

Original Article

Study of the genetic load and diversity of hereditary diseases in the Russian population of the Karachay-Cherkess Republic

Rena A Zinchenko^{1,2}, Vitaly V Kadyshev¹, Galina I El'chinova¹, Andrey V Marakhonov¹, Varvara A Galkina¹, Elena L Dadali^{1,2}, Olga V Khlebnikova¹, Lyudmila K Mikhailova³, Nika V Petrova¹, Nina E Petrina¹, Tatyana A Vasilyeva¹, Polina Gundorova¹, Alexander S Tanas^{1,2}, Vladimir V Strelnikov^{1,2}, Alexander V Polyakov¹, Eugeny K Ginter^{1,4}

¹Research Centre for Medical Genetics, Moscow 115522, Russian; ²Pirogov Russian National Research Medical University, Moscow 117997, Russian; ³Central Research Institute of Traumatology and Orthopedics by N.N. Priorova, Moscow 127299, Russian; ⁴Russian Medical Academy of Postgraduate Education, Moscow 125993, Russian

Received June 25, 2018; Accepted August 12, 2018; Epub August 20, 2018; Published August 30, 2018

Abstract: The genetic load and diversity of monogenic hereditary diseases (HD) in the Russian population of Karachay-Cherkess Republic (KCHR), living in 10 administrative and municipal divisions, were studied. The total size of the population surveyed was 410,367 people, including 134,756 Russians. In total, 385 patients from 281 families were registered among Russians of KCHR. Genetic load of AD, AR, and X-linked diseases (3.01 ± 0.32 , 1.98 ± 0.26 , and 1.23 ± 0.29 , respectively) are more than twice higher in cities and municipal centers than in corresponding rural regions (1.00 ± 0.10 , 0.89 ± 0.09 , and 0.42 ± 0.09 , respectively). The diversity of HD was 96 nosological forms: 56 diseases with AD type of inheritance (193 patients from 126 families), 28 clinical forms with AR (152 patients out of 124 families) and 12 diseases with the X-linked type of inheritance (40 affected from 31 families). A comparative analysis of the diversity of AD and AR HD with the previously studied populations and ethnic groups of the European part of Russia (Russians of 7 regions, 5 peoples of the Volga-Ural region, and 5 populations of the North Caucasus) was conducted, showing that Russians in the KCHR preserved genetic load with other Russian populations and its difference from the same mutation pool of Karachays and Circassians.

Keywords: Genetic epidemiology, genetic load, diversity of monogenic hereditary diseases, Karachay-Cherkess Republic, Russians

Introduction

This report continues a series of publications on the integrated medical and population genetic study of the population of the Karachay-Cherkess Republic (KCHR).

Representatives of more than 50 ethnic groups live in the KCHR, among which Russians are on the second place (more than 130 thousand people). When studying hereditary diseases (HD) in human populations, it is important to make a comparative assessment of the diversity of HD and gene frequencies, which can reveal differences in these characteristics both in populations of different ethnic ancestry, and

in populations of the same origin. These differences can be caused by the effects of various factors of the microevolution process, as well as their combinations, including the cross-breeding of populations of different ethnic groups [1-3]. Theoretically, cross-breeding should lead to equalization of the gene frequencies, including those causing hereditary pathology, in populations where cross-breeding takes place and, at the same time, to the expansion of genetic diversity in both populations [4]. Along with it, in the absence of other factors of population dynamics, such equalization will necessarily occur, regardless of the intensity of cross-breeding, if the populations coexist long enough. However, other factors of population dynamics,

Study of genetic load and hereditary diseases in Russian population of the KChR

migration, in particular, can significantly influence this process and cause the emergence of a new equilibrium state in gene frequencies.

The aim of this publication is to study the HD of the Russian population of the KCHR and to perform a comparative genographic analysis of load and diversity of monogenic hereditary diseases in populations and different ethnic groups in the European part of Russia, as well as to study the main causes of genetic variability and heterogeneity of Russian populations according to these characteristics.

Materials and methods

The material for this study was collected in the period from 2013 to 2018 while conducting expeditionary studies of the population of KCHR. The population survey was carried out in accordance with the protocol of genetic and epidemiological studies, providing, in addition to medical and genetic characteristics, an assessment of the genetic structure of the studied population, which established the basis for the analysis of the influence of the main factors of microevolution processes in the examined population [5].

Only the population actually received the care in local medical institutions was taken into account. The total number of the surveyed population of the KCHR is 410367 people, including Russians-134756. Russians compactly live in the city of Cherkessk (69785) and in 4 districts of the KCHR: Ust-Dzhegutinsky (9488), Prikubansky (4656), Urupsky (13965) and Zelenchuksky (25336). In the remaining 6 districts of KCHR (Karachayevsky, Malokarachayevsky, Khabezsky, Abazinsky, Nogaysky, Adyge-Khablsky), the total number of the Russian population is 11526 people.

The values of the genetic load of HD are calculated as the ratio of the absolute number of patients with autosomal dominant (AD) and autosomal recessive (AR) types of inheritance to the number of the examined population (per 1000 people). The load of X-linked pathology is calculated for 1000 men. When comparing the indicators of burden between populations, the criterion χ^2 (significance level $P < 0.05$) was used [6].

Nosological spectrum of HD is presented in the tables, formed as a list of AD, AP and X-linked

diseases (neurological, ophthalmic, genodermatoses, skeletal, hereditary syndromes and other diseases).

Confirmatory DNA diagnostics was carried out in the laboratories of the Federal State Budgetary Institution «Research Centre for Medical Genetics»: Laboratory of Genetic Epidemiology (head-Prof. Zinchenko R.A.), Laboratory of Epigenetics (head-DSci Strelnikov V.V.), Laboratory of DNA diagnostics (head-Prof. Polyakov A.V.). DNA diagnosis was conducted with respect to a number of nosological forms and in an incomplete volume.

Comparative analysis of the diversity of HD was carried out for a number of Russian regions of the European part of Russia: seven Russian populations (Krasnodar krai, Kirov, Kostroma, Bryansk, Rostov, Tver regions, Karachay-Cherkess Republic), five ethnic groups of the Volga-Ural region (Mari people of Mari El Republic, Chuvash people of Chuvash Republic, Udmurt people of Udmurtia, Bashkirs of Republic of Bashkortostan, Tatars of Republic of Tatarstan) and five North Caucasian ethnic groups (Karachays, Cherkess, Abazins, Nogais of KCHR, and Adygeans of Adygea), the total size of the population examined exceeds 3700 thousand people who represent 11 ethnic groups of the Russian Federation [7-9]. Analysis of the genographic interrelations between ethnic groups/populations was carried out using the software package “Statistica10”, cluster analysis by the weighted average method. Analysis of the uniformity of the territorial distribution of individual nosological forms among populations of KCHR and other regions of the Russian Federation was carried out using the F-distribution (significance level $\alpha < 0.001$) [6], which allowed to identify the local accumulation of some diseases in Russians.

From all identified and examined families written informed consent was obtained for voluntary participation in the study. The study was approved by the ethical committee of the FSBI “Research Centre for Medical Genetics”.

Results and discussion

As a result of the expeditions conducted in the KCHR, data were collected on the patients with HD of Russian nationality in various populations of the KCHR. A total of 385 patients from 281 families were identified (193 patients from

Study of genetic load and hereditary diseases in Russian population of the KChR

Table 1. The load of hereditary pathology (per 1000 examined) of the Russian population of Karachay-Cherkess Republic

Ethnic group	Population	Prevalence per 1000 people/men*				Occurrence
		AD	AR	XL*	Total	
Cities and district centers						
Cherkessk City	69785	0.97 ± 0.13	0.93 ± 0.13	0.37 ± 0.10	2.09 ± 0.17	1:478
Ust-Dzheguta Town	6499	1.08 ± 0.41	1.08 ± 0.41	0.62 ± 0.44	2.46 ± 0.61	1:406
Kavkazsky Settlement	2500	1.20 ± 0.69	0.80 ± 0.57	1.60 ± 1.13	2.80±1.06	1:357
Pregradnaya Stanitsa	5153	1.36 ± 0.51	0.78 ± 0.39	0.78 ± 0.55	2.52 ± 0.70	1:396
Zelenchukskaya Stanitsa	16200	1.11 ± 0.26	0.74 ± 0.21	0.37 ± 0.21	2.04 ± 0.35	1:491
Other	5372	0.37 ± 0.26	0.74 ± 0.37	0	1.12 ± 0.46	1:895
Weighted average	105509	1.00 ± 0.10	0.89 ± 0.09	0.42 ± 0.09	2.09 ± 0.14	1:445
Rural population (districts)						
Ust-Dzhegutinsky	2989	3.35 ± 1.06	3.35 ± 1.06	0	6.69 ± 1.49	1:149
Prikubansky	2156	2.78 ± 1.13	2.78 ± 1.13	1.86 ± 1.31	6.49 ± 1.73	1:154
Urupsky	8812	2.38 ± 0.52	1.36 ± 0.39	2.19 ± 0.69	3.97±0.67	1:252
Zelenchuksky	9136	2.74 ± 0.55	1.75 ± 0.44	0.44 ± 0.31	5.58 ± 0.78	1:179
Other	6154	4.22 ± 0.83	2.27 ± 0.61	1.30 ± 0.65	7.15 ± 1.07	1:140
Weighted average	29247	3.01 ± 0.32	1.98 ± 0.26	1.23 ± 0.29	5.61 ± 0.44	1:178
Total/average	134756	1.43 ± 0.10	1.13 ± 0.09	0.59 ± 0.09	2.86 ± 0.15	1:350

Note: AD-autosomal dominant type of inheritance, AR-autosomal recessive type of inheritance, XL-X-linked type of inheritance. *prevalence per 1000 men was shown for the XL disorders.

Table 2. Nosological spectrum and prevalence (per 100,000) of diseases with autosomal dominant type of inheritance

No	NoOMIM	Diagnosis	Number of patients						Occurrence	Prevalence	
			1	2	3	4	5	6			All
1	PS 156200	Nonsyndromic mental retardation				4		5	9	1:14897	6, 71
2	PS 158600	Spinal muscular atrophy, juvenile, proximal, autosomal dominant						2	2	1:67038	1, 49
3	#118220	Charcot-Marie-Tooth disease, type 2A1			3				3	1:44692	2, 24
4	PS 118220	Charcot-Marie-Tooth disease, axonal, type 1A			4				4	1:33519	2, 98
5	#615369	Epileptic encephalopathy, childhood-onset				3			3	1:44692	2, 24
6	PS 161800	Myopathy, actin, congenital, with cores			2				2	1:67038	1, 49
7	PS 164400	Spinocerebellar ataxia, type 1			1		1	2	2	1:67038	1, 49
8	PS 303350	Strumpell disease, familial spastic paraplegia			1				1	1:134075	0, 75
9	#162200	Neurofibromatosis, type 1			1	1	1	6	9	1:14897	6, 71
10	#143100	Huntington disease			4				4	1:33519	2, 98
11	PS 128100	Early-onset torsion dystonia			1		1	2	2	1:67038	1, 49
12	PS 308350	Epileptic encephalopathy, early infantile, (Dravet syndrome)			1				1	1:134075	0, 75
13	#180200	Retinoblastoma				1			1	1:134075	0, 75
14	#137750	Glaucoma, primary open angle, juvenile-onset					3		3	1:44692	2, 24
15	#110100	Blepharophimosis, epicanthus inversus, and ptosis			1				1	1:134075	0, 75
16	PS 116200	Congenital hereditary cataract			3	7	4	5	19	1:7057	14, 17
17	#106210	Aniridia			3				3	1:44692	2, 24
18	#120200	Coloboma, ocular, autosomal dominant			1		1		2	1:67038	1, 49
19	#614497	Microphthalmia, isolated, with coloboma 7			4				4	1:33519	2, 98
20	156850	Cataract, congenital, with microphthalmia					2		2	1:67038	1, 49
21	#120970	Cone-rod retinal dystrophy			2				2	1:67038	1, 49
22	#606952	Albinism, oculocutaneous, type IB				4			4	1:33519	2, 98
23	PS 148300	Keratoconus					1		1	1:134075	0, 75
24	#178300	Ptosis, hereditary congenital						1	1	1:134075	0, 75
25	PS 180100	Retinitis pigmentosa			2	1			3	1:44692	2, 24
26	#600059	Retinitis pigmentosa, 13			1				1	1:134075	0, 75

Study of genetic load and hereditary diseases in Russian population of the KCHR

27	#153700	Macular dystrophy, Best disease		3	1 4	1:33519	2, 98
28	#131900	Epidermolysis bullosa simplex, Koebner type		1	1	1:134075	0, 75
29	#146700	Ichthyosis vulgaris		4 1 6	11	1:12189	8, 20
30	#148700	Keratosis palmoplantaris striata I		4	4	1:33519	2, 98
31	#100800	Achondroplasia		1	1 2	1:67038	1, 49
32	#146000	Hypochondroplasia		1	1	1:134075	0, 75
33	#133700	Multiple cartilaginous exostoses			1 1	1:134075	0, 75
34	PS 183600	Split hand/foot malformation			3 3	1:44692	2, 24
35	#185900	Syndactyly, type 1 (Zygodactyly)		5	5	1:26815	3, 73
36	PS 166200	Osteogenesis imperfecta		1 7	8	1:16759	5, 97
37	#108120	Arthrogyrosis multiplex congenita, distal, type 1		1	1	1:134075	0, 75
38	#174500	Polydactyly, preaxial type II			2 2	1:67038	1, 49
39	#174200	Polydactyly, postaxial			1 1	1:134075	0, 75
40	#186200	Syndactyly, type IV			1 1	1:134075	0, 75
41	156232	Mesomelic dysplasia		1	1	1:134075	0, 75
42	#183900	Spondyloepiphyseal dysplasia, congenital type		1	1	1:134075	0, 75
43	181800	Scoliosis, idiopathic 1		1 1	2	1:67038	1, 49
44	156620	Syndrome of microcephaly, deafness/malformed ears, mental retardation		1	1	1:134075	0, 75
45	#113620	BOF syndrome (Branchiooculofacial syndrome)		3	3	1:44692	2, 24
46	164210	Goldenhar syndrome (Hemifacial microsomia)		1	1	1:134075	0, 75
47	PS 118100	Klippel-Feil syndrome 1, autosomal dominant			1 1	1:134075	0, 75
48	PS 136760	Frontonasal dysplasia 1			2 2	1:67038	1, 49
49	#182940	Neural tube defects		2	2	1:67038	1, 49
50	157900	Moebius syndrome		1	1	1:134075	0, 75
51	PS 163950	Noonan syndrome		1	1	1:134075	0, 75
52	173800	Poland syndrome			1 1	1:134075	0, 75
53	#101400	Saethre-Chatzen syndrome			1 1	1:134075	0, 75
54	PS 130000	Ehlers-Danlos syndrome		5 1	4 5 15	1:8983	11, 19
55	#613695	Long QT syndrome 5		2	2	1:67038	1, 49
56	#193400	von Willebrand disease, type 1		1	1	1:134075	0, 75

Note: 1-Cherkessk; 2-Urupsky district; 3-Zelenchuksky district; 4-Ust-Dzhegutinsky district; 5-Prikubansky district; 6-all other districts of the KCHR; All-total Russian population of KCHR. Frequent diseases are highlighted in bold.

126 families with AD pathology; 152 patients from 124 families with AR pathology, and 40 patients from 31 families with X-linked pathology). Thus, the distribution of HD among the Russian population was 1:350 people (1:698 with AD, 1:887 with AR and 1:1684 men with X-linked inheritance). **Table 1** shows the load (per 1,000 surveyed) of the Russian population of the KCHR with the main types of the HD.

Analysis of the genetic load of urban and rural Russian population showed that there are no statistically significant differences between cities and regional centers ($\chi^2 = 2.01$; 1.53; d.f. = 5; $P > 0.05$). Differentiation is determined when analyzing the load of AD and AR pathologies in the rural population ($\chi^2_{AD} = 28.28$; $\chi^2_{AR} = 10.04$; d.f. = 5; $P < 0.05$). Comparative analysis within the groups “cities and regional centers” vs “rural population” did not show any differences in the burden of X-linked pathology ($\chi^2 = 0.59$, and $\chi^2 = 3.65$; d.f. = 4; $P > 0.05$, respectively). Differences in the indices of burden AD, AR and

X-linked pathologies were revealed when comparing “urban” and “rural” populations ($\chi^2 = 64.67$; $\chi^2 = 24.17$; $\chi^2 = 12.76$; d.f. = 1, $P < 0.05$).

A comparative analysis of the load in the Russian population with other ethnic groups of the KCHR was not carried out so far, as the study of the remaining groups has not yet been completed and data on the burden are not available.

Nosological spectrum of the HD is represented by 96 diseases (56 with AD type of inheritance, 28 with AR and 12 with X-linked type of inheritance). **Table 2** presents the nosological spectrum of diseases with AD type of inheritance. All diseases were found in previously surveyed Russian populations [7-9].

7 AD diseases were identified as frequent (more often than 1:30000): undifferentiated mental retardation 1:14897 (average for the populations of the European part of the Russian

Study of genetic load and hereditary diseases in Russian population of the KCHR

Table 3. Nosological spectrum and prevalence (per 100,000) of diseases with autosomal recessive type of inheritance

No	NoOMIM	Diagnosis	Number of patients							Occurrence	Prevalence	
			1	2	3	4	5	6	All			
1	PS 249500	Nonsyndromic mental retardation, autosomal recessive 1		8	15	2		11	36	1:3724	26, 85	
2	PS 253600	Muscular dystrophy, limb-girdle, type 2A	2						2	1:67038	1, 49	
3	#250100	Metachromatic leukodystrophy			1				1	1:134075	0, 75	
4	#270800	Spastic paraplegia, autosomal recessive		1					1	1:134075	0, 75	
5	#236600	Hydrocephalus, nonsyndromic, autosomal recessive		2					2	1:67038	1, 49	
6	#254800	Epilepsy, progressive myoclonic 1A (Unverricht and Lundborg)						1	1	1:134075	0, 75	
7	#253400	Spinal muscular atrophy, type III						1	1	1:134075	0, 75	
8	#251200	Microcephaly, primary, autosomal recessive	1						3	4	1:33519	2, 98
9	PS 251600	Microphthalmia, isolated		1					1	1:134075	0, 75	
10	#611040	Microphthalmia, isolated 5			1				1	1:134075	0, 75	
11	251505	Microphthalmia with coloboma			1				1	1:134075	0, 75	
12	#248200	Macular degeneration, juvenile (Stargardt disease)			4				4	1:33519	2, 98	
13	#264800	Pseudoxanthoma elasticum					1		1	1:134075	0, 75	
14	#242100	Ichthyosiform erythroderma, Brocq congenital, nonbullous form	1	2					3	1:44692	2, 24	
15	#271640	Spondyloepimetaphyseal dysplasia with joint laxity, type 1, with or without fractures						1	1	1:134075	0, 75	
16	#228930	Fuhrmann syndrome (fibular aplasia or hypoplasia, femoral bowing and poly-, syn-, and oligodactyly)		1					1	1:134075	0, 75	
17	#236670	Cerebroocular dysplasia-muscular dystrophy syndrome				1			1	1:134075	0, 75	
18	251800	Microtia with meatal atresia and conductive deafness	2	1					3	1:44692	2, 24	
19	#274600	Pendred syndrome	1						1	1:134075	0, 75	
20	#143500	Hyperbilirubinemia, Gilbert syndrome			1				1	1:134075	0, 75	
21	PS 276900	Usher syndrome			2				2	1:67038	1, 49	
22	234100	Hallermann-Streif syndrome	1						1	1:134075	0, 75	
23	#261600	Phenylketonuria/Hyperphenylalaninemia	1	4	1				6	1:22346	4, 48	
24	#219700	Cystic fibrosis	1		1		1	3	1:44692	2, 24		
25	#262400	Growth hormone deficiency, isolated, type IA	2						2	1:67038	1, 49	
26	#607014	Mucopolysaccharidosis, type I _h (Hurler syndrome)				1			1	1:134075	0, 75	
27	#257220	Niemann-Pick disease, type C1	1						1	1:134075	0, 75	
28	PS 220290	Deafness, autosomal recessive 1A	50	5	6	11	3	75	1:1788	55, 94		

Note: 1-Cherkessk; 2-Urupsky district; 3-Zelenchuksky district; 4-Ust-Dzhegutinsky district; 5-Prikubansky district; 6-all other districts of the KCHR; All-total Russian population of KCHR. Frequent diseases are highlighted in bold.

Federation 1:17050), type 1 neurofibromatosis 1:14897 (average for the Russian Federation 1:16585), various forms of congenital cataracts 1:7057 (the average for the Russian Federation is 1:14943), ichthyosis vulgaris 1:12189 (the average for the Russian Federation is 1:4989), zygodactyly 1:26815 (the average for the Russian Federation is 1:39200), osteogenesis imperfecta 1:16585 (1:37267 in the Russian Federation), Ehlers-Danlos syndromes 1:8983 (the average for the Russian Federation is 1:24342). No statistically significant accumulation was detected for either disease.

Confirmatory DNA diagnosis was performed in several cases. In neurofibromatosis, the previously described missense mutation in *NF1*: c.4402A>G, p.S1468G, was revealed. In two families with Huntington disease, an increased

number of CAG repeats (with variation 36-87) in the 5'-region of the *HTT* gene was identified. A duplication of the *PMP22* gene was detected for 3 patients with a clinical picture of demyelinating polyneuropathy 1A. The p.G380R mutation in the *FGFR3* gene was determined for one patient with achondroplasia. Mutation c.2282-del4 in the *FLG* gene in the heterozygous state was detected in 2 patients with ichthyosis vulgaris. In one family with three patients with aniridia, a known nonsense mutation c.607C>T, p.R203*, in the *PAX6* gene was found in the heterozygous state. In a family with a diagnosis of retinitis pigmentosa, a single nucleotide substitution in the exon 4 of the *PRPF8*: c.428A>G gene (p.Gln143Arg) in the heterozygous state was revealed. In the family diagnosed with long QT syndrome, the mutation c.2863G>T (p.Asp-821Tyr) in the gene *KCNE1* was revealed.

Study of genetic load and hereditary diseases in Russian population of the KChR

Table 4. Nosological spectrum and prevalence (per 100,000 men) of diseases with X-linked type of inheritance

No	NoOMIM	Diagnosis	Number of patients						Occurrence	Prevalence
			1	2	3	4	5	6		
1	#309530PS	X-linked mental retardation	2	2	10		4	18	1:3724	26, 85
2	#302800	Charcot-Marie-Tooth neuropathy, X-linked dominant, 1	2					2	1:33519	2, 98
3	#310200	Muscular dystrophy, Duchenne type	1					1	1:67038	1, 49
4	#300376	Muscular dystrophy, Becker type	1					1	1:67038	1, 49
5	#307000	Hydrocephalus, X-linked			1			1	1:67038	2, 98
6	#308100	Ichthyosis, X-linked	2					2	1:33519	2, 98
7	#300834	Macular degeneration, X-linked atrophic						2	1:33519	1, 49
8	#301050	Alport syndrome, X-linked	1					1	1:67038	2, 98
9	#312750	Rett syndrome	1		1			2	1:33519	1, 49
10	#305600	Focal dermal hypoplasia (Goltz syndrome)			2			2	1:33519	2, 98
11	#306900	Hemophilia B	1		2			3	1:22346	4, 48
12	#306700	Hemophilia A	2		2		2	6	1:11173	8, 95

Note: 1-Cherkessk; 2-Urupsky district; 3-Zelenchuksky district; 4-Ust-Dzhegutinsky district; 5-Prikubansky district; 6-all other districts of the KCHR; All-total Russian population of KCHR. Frequent diseases are highlighted in bold.

The nosological spectrum of diseases with AR type of inheritance is presented in **Table 3**. In a variety of AR diseases, as well as in cases with AD pathology, every nosology were previously described in our studies [7-9].

Three AR diseases were identified as frequent (with prevalence more often than 1:30000): undifferentiated mental retardation 1:3724 (average for the populations of the European part of the Russian Federation 1:7238), phenylketonuria 1:22346 (average for the Russian Federation 1:22359) and non-syndromic sensorineural hearing loss 1:1788 (average for the Russian Federation 1:4629). There was no reliable accumulation for any nosological form.

Confirmatory DNA diagnosis was performed for 6 patients with phenylketonuria. The spectrum of *PAH* mutations in Russians of KCHR included 9 different genetic variants: R408W (4/12 chromosomes), V230I (1/12), Y414C (1/12), IVS10-11G>A (1/12), IVS1+5G>T (1/12), c.664_665delGA (1/12), R158Q (1/12), S349P (1/12), ex5del (1/12). In a family with spinal muscular atrophy of type 3, a deletion of the exons 7 and 8 of the *SMN1* (del/del) gene was determined; for one patient with cystic fibrosis, two mutations F508del and 2184insA were detected in the *CFTR* gene in the compound heterozygous state; in a family with Gilbert syndrome increase in the number of TA repeats (7/7) in *UGT1A1* gene was determined. DNA diagnosis was performed for 50 patients (of 39 families) with non-syndromic sensorineural hearing loss: mutations were detected for 28 patients in *GJB2* gene (47.44%). The following

pathogenic variants were determined: c.35delG (41.03%), c.313_326del14 (2.56%), c.-23+1G>A (2.56%), c.269T>C (2.56%).

Table 4 shows the diversity of X-linked diseases. For the first time in our studies we detected the Gorlin-Goltz syndrome. The remaining diseases were found in previously surveyed RF populations [7-9].

Among the X-linked diseases the 3 frequent nosological forms were identified (more often than 1:30000 men): undifferentiated mental retardation 1:3724 (average for the populations of the European part of the Russian Federation 1:7291 men), hemophilia A 1:11173 (average for the Russian Federation 1:18694 men) and hemophilia B 1:7057 (average for the Russian Federation is 1:141197 men). Statistically significant accumulation was revealed for hemophilia B ($F = 9.62$).

Molecular genetic analysis was performed in several cases. In patients with Duchenne muscular dystrophy, the deletion of exons Pm-8 and 3-4 of the *DMD* gene were revealed. In case of hemophilia B, a mutation c.508C>T, p.Cys170Arg in the *F9* gene was revealed. In a family with retinitis pigmentosa, the previously described pathogenic single nucleotide variant in the exon 8 of the *RPGR* gene (chrX: 38164022C>T) leading to missense substitution p.Gly267Glu in the hemizygous state was revealed. DNA-diagnostics carried out for 6 patients with intellectual disability and presumptive diagnosis of fragile X syndrome and did not reveal methylation of the *FMR1* gene promoter.

Study of genetic load and hereditary diseases in Russian population of the KChR

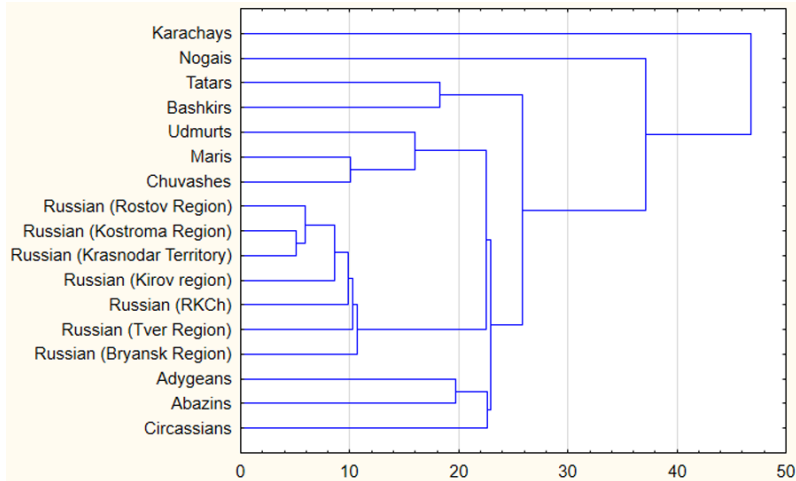


Figure 1. Dendrogram of genetic distances built according to the distribution of 226 AR diseases.

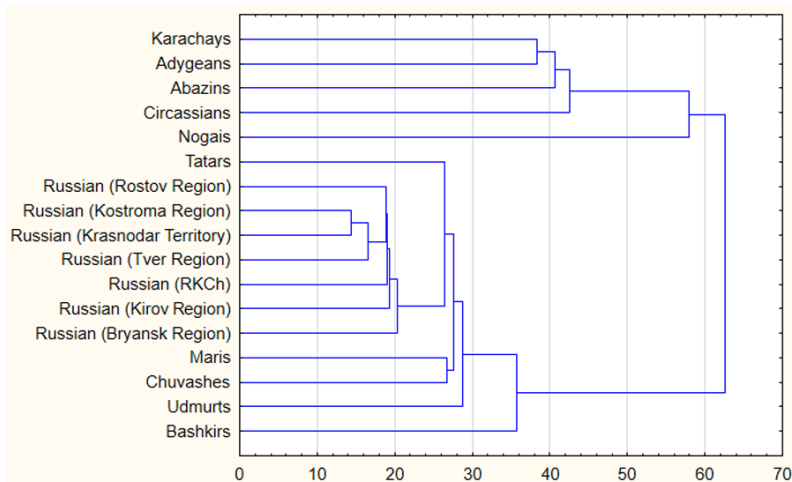


Figure 2. Dendrogram of genetic remoteness built according to the distribution of 259 AD diseases.

Thus, the analysis of the diversity of HD in Russian KCHR showed that the spectrum is characterized by similarity to one in other populations of the Russian Federation [7-10] and in the world [11-13]. When carrying out DNA diagnostics in all cases, frequent mutations were identified for other Russian populations of the Russian Federation.

Comparative analysis of the variety of hereditary diseases in different populations/ethnic groups of the European part of the Russian Federation

A comparative analysis of the diversity of 14 regions of the European part of the Russian

Federation was carried out: seven Russian populations (Krasnodar krai, Kirov, Kostroma, Bryansk, Rostov, Tver regions, and Karachay-Cherkess Republic), five ethnic groups of the Volga-Ural region (Mari people of Mari El Republic, Chuvash people of Chuvash Republic, Udmurt people of Udmurtia, Bashkirs of Republic of Bashkortostan, Tatars of Republic of Tatarstan) and five North Caucasian ethnic groups (Karachays, Cherkess, Abazins, Nogais of KCHR, and Adygeans of Adygea [7-9, 14].

Figure 1 presents the results of a cluster analysis conducted on the distribution of 226 diseases with an AR type of inheritance. As follows from **Figure 1**, at the very first step, the Russians of different regions are united. And the Russian KCHR also entered the “Russian” cluster.

Karachay-Cherkessia has repeatedly changed its administrative boundaries and subordination since the time of the Russian Empire [15, 16]. According to the published data, the

Russian population in the KCHR was formed mainly by Russian Cossack troops, primarily from the Stavropol Territory. In the period 1800-1900, the migration flows of Russians to the territory of modern Karachay-Cherkessia were noted mainly from the south of Russia and Ukraine: the Voronezh, Don, Poltava, Kharkov governorates and from the Black Sea coast [15-17].

At the next step of clustering, a cluster of Finno-Ugric peoples “Mari-Chuvash-Udmurt” is allocated. In the ethnogenesis of the Chuvash people, a significant role was played by the local Finno-Ugric tribes. Abkhaz-Adyghe peoples, the Adygeans, the Abazins, the Cherkess, form a

separate cluster. According to anthropologists, the interrelation of these peoples has been going on for a long time from ancient times (VIII-IX centuries AD), which affected not only common customs, culture, but also the gene pool of peoples [15, 16]. At the last step four Turkic-speaking peoples-Tatars, Bashkirs, Nogais, and Karachays-associate. As follows from the results of the dendrogram constructed according to the distribution of AR diseases, the ethnogenesis of peoples plays an important role in the formation of both the nosological spectrum of the HB and the distribution of certain diseases.

Figure 2 shows a dendrogram constructed on the basis of the results of a cluster analysis conducted on the distribution of 259 diseases with AD type of inheritance. In this dendrogram (**Figure 2**), similar to the analysis of AR diseases at the first step, all Russian populations including Russians of the KCHR, are combined. Then the peoples of the Volga-Ural region attach sequentially, whereas the five ethnic groups of the North Caucasus demonstrate the maximum genetic remoteness from the other populations surveyed by us. The formation of clusters correlates both with the ethnogenesis of peoples and with geographical distances.

Thus, the Russian population of the KCHR was formed from representatives of various regions (mainly the southern territories of Russia and Ukraine), which affects the genetic structure (a wide variety of surnames, low endogamy and random inbreeding) [18]. The total share of mono-ethnic marriages among the Russian KCHR, both in urban and rural populations, accounts to 80%, the share of inter-ethnic marriages -20%. Analysis of ethnic marriage assortative mating showed that in the presence of cross-breeding with different ethnic groups living on the territory of KCHR from the Russian Karachay-Cherkess Republic, there is a significant increase in the number of Russian-Ukrainian and Russian-Tatar marriages than is expected with panmixia [18].

The Russian population in its gene pool has retained both the specific for the Russian population of different regions of the Russian Federation spectrum of distribution of HD and the frequency spectrum of frequent mutations in individual genes. Thus, despite a significant share of interethnic marriages (20%), there is

no equalization in gene frequencies in the populations of different ethnic extraction studied by us and the growth of the diversity of hereditary pathology in them. Probably, this is connected, firstly, with the relatively short (from a historical point of view) period of the studied ethnic groups living together on one territory. Secondly, we did not estimate the intensity of migration of the Russian population living on the territory of Karachay-Cherkessia, which can hinder the identification of the effects of cross-breeding.

Acknowledgements

The research was carried out within supported in part by RFBR (project No. 17-04-00288), and the state assignment of FASO Russia.

Disclosure of conflict of interest

None.

Address correspondence to: Rena A Zinchenko, Research Centre for Medical Genetics, Moscow 115522, Russian. E-mail: renazinchenko@mail.ru

References

- [1] Ginter EK, Mamedova RA, El'chinova GI, Brusintseva OV, Kadoshnikova MI, Petrova NV, Bukina AM, Alalykin AM. Load of autosomal recessive diseases in populations of Kirov province and its relationship to consanguinity. *Genetika* 1993; 29: 1042-1046.
- [2] Ginter EK, Zinchenko RA, El'chinova GI, Nurbaev SD, Balanovskaya EV. The role of population dynamics factors in the prevalence of hereditary pathology in Russian populations. *Medical Genetics* 2009; 3: 548-555.
- [3] Wu DD, Zhang PP. Different level of population differentiation among human genes. *BMC Evol Biol* 2011; 11: 16.
- [4] Cavalli-Sforza LL, Bodmer WF. The genetics of human populations. San Francisco: Freeman WH and Company; 1971. pp. 965.
- [5] Ginter EK, Revazov AA, Talanov MI, Nechvolodova OL, Khlebnikova OV. Medical genetics study of the population of Kostroma province. II. The diversity of hereditary pathology in 5 districts of the province. *Genetika* 1985; 21: 1372-1379.
- [6] Zhivotosky LA. *Populational biometry*. Moscow: Nauka; 1991. pp. 271.
- [7] Zinchenko RA, El'chinova GI, Rudenskaia GE, Galkina VA, Larina TI, Kozlova SI, Izhevskii PV, Ginter EK. Integrated population genetic and medical genetic study of two raions of the Tver oblast. *Genetika* 2004; 40: 667-76.

Study of genetic load and hereditary diseases in Russian population of the KChR

- [8] Zinchenko RA, El'chinova GI, Baryshnikova NV, Poliakov AV, Ginter EK. Prevalences of hereditary diseases in different populations of Russia. *Russ J Genet* 2007; 43: 1038-1045.
- [9] Zinchenko RA, El'chinova GI, Ginter EK. Factors determining the spread of hereditary diseases in Russian populations. *Medical Genetics* 2009; 8: 7-23.
- [10] Puzyrev VP, Nazarenko LP. Genetic-epidemiological study of hereditary pathology in Western Siberia. Tomsk: STT; 2000. pp. 187.
- [11] Online Mendelian Inheritance in Man. URL: <http://www.ncbi.nlm.nih.gov/OMIM> (accession date 05.02.2018).
- [12] Orphanet Reports Series: Diseases listed by decreasing prevalence or number of published cases. URL: <http://www.orpha.net/>(accession date 12.02.2018).
- [13] Canadian Congenital Anomalies Surveillance Network. Directory of surveillance systems. British Columbia: health status registry (HSR). URL: <https://www.canada.ca/en/public-health/services/health-promotion/what-is-ccasn/results-2006-2007-survey-availability-selected-data-variables-canadian-provinces-territories/methods.html/> (accession date 12.02.2018).
- [14] Ginter EK. Medical genetic description of the population of adygea. Maykop; 1997. pp. 225.
- [15] Full collection of legislation of the USSR. About changes in the administrative-territorial division. <http://www.ussrdoc.com/> (accession date 20.03.2018).
- [16] Tishkov VA. The Russian caucasus. Book for politicians. Moscow; 'Rosinformagrotech': 2007. pp. 384.
- [17] Atlas of the ethnopolitical history of the caucasus. http://www.iriston.com/books/cuciev_-_etno_atlas/cuciev_etno-polit_map.htm (accession date 20.03.2018).
- [18] El'chinova GI, Makaov AHM, Petrin AN, Zinchenko RA. Marriage ethnic assortative mating of urban and rural population of Karachay-Cherkessia. *Russ J Genet* 2017; 53:838-841.