the gene GJB2, mutation g.919-2A> G (1 1%) in the gene SLC26A4. Mutations c.35delG (13,3%), c.235delC (1,67%) and r.Val27Ile (c.79G> A) + r.Glu114Gly (c.341G> A) (1,67%) and c.101T> C (3,33%) were found among the patients of Bashkir ethnicity. r.Val27Ile (c.79G> A) turned out to be the most common polymorphic variant, occurring among Bashkirs; its frequency on the chromosomes of patients with hearing loss was 15%. A small contribution of the GJB2 gene mutations in the

development of nonsyndromic deafness among Bashkirs (35%), is possibly connected to the presence of mutations in other genes involved in the process of sound perception. The following mutations were identified on chromosomes of mestizo NSD patients: c.35delG (34%), c.167delT (4,55%), c.551G> C (4,55%), c.299_300delAT (2,27%), c.314_327del14 (2,27%), c.109G> A (2,27%), c.95G> A (2,27%), c.101T> C (2,27%) and polymorphic variants c.79G> A (4,55%). c.35delG (39%) and c.299_300delAT (5,56%) mutations and polymorphic variant c.79G> A (11,1%) were revealed in NSD patients - Ukrainians, Armenians, and Mari. Thus, all the mutations and polymorphic variants detected in genes GJB2, GJB3, GJB6, SLC26A4, SLC26A5 and MYO7A in patients from RB are specific mainly for NSD patients from both European and Asian populations. The most common mutation, identified in chromosomes of 34% of NSD patients from RB was c.35delG mutation which corresponds to the literature data on high frequency of this deletion among the population of Europe and the Near East (Mahdieh et al., 2009). The proportion of chromosomes with c.314_327del14 and c.299_300delAT was 3,94%. c.314_327del14 mutation is the second most common mutation in the GJB2 gene among the patients of RB (mainly among the patients of Tatar ethnicity). Also, c.167delT and c.235delC mutations were identified in 1% of NSD patients from RB.

mtDNA mutations affecting the auditory function are mainly found in the genes encoding components of protein synthesizing apparatus of mitochondria - rRNA and tRNA. There are mutations known (m.7445A> G, m.7472insC, m.7510T> C, m.7511T> C) in $tRNA^{Ser(UCN)}$ gene causing nonsyndromic sensorineural deafness (NSD) and in 12S rRNA gene (m.1555A> G, m.1494C> T variations near nucleotide at position 961), leading to NSD, including after taking aminoglycoside antibiotics. Participation of these mtDNA mutations in hearing loss is confirmed by numerous studies (Berrettini et al., 2008). Violation of auditory function in carriers of m.1555A> G mutation is characterized by different age of the disease onset, varying degree of hearing loss and progression. m.1555A> G mutation was detected in samples of two family members K. (proband and her mother) of mixed ethnicity from Yakutia, as well as in two family members (proband, a son, and his mother) in Russian family from St. Petersburg. The presence of m.1555A> G mutation was verified by direct sequencing. In population samples of Vilyuysk Yakuts m.1555A> G mutation was found in population samples of Yakuts (N = 120) and it was 0,83%. m.1555A> G was not found in other samples of studied population.

Three Russian unrelated patients from St. Petersburg were found to have m.961insC insertion. Two of them, having m.961insC mutation, had IV degree of ASD from early childhood after treatment of pneumonia with antibiotics. The third m.961insC patient had a clinical diagnosis of III-IV NSD degree. m.961insC (n) mutation was detected in RB patient of Tatar ethnicity diagnosed with IV degree of NSD. m.961delTinsC (n) mutation was detected in three patients (3 Russians) of RB diagnosed with III degree of NSD. m.961T> G replacement was revealed in three unrelated Russian patients, one of them (from St. Petersburg) was diagnosed with ASD of unknown etiology, the other two (from Altai Republic) had NSD of unknown etiology that occurred at an early age. m.961T> A replacement was detected in one Russian patient (St. Petersburg) with congenital NSD, with mtDNA change, what is more, such change was detected by us for the first time. m.1095T> C mutation (the gene 12S rRNA) was revealed by us in two individuals, Altaians: NSD patient with IV degree and in a healthy individual from the Altai population sample. m.1005T> C mutation was found in one individual from Altai population samples, and was previously identified in a Chinese family with hearing loss caused by the use of aminoglycosides. m.827A> G mutation was detected in an individual of Russian ethnicity, from samples of patients with ASD from St. Petersburg. He had c.35delG mutation in GJB2 gene in homozygous state. m.7444G>A and m.7445A>C mutations were found in two unrelated Russian patients with ASD and NSD (IV degree) from St. Petersburg and RB, respectively, and in three siblings from one Kazakh family (with progressive NSD (III degree) occurred in adulthood).

Nucleotide substitution m.7444G> A in conjunction with m.1555A>G mutation (gene 12S rRNA) with 1,33% frequency was found, for the first time, during the study of deaf patients from Mongolia (Pandya et al., 1999). The mechanism of pathogenic influence of m.7444G>A and m.7445A> C may be similar to the effects of known m.7445A> G mutation associated with hearing loss (Jin et al., 2007); it violates normal processing of precursor tRNA $^{Ser\ (UCN)}$ and mRNA of gene ND6, transcribed together from the light strand.

The prevalence of the most important GJB2 gene deletions, especially c. 35delG mutation, is well studied in a number of the world populations (Mahdieh et al., 2009; Kokotas et al., 2010c), but until recently such data on populations living in the territory of the Russian Federation have been limited (Anichkina et al. 2001; Khidiyatova et al., 2002; Posukh et al., 2005, Shokarev et al., 2005; Zinchenko et al., 2007; 2008). New data obtained in our work, allow, to some extent, to fill in the existing information gaps on the prevalence

of c.35delG, s.167delT and s.235delC mutations of GJB2 gene in the Volga-Ural region, Central Asia, North Caucasus and Yakutia.

We studied the frequency of heterozygous carrier of c.35delG among both different populations of aboriginal population of the Volga-Ural region (Bashkirs, Tatars, Chuvashes, Mordovians, Udmurts, Komi-Permyaks) and in Russians samples. In the Turkic-speaking populations of the Volga-Ural region c.35delG mutation was detected with a frequency of 1%, 0,3% and 0% in Tatars, Bashkirs and Chuvashes, respectively. Among the Finno-Ugric populations of the Volga-Ural region c.35delG mutation was detected with an extremely high frequency of 6,2% in Mordvinians, with 3,7% frequency in Udmurts and absent in Komi-Permyaks. Previously, high frequency of c.35delG (4,4%) was found among Estonians which was obvious exception among the populations of Northern Europe with low frequencies of c.35delG (Gasparini et al., 2000). Data on the frequency of c.35delG mutations among the populations of Volga-Ural region, obtained by us and in other studies (Anichkina et al., 2001; Khidiyatova et al., 2002; Shokarev et al., 2005; Zinchenko et al., 2007; Khusnutdinova et al., 2005; Dzhemileva et al., 2010), show variability in the frequency of heterozygous carrier c.35delG among indigenous populations of the Volga-Ural region.

The frequency of heterozygous carrier c.35delG detected by us in Russians (2,2%) is comparable to the data obtained in other studies of the Russian population in central regions of Russia (Anichkina et al., 2001; Shokarev et al., 2005; Zinchenko et al., 2007; Barashkov et al., 2011).

In the studied Turkic-speaking populations of Central Asia (Kazakhs, Uighurs, Uzbeks), c.35delG mutation of low frequency was found among Kazakhs (0,8%) and Uighurs (0,9%) and was not found among Uzbeks. In the Turkic-speaking populations of Siberia (Yakuts, Altaians) c.35delG mutation with a relatively low frequency (0,4%) was found among the population of Yakuts, but is not detected among the Altai population (Posukh et al., 2005).

In the studied populations of the North Caucasus (Abkhazians, Avars, Cherkessians, Ingushes) c.35delG mutation was revealed only among Abkhazians (3,8%) and Cherkessians (1,3%).

The spatial frequency distribution of c.35delG mutation in Eurasia created on the basis of the data obtained in this study and available in 2010 literature data is presented in Figure 1. The obtained data on c.35delG mutation prevalence among different populations located on spacious areas of Eurasia, will allow, to some extent, to clarify or perhaps reconsider modern concepts of origin center, age and prevalence mechanisms of c.35delG mutation.

Thus, the data obtained by us confirm the descent gradient of heterozygous carrier frequency of c.35delG mutations from West to East: high frequency of c.35delG among the populations of Eastern Europe (Belarusians, Ukrainians), intermediate c.35delG frequency is revealed among the populations of the Volga-Ural region and Central Asia, and minimum frequency of c.35delG is among Yakuts in East Siberia.

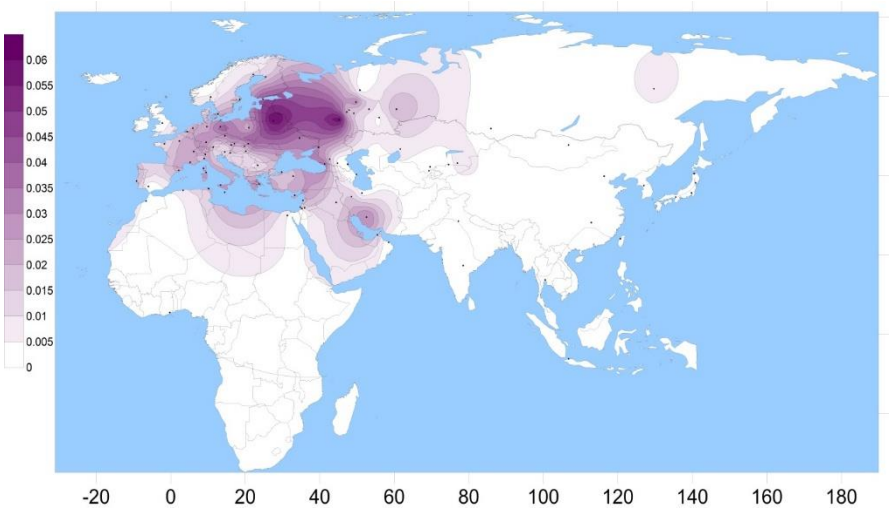

Figure 1. The spatial distribution of c.35delG mutation frequency in GJB2 gene among the populations of Eurasia.

The observed decrease gradient in c.35delG frequency generally corresponds to the data of comparative analysis of mtDNA strands in Finnish and Turkic-speaking populations of Northern Eurasia, where reduction of Caucasoid component in the gene pool of these populations as observed, in the direction from West to East from Eastern Europe to Siberia (Khusnutdinova E. et al., 2011).

Previously, it was shown that the frequency of c.167delT heterozygous carrier in Ashkenazi Jewish population samples is averagely 4,03%, reaching7.5% in some samples, and that there is common ancestral haplotype revealed on patients' chromosomes carrying c.167delT; that may indicate the founder effect in the origin of this mutation (Lerer et al., 2000). Prevalence of c.167delT in Eurasia is limited, mainly by the territory of the Near East, although this mutation is detected sporadically in other regions (Padma et al., 2009).

In the studied populations c.167delT mutation was found in the aboregenic ethnic groups of the Volga-Ural region: the Chuvashes (1%) and Komi-Permyaks (2,5%). These data may indicate both outspread of chromosomes having c.167delT mutation of Near-Eastern origin among the populations of Chuvashes and Komi-Permyaks and independent occurrence of this mutation as c.167delT mutation was not found among the peoples neighboring to Chuvashes and Komis.

During the analysis of the GJB2 gene in several Asian countries, it was found that c.235delC mutation is major in Japan, China, Korea and Mongolia; its frequency is 1,6% - 20,3% on the chromosomes in the samples of deaf patients, and the frequency of heterozygous c.235delC carrier ranges from 0,8% to 1,3% (Han et al., 2008; Dai et al., 2009), but c.235delC mutation is virtually absent among the populations of South and South-East Asia, and it is found only sporadically in other regions of Eurasia, having a complex ethnic composition of the population (Snoeckx et al., 2005).

c.235delC mutation was detected on the territory of the former Soviet Union with a frequency of 3,5% among the Turkic-speaking Altaians (South Siberia) (Posukh et al., 2005) with a frequency of 1,3% among Mordvinians (Volga-Ural region), with a frequency of 1,7% in the Avars, local group in the Caucasus with a complex ethnogenesis, and with a relatively low frequency of 0,4% in the population samples of Kazakhs.

It is interesting to note that c.235delC mutation was not detected among the Turkic-speaking Yakuts (Eastern Siberia), although, based on the data of archaeologists, anthropologists and linguists, as well as taking into account the data on mtDNA and Y-chromosome study, it is assumed that Yakuts migrated to North from their the original settlement on the Lake Baikal region under the pressure the Mongols expansion between the thirteenth and fifteenth centuries AD.

The spatial distribution of the c.235delC mutations frequency on the territory of Eurasia shows c.235delC frequency descent gradient from East to West across Eurasia and demonstrates that the Altai-Sayan region could be a potential region of the origin of this mutation (Figure 2).

Thus, results obtained by us contribute to the clarification of heterozygous carrier frequency of major recessive mutations c.35delG, c.235delC and c.167delT in the GJB2 (Cx26) gene which play an important role in the development of hearing loss among the populations of Eurasia. The prevalence nature of these major deletions in the GJB2 gene in patients belonging to different ethnic groups may further be an evidence of the alleged role of the founder effect in the origin and prevalence of these mutations in the world

populations. In addition, data on the frequency of occurrence of diagnostically significant mutations in the genes GJB2, GJB3, GJB6, SLC26A4, SLC26A5 and MYO7A in ethnically heterogeneous population of the Russian Federation should be considered when performing DNA diagnosis of hereditary hearing impairment.

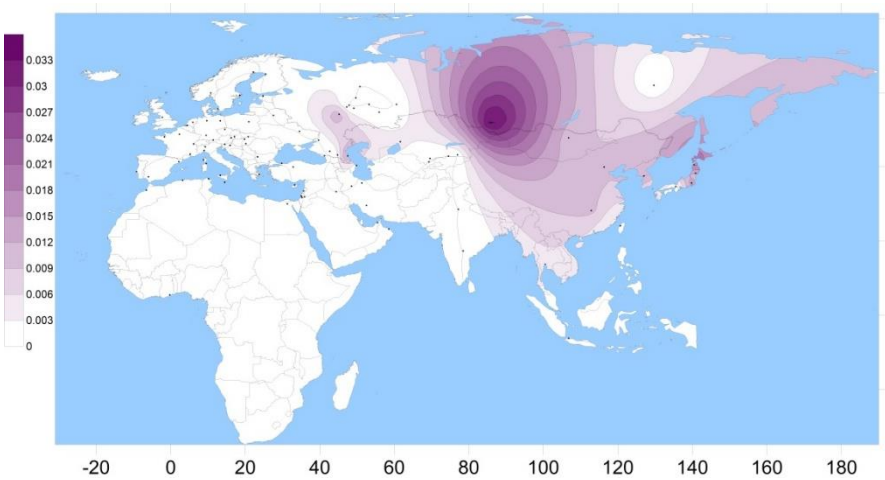

Figure 2. Spatial distribution of c.235delC mutation frequency in the GJB2 gene among the populations of Eurasia.

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