CLINICAL POPULATION GENETIC STUDIES OF HEREDITARY DISEASES IN THE PEDIATRIC POPULATION OF NORTH OSSETIA – ALANIA

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Currently, there is limited understanding about the cumulative prevalence, diversity, and frequency of distinct orphan hereditary diseases (OHDs) in the pediatric population, both within the Russian Federation and in the global literature. This gap exists despite a significant demand for such knowledge in healthcare and society. Variability and heterogeneity of the above indicators are common across different populations, reflecting significant genetic heterogeneity of OHDs. The study aimed to assess OHDs in the pediatric population of the Republic of North Ossetia – Alania (RNO-A). A total of 543,817 people were evaluated, including 145,560 children aged 0–18 years. The cumulative prevalence of autosomal recessive (AR), autosomal dominant (AD), and X-linked (XL) OHDs was determined. The findings indicate an overall prevalence of OHDs among children of the RNO-A of 1 : 119, meaning that approximately 1% of children are diagnosed with these conditions. Notably, the total burden in children of all types of OHDs in rural areas exceeds that in urban areas and district centers by more than twofold. We identified 1,241 patients from 1,037 families with 241 distinct OHDs (109 with AD inheritance, 102 with AR inheritance, and 30 with XL inheritance). Three diseases were particularly prevalent in this population and have not been documented in similar studies: congenital myasthenia type 12, a rare form of congenital adrenal cortex dysfunction (3-beta-hydroxysteroid dehydrogenase deficiency), and brachydactyly E — amelogenesis — mental retardation — nanism syndrome. Thus, the population of the RNO-A exhibits a unique spectrum of OHDs caused by rare mutations, some of which are infrequent in other populations of the world and the Russian Federation. The significantly higher prevalence of these disorders in rural populations is noteworthy, underscoring the need for tailored, region-specific programs aimed at preventing childhood disability and/or mortality.

Keywords: orphan hereditary diseases, cumulative prevalence of hereditary diseases among children, diversity of hereditary diseases common among children, Republic of North Ossetia–Alania, Russian Federation

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Centre for Medical Genetics (protocol No. 7 dated 20 December 2017), it was compliant with the standards of Good Clinical Practice and evidence-based medicine. All patients submitted informed consent to participate in the study.

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КЛИНИЧЕСКИЕ ПОПУЛЯЦИОННО-ГЕНЕТИЧЕСКИЕ ИССЛЕДОВАНИЯ НАСЛЕДСТВЕННЫХ БОЛЕЗНЕЙ СРЕДИ ДЕТСКОГО НАСЕЛЕНИЯ СЕВЕРНОЙ ОСЕТИИ – АЛАНИИ

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Современные знания о кумулятивной распространенности, разнообразии и частоте встречаемости отдельных орфанных наследственных болезней (ОНБ) среди детского населения ограничены в РФ и мировых исследованиях несмотря на широкую востребованность для здравоохранения и общества. Для ОНБ характерны изменчивость и неоднородность вышеперечисленных показателей для разных популяций, которая также проявляется в широкой генетической гетерогенности. Целью работы было изучение ОНБ среди детского населения Республики Северная Осетия – Алания (РСО-А). Обследовано 543 817 человек, в том числе 145560 детей (от 0 до 18 лет). Рассчитана кумулятивная распространенность аутосомно-рецессивной (АР), аутосомно-доминантной (АД) и Х-сцепленной (Х-сц.) наследуемой патологии. По полученным результатам, суммарная распространенность ОНБ среди детей РСО-А составляет 1 : 119, т. е. 1% детей имеет диагноз ОНБ. В сельской местности суммарная отягощенность детского населения всеми типами ОНБ более чем в 2 раза выше, чем в городах и районных центрах. Выявлен 1241 пациент (из 1037 семей) с 241 нозологической формой ОНБ (109 форм — с АД-наследованием, 102 — с АР и 30 — с Х-сц.). Особенностью обследованной популяции является высокая распространенность трех заболеваний, ранее не установленных в подобных исследованиях: врожденная миастения 12-го типа, редкая форма врожденной дисфункции коры надпочечников — дефицит 3-бета-гидроксистероиддегидрогеназы, синдром брахидактилии типа Е — амелогенеза — умственной отсталости — нанизма. Таким образом, население РСО-А характеризуется специфическим спектром ОНБ, обусловленных редкими мутациями, часть из которых редко встречается в других популяциях мира и РФ. Обращает на себя внимание более высокая распространенность данного спектра патологий в сельских популяциях. Выявленные показатели свидетельствуют о необходимости разработки специализированных регион-специфических программ для профилактики детской инвалидности и/или летальности.

Ключевые слова: орфанные наследственные заболевания, кумулятивная распространенность наследственных болезней среди детей, разнообразие частых наследственных болезней среди детей, Республика Северная Осетия – Алания, Российская Федерация

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According to the international OMIM database, the number of nosological forms of orphan hereditary diseases (OHDs) is about 7000–8000. The majority of these (more than 80%) are considered to be rare, i.e. the prevalence is less than 1 case per 1 million population [1]. A total of 10–20% of nosological forms fall on common OHDs, however, the number of patients with such disorders exceeds 60% [2, 3]. According to the research, the OHD burden on the population varies between 5–17 per 1000 people [4], and the pediatric population accounts for the major share (> 2%) due to the lower survival rate and adaptability of children with severe diseases. In 30% of cases, OHDs manifest at birth, while in 87% of cases these manifest by the end of puberty [5]. The issue of OHDs is very important for both healthcare and society in general since many cases of such disorders are characterized by high disability and mortality rates: at least 35% of childhood mortality in developed economies is associated with OHDs [2, 3].

Variability and heterogeneity of the OHD cumulative prevalence and diversity reported for various countries and populations, which are also manifested in genetic heterogeneity, are typical for OHDs [6]. Current knowledge about the genetic burden in human populations, diversity, prevalence, and heterogeneity of OHDs among children is scarce; the main reports issued both in Russia and abroad are focused on the analysis of data by hospitals or on certain ethnic populations [2, 7–16]. In the Russian Federation, the clinical population genetic studies of OHDs in the pediatric population involving recording of the maximum number of disorders in distinct federal entities are conducted only by the Research Centre for Medical Genetics and are under development. Differentiation of populations by both the prevalence of certain diseases and the cumulative prevalence of OHDs has been shown, which confirms the need to study each region in order to ensure the possibility of optimizing the region-specific care provided to patients [17–20].

The study aimed to assess OHDs in the pediatric population of the Republic of North Ossetia – Alania (RNO-A).

METHODS

We performed a medical genetic examination of the population of RNO-A. People of various age groups in all eight rural districts and the city of Vladikavkaz were examined in order to identify OHDs. The population survey was conducted in accordance with the examination protocol developed by the team of the Research Centre for Medical Genetics more than 40 years ago for small populations of the Russian Federation (populations of districts and towns) and tested in 15 Russian regions (110 rural districts) over this period. The protocol was published earlier [21–24]. Patients with congenital and presumably hereditary diseases were found via physicians and paramedical staff of medical institutions of the Republic using the questionnaire developed. The questionnaire represents the list of symptoms (neurological, ophthalmological, dermatological, skeletal, endocrinological, genetic, etc.) of various OHDs distributed across the main medical specialties. In addition to the lists obtained, we used the data from the medical and social examination service and from other medical and social sources. Given the fact that each symptom can be typical for more than one disease and is usually typical for a group of diseases, the entire clinical picture entails identifying the highest possible number of cases of OHDs (affecting both individual systems and multiple organs). Examination of families and patients of various age groups was performed during the meeting of experts in various medical specialties, which made it possible to identify a broad range of OHDs [20–24]. The diagnoses were verified by clinical, instrumental, and laboratory methods (biochemical, cytogenetic, molecular genetic, etc.).

The size of the actually examined population of the RNO-A (2017–2023) was 543,817 people, including 145,560 (26.77%) children aged 0–18 years (Table 1). Epidemiological analysis of OHDs in the pediatric population of the RNO-A was performed.

Considering the heterogeneity of many OHDs, we performed segregation analysis aimed to confirm certain inheritance types (autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL)) showing that the resulting distribution was correct: $p = 0.27 \pm 0.06$ (expected value 0.25) for AR inheritance and $p = 0.49 \pm 0.04$ (expected value 0.5) for AD inheritance [25–26].

The cumulative prevalence, or genetic burden, of OHDs per 1000 examined individuals by populations was calculated using the following formula: $n / (N / 1000)$, where n was the number of affected individuals, and N was the number of children. The standard error of the OHD genetic burden values was calculated using the formula $((n / N) \times (1 - (n / N)) / N) / 0.5 \times 1000$, where n was the number of affected individuals, N was the number of children [25–26].

To analyze the OHD diversity, we compiled the list of diseases and calculated the disease prevalence (n / N) per 100,000 children. The genetic burden and prevalence of X-linked OHDs were calculated for boys. The genetic burden values were compared by the χ^2 method [17–26].

RESULTS

Cumulative prevalence of OHDs in pediatric population of the RNO-A

Comprehensive assessment of the population of the RNO-A resulted in the identification of 1241 patients (from 1037 families)

Table 1. Size of the population examined

№	District	Urban population		Rural population		Entire population	
		All	Children	All	Children	All	Children
1	Ardonsky	19 800	4296 (21.70%)	11 632	2700 (23.21%)	31 432	6996 (22.06%)
2	Pravoberezhny	37 029	13 147 (35.50%)	22 683	4224 (18.62%)	59 712	17 371 (29.09%)
3	Kirovsky	13 500	2374 (17.59%)	14 916	2655 (17.80%)	28 416	5029 (17.70%)
4	Alagirsky	20 950	5435 (25.94%)	16 577	2351 (14.18%)	37 527	7786 (20.75%)
5	Digorsky	11 072	2784 (25.14%)	9224	2200 (23.85%)	20 296	4984 (24.56%)
6	Irafsky	7700	2150 (27.92%)	7679	1650 (21.49%)	15 377	3800 (24.71%)
7	Prigorodny	10 067	2228 (22.13%)	43 361	9529 (21.98%)	53 428	11 757 (22.01%)
8	Mozdoksky	42 155	11 630 (27.59%)	48 089	10 469 (24.77%)	90 244	22 099 (24.49%)
9	City of Vladikavkaz	220 167	65 738 (29.86%)	–	–	220 167	65 738 (29.86%)
	total	378 873	114 782 (30.29%)	174 161	35 778 (19.08%)	543 817	145 560 (26.77%)

Table 2. Cumulative prevalence of hereditary diseases (per 1000 examined children) in pediatric populations of eight districts of the RNO-A and the city of Vladikavkaz

District/subpopulations	Population size	Genetic burden per 1000 children/boys*				Prevalence
		AD	AR	XL*	Total	
	Children from rural areas					
Ardonsky	2700	9.26 ± 1.84	6.30 ± 1.52	5.19 ± 1.96	20.37 ± 2.56	1 : 55
Pravoberezhny	4224	6.16 ± 1.20	6.16 ± 1.20	1.42 ± 0.82	13.73 ± 1.74	1 : 77
Kirovsky	2655	6.40 ± 1.55	6.40 ± 1.55	6.03 ± 2.12	18.83 ± 2.42	1 : 63
Alagirsky	2351	13.19 ± 2.35	7.23 ± 1.75	2.55 ± 1.47	22.97 ± 3.01	1 : 46
Digorsky	2200	10.00 ± 2.12	8.18 ± 1.92	1.82 ± 1.28	20.00 ± 2.92	1 : 52
Irafsky	1650	16.97 ± 3.18	10.30 ± 2.49	3.64 ± 2.09	30.91 ± 4.14	1 : 34
Prigorodny	9529	4.51 ± 0.69	4.41 ± 0.68	2.10 ± 0.66	11.02 ± 1.02	1 : 100
Mozdoksky	10469	7.55 ± 0.85	7.26 ± 0.83	2.29 ± 0.66	17.10 ± 1.23	1 : 63
Weighted average	35778	7.57 ± 0.46	6.43 ± 0.42	2.29 ± 0.66	16.69 ± 0.65	1 : 65
Pediatric populations of towns (district centers)						
Ardonsky (town of Ardon)	4296	7.22 ± 1.29	3.96 ± 0.96	1.86 ± 0.93	13.04 ± 1.68	1 : 83
Pravoberezhny (town of Beslan)	13147	2.36 ± 0.42	2.36 ± 0.42	0.76 ± 0.34	5.48 ± 0.62	1 : 196
Kirovsky (rural locality of Elkhotovo)	2374	5.05 ± 1.39	2.95 ± 1.11	2.53 ± 1.46	10.53 ± 1.97	1 : 108
Alagirsky (town of Alagir)	5435	4.42 ± 0.89	3.31 ± 0.78	2.58 ± 0.97	10.30 ± 1.28	1 : 111
Digorsky (town of Digora)	2784	5.39 ± 1.39	4.31 ± 1.24	1.44 ± 1.02	11.14 ± 1.92	1 : 96
Irafsky (rural locality of Chikola)	2150	4.65 ± 1.47	4.65 ± 1.47	0.93 ± 0.93	10.70 ± 2.17	1 : 102
Prigorodny	2228	3.14 ± 1.19	3.14 ± 1.19	2.10 ± 0.66	11.02 ± 1.02	1 : 149
Mozdoksky	11630	3.10 ± 0.52	2.32 ± 0.45	2.24 ± 0.62	7.65 ± 0.75	1 : 153
City of Vladikavkaz	65738	2.08 ± 0.18	2.49 ± 0.19	1.83 ± 0.24	6.40 ± 0.29	1 : 182
Weighted average	109782	2.76 ± 0.16	2.67 ± 0.16	1.75 ± 0.18	7.18 ± 0.24	1 : 159
Burden of the entire pediatric population of districts and towns						
Ardonsky	6996	8.00 ± 1.07	4.86 ± 0.83	3.14 ± 0.95	16.01 ± 1.43	2:09
Pravoberezhny	17371	3.28 ± 0.43	3.28 ± 0.43	0.92 ± 0.33	7.48 ± 0.63	3:22
Kirovsky	5029	5.57 ± 1.07	4.77 ± 0.97	4.37 ± 1.32	14.91 ± 1.58	2:19
Alagirsky	7786	7.06 ± 0.95	4.50 ± 0.76	2.57 ± 0.81	14.13 ± 1.28	1 : 78
Digorsky	4984	7.42 ± 1.22	6.02 ± 1.09	1.61 ± 0.80	15.05 ± 1.68	1 : 70
Irafsky	3800	10.00 ± 1.61	7.11 ± 1.36	2.11 ± 1.05	19.21 ± 2.10	1 : 55
Prigorodny	11757	4.25 ± 0.60	4.17 ± 0.59	1.87 ± 0.56	10.29 ± 0.89	1 : 107
Mozdoksky	22099	5.20 ± 0.48	4.66 ± 0.46	2.26 ± 0.45	12.13 ± 0.70	1 : 91
City of Vladikavkaz	65738	2.08 ± 0.18	2.49 ± 0.19	1.83 ± 0.24	6.40 ± 0.29	1 : 182
Weighted average	145560	3.94 ± 0.16	3.59 ± 0.16	1.98 ± 0.16	9.51 ± 0.24	1 : 117

with various nosological forms of OHDs, which accounted for 58.62% of the total number of affected individuals of various age groups identified in this region (2115 patients from 1489 families). We calculated the genetic burden of OHDs in the city of Vladikavkaz and eight rural districts of the RNO-A.

The cumulative prevalence (per 1000 children) of the main types of OHDs (AD, AR, and XL) in the pediatric population of the RNO-A (in the city of Vladikavkaz, Ardonsky, Pravoberezhny, Kirovsky, Alagirsky, Digorsky, Irafsky, Prigorodny, and Mozdoksky districts) was calculated (Table 2).

We revealed variability of cumulative prevalence by subpopulations between 5.48 ± 0.621 (1 : 196) in the town of Beslan and 30.91 ± 4.137 (1 : 34) in rural areas of the Irafsky District (Table 2). The analysis of 17 subpopulations showed that the cumulative prevalence of all types of OHDs in rural areas was more than twice higher compared to that in towns and district centers (χ^2AD = 54.35; χ^2AR = 48.89; χ^2XL = 29.46; χ^2Tot. = 136.18; d.f. = 16; $p < 0.05$), which is typical for populations of the Russian Federation [17–20].

The average prevalence in the surveyed sample was 1 : 117 children, i.e. about 1% of children were diagnosed with OHDs. This indicator varies widely: between 1 : 34 in rural areas of the Irafsky District (more than 2% of children) and 1 : 196 (0.5%) in the town of Beslan.

Comparative analysis of the cumulative prevalence of hereditary diseases among children in the surveyed pediatric populations of the Russian Federation

We conducted a comparative analysis of the cumulative prevalence of hereditary diseases among children in the surveyed pediatric populations of the Russian Federation, including the data reported for the RNO-A. It should be noted that the share of the total number of affected children among all the OHD patients identified was 58.62% (1241/2117, respectively), even though the share of the pediatric population in the Republic is 26.77%.

A comparison of the cumulative prevalence values reported for the AD, AR, and XL diseases in the pediatric population showed that the genetic burden of OHDs in children was higher in rural areas than in towns and district centers (Table 3). The analysis conducted showed differentiation and revealed

Table 3. Weighted average values of cumulative prevalence (genetic burden) of OHDs in pediatric populations of the rural areas, towns, and district centers by surveyed populations of Russia (per 1000 examined children) [17–20]

Subpopulations/regions	Population size	Genetic burden per 1000 children/boys*				Prevalence
		AD	AR	XL*	Total	
	Genetic burden in rural pediatric populations					
Kirov Region	17 032	6.22 ± 0.60	4.40 ± 0.51	2.35 ± 0.53	12.98 ± 0.83	1 : 85
Rostov Region	55 489	4.99 ± 0.29	3.78 ± 0.26	1.51 ± 0.23	10.29 ± 0.41	1 : 105
Karachay-Cherkessia	38 033	7.47 ± 0.44	5.52 ± 0.38	3.21 ± 0.41	16.20 ± 0.62	1 : 69
North Ossetia – Alania	35 778	7.57 ± 0.46	6.43 ± 0.42	2.29 ± 0.66	16.69 ± 0.65	1 : 65
Udmurt Republic	34 400	7.18 ± 0.46	4.24 ± 0.35	2.56 ± 0.39	13.98 ± 0.60	1 : 79
Republic of Bashkortostan	27 512	5.05 ± 0.43	2.51 ± 0.30	1.96 ± 0.38	9.52 ± 0.56	1 : 117
Republic of Tatarstan	49 612	4.37 ± 0.29	2.70 ± 0.23	1.09 ± 0.219	8.16 ± 0.39	1 : 131
Chuvash Republic	47 226	2.86 ± 0.25	2.22 ± 0.22	0.93 ± 0.19	6.01 ± 0.34	1 : 180
In all rural populations	305 082	5.49 ± 0.13	3.86 ± 0.11	1.91 ± 0.11	11.27 ± 0.18	1 : 97
Genetic burden in pediatric populations of towns and district centers						
Kirov Region	20 316	2.31 ± 0.34	1.58 ± 0.28	0.69 ± 0.26	4.58 ± 0.46	1 : 236
Rostov Region	46 356	1.68 ± 0.19	1.42 ± 0.16	0.43 ± 0.14	3.54 ± 0.27	1 : 301
Karachay-Cherkessia	52 706	3.57 ± 0.26	2.73 ± 0.23	1.25 ± 0.22	7.55 ± 0.36	1 : 144
North Ossetia – Alania	109 782	2.76 ± 0.16	2.67 ± 0.16	1.75 ± 0.18	7.18 ± 0.24	1 : 159
Udmurt Republic	23 248	2.84 ± 0.35	1.94 ± 0.29	1.20 ± 0.32	5.98 ± 0.48	1 : 186
Republic of Bashkortostan	32 685	1.90 ± 0.24	1.25 ± 0.19	1.16 ± 0.27	4.31 ± 0.34	1 : 268
Republic of Tatarstan	15 323	2.22 ± 0.38	1.89 ± 0.35	0.39 ± 0.23	4.50 ± 0.53	1 : 232
Chuvash Republic	20 637	1.45 ± 0.27	2.08 ± 0.32	0.48 ± 0.22	4.02 ± 0.43	1 : 265
In all urban populations	300 416	2.59 ± 0.09	2.16 ± 0.09	1.13 ± 0.08	5.89 ± 0.14	1 : 178
Genetic burden by regions						
Kirov Region	37 348	4.10 ± 0.33	2.86 ± 0.28	1.45 ± 0.28	8.41 ± 0.45	1 : 130
Rostov Region	101 845	3.49 ± 0.18	2.71 ± 0.16	1.02 ± 0.14	10.14 ± 0.73	1 : 149
KKarachay-Cherkessia	90 739	5.20 ± 0.23	3.90 ± 0.21	2.07 ± 0.21	11.17 ± 0.33	1 : 99
North Ossetia – Alania	145 560	3.94 ± 0.16	3.59 ± 0.16	1.98 ± 0.16	9.51 ± 0.24	1 : 117
Udmurt Republic	60 197	3.34 ± 0.23	1.83 ± 0.17	1.53 ± 0.23	6.69 ± 0.31	1 : 173
Republic of Bashkortostan	64 935	3.87 ± 0.24	2.51 ± 0.19	0.92 ± 0.17	7.30 ± 0.32	1 : 146
Republic of Tatarstan	57 648	5.43 ± 0.31	3.31 ± 0.24	2.01 ± 0.26	10.75 ± 0.4	1 : 103
Chuvash Republic	67 863	2.43 ± 0.19	2.18 ± 0.18	0.80 ± 0.15	5.41 ± 0.27	1 : 200
In all pediatric populations	626 135	3.97 ± 0.08	2.99 ± 0.07	1.53 ± 0.07	8.48 ± 0.11	1 : 130

the differences in this indicator between the rural and urban populations. In rural populations, the highest prevalence values were reported for the RNO-A (1 : 65), Karachay-Cherkessia (1 : 69), Udmurt Republic (1 : 79), Kirov Region (1 : 85), while the average value for rural areas was 1 : 97, i.e. more than 1% of children. As for towns and district centers, the prevalence ranged between 1 : 144 in Karachay-Cherkessia and 1 : 301 in the Rostov Region [17–20].

According to Table 3 and Figure, the average values of OHDs prevalence in the pediatric population of the RNO-A obtained in our study (1 : 117) are similar to the values reported for other regions of the Russian Federation we have assessed (1 : 103 for Tatarstan, 1 : 146 for Bashkortostan, 1 : 200 for the Chuvash Republic, 1 : 173 for the Udmurt Republic, 1 : 149 for the Rostov Region, 1 : 130 for the Kirov Region, 1 : 99 for the Republic of Karachay-Cherkessia). It is important that the average prevalence among children is 1 : 130, i.e. 1% of children are diagnosed with OHDs, which has to be taken into account when developing prevention programs and treatment programs for orphan diseases.

OHD diversity in pediatric population of the RNO-A

A total of 1241 patients with various OHD forms from 1037 families were identified in the pediatric population of the RNO-A. The diversity of OHDs is made up of 241 nosological forms: 109 ones with AD inheritance, 102 ones with AR inheritance, and 30 XL diseases. The largest number of affected individuals (n = 880, 70.91%) is reported for the group of 57 (23.65%) common OHD disease entities. In contrast, the smallest number (n = 87, 7.01%) is noted for the group of 87 (36.10%) rare diseases (Table 4).

The majority of diseases have been already found in the surveyed populations of the Russian Federation. Table 5 presents the diversity of common (with the prevalence exceeding 1 : 30 000) OHDs in the RNO-A, along with the average prevalence in seven previously assessed regions of European Russia (ER) and the disease prevalence according to the data of the international Orphanet database [6, 17–20].

High prevalence (per 100,000 children) of 11 diseases is the feature of the surveyed population: childhood myotonic

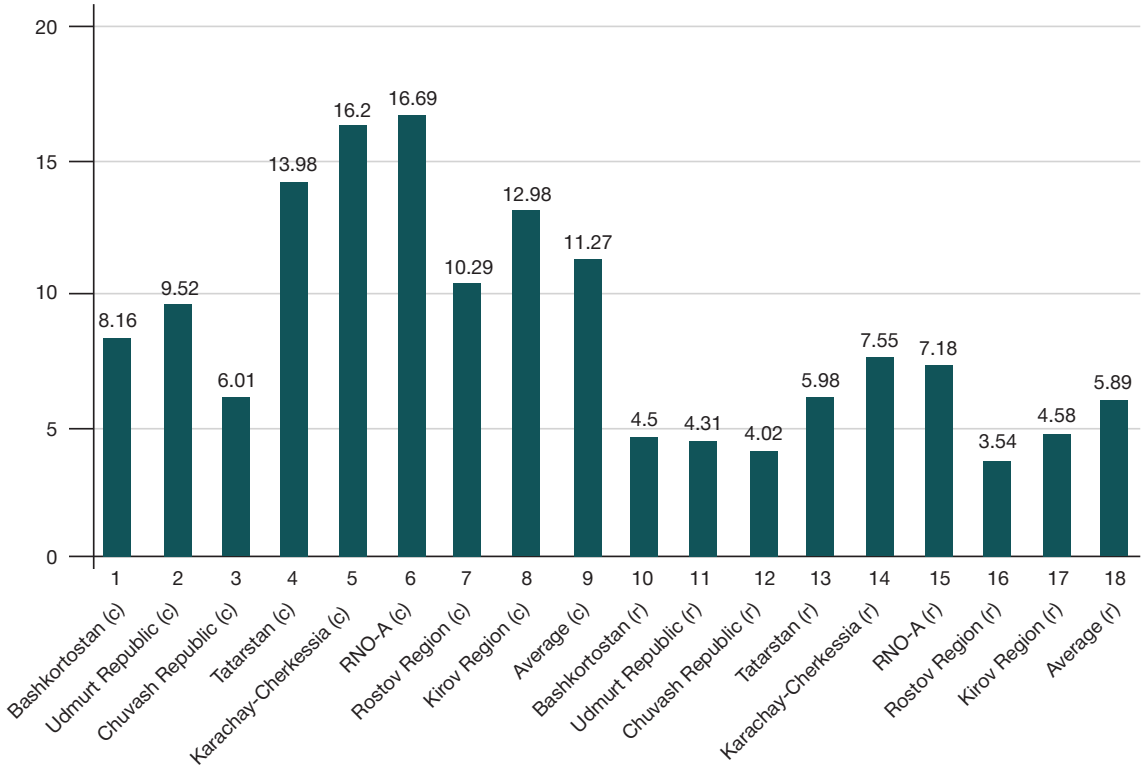

Fig. Cumulative prevalence of OHDs in urban and rural pediatric population of the surveyed regions of Russia

dystrophy — 6.87 (1 : 14.556), Duchenne muscular dystrophy — 37.10 (1 : 2696 boys), type I neurofibromatosis — 18.06 (1 : 7661), type 12 congenital myasthenia — 3.44 (1 : 29.112), congenital X-linked ichthyosis — 12.37 (1 : 8087 boys), fragile X syndrome — 9.62 (1 : 10,327 boys), Rett syndrome — 9.62 (1 : 12,130 boys), achondroplasia — 9.62 (1 : 10.397), AR deafness — 70.76 (1 : 1413), rare form of congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency — 6.18 (1 : 16.173). All patients with the above diseases were genotyped, and the locus and allelic heterogeneity were determined. The previously unreported brachydactyly E–amelogenesis–mental retardation–nanism syndrome showing high prevalence (11.28/100,000) was identified in four families. This syndrome was submitted to Orphanet, but it has not been mapped.

The prevalence of other diseases in the RNO-A was similar to that observed in other regions and aligned with the frequency reported in Europe as documented in Orphanet [6, 17–20]. However, we would like to note the high prevalence of undifferentiated intellectual developmental disorder with all types of inheritance (AD, AR, XL) in the RNO-A (13.74/100,000; 39.85/100,000 and 35.72/100,000 boys, respectively), the overall prevalence was 1 : 1400 children.

Thus, the OHD analysis conducted revealed regional specifics of the spectrum and showed the need to develop specific regional prevention programs.

DISCUSSION

In global practice, there is a limited number of studies focused on assessing the cumulative prevalence, diversity, and features of the spread of OHDs in pediatric populations [2, 7–16]. In the Russian Federation, such studies are conducted only by the team of the Research Centre for Medical Genetics. Assessment of the OHD cumulative prevalence in the pediatric population of the RNO-A revealed variability of this indicator in 17 subpopulations of the region: between 5.48 ± 0.621 (1 : 196) in the town of Beslan and 30.91 ± 4.137 (1 : 34) in rural areas of the Irafsky District. A more than 2-fold increase in genetic burden relative to the values reported for towns and district centers

Table 4. Distribution of patients and disease entities with OHDs depending on the disease prevalence

	Prevalence	Number (%) of affected individuals				Number (%) of diseases			
		AD	AR	XL	Σ	AD	AR	XL	Σ
1	1 : 30 000 and higher	379	388	113	880	23	23	11	57
		69.41%	70.93%	76.35%	70.91%	20.91%	22.33%	39.29%	23.65%
2	1 : 30 001 – 1 : 50 000	69	66	14	149	17	16	4	37
		12.64%	12.07%	9.46%	12.01%	15.45%	15.53%	14.29%	15.35%
3	1 : 50 001 – 1 : 100 000	52	52	21	125	24	23	13	60
		9.52%	9.51%	14.19%	10.07%	21.82%	22.33%	46.43%	24.90%
4	1 : 100 001 – and lower	46	41		87	46	41		87
		8.42%	7.50%		7.01%	41.82%	39.81%		36.10%
	TOTAL	546	547	148	1241	110	103	28	241

Table 5. Nosological spectrum and prevalence (per 100,000 children) of common hereditary diseases (with the prevalence exceeding 1 : 30,000) identified in the pediatric population of the RNO-A

№	№ OMIM	Diagnosis	I/T	N/P	Prevalence		
					RNO-A	ER	Orphanet
Hereditary neurological diseases							
1	162200	Neurofibromatosis, type I	AD	29	18.06	13.58	10–15
2	PS308350	Epileptic encephalopathy, early infantile	AD	8	5.5	2.56	n/d
3	PS191100	Tuberous sclerosis	AD	7	4.81	5.75	1–4
4	160900	Myotonic dystrophy	AD	10	6.87	2.4	1–9
5	PS156200	Intellectual developmental disorder, AD	AD	20	13.74	13.42	n/d
6	PS249500	Intellectual developmental disorder, AR	AR	58	39.85	39.45	n/d
7	PS309530	Intellectual developmental disorder, X-linked	XL	26	35.72	37.69	n/d
8	PS251200	Microcephaly, primary	AR	23	15.8	17.25	n/d
9	PS251280	Microcephaly, seizures with spastic quadriplegia	AR	7	4.81	4.95	n/d
10	610542	Myasthenia, congenital, 12	AR	5	3.44	н/д	0.1–0.9
11	PS117000	Congenital myopathy	AR	8	5.5	2.56	n/d
12	310200	Duchenne muscular dystrophy	XL	27	37.1	17.25	1–9
13	310376	Becker muscular dystrophy	XL	3	4.12	2.24	5.4–6
Hereditary eye diseases							
14 15	PS116200	Congenital hereditary cataract	AD, AR	15 11	10.31 7.56	10.54 8.15	n/d
16	231300	Glaucoma, primary open angle, congenital	AR	7	4.81	3.83	1–9
17	PS310700	Nystagmus, congenital, X-linked	XL	8	10.99	11.82	n/d
18	120200	Coloboma, ocular	AD	6	4.12	4.47	n/d
19	PS148300	Keratoconus	AD	5	3.44	1.12	n/d
20	PS268000	Retinitis pigmentosa	AR	5	3.44	2.4	10–50
Hereditary genodermatoses							
21	148700	Keratosis palmoplantaris	AD	15	11.68	13.89	2.5–50
22	146700	Ichthyosis vulgaris	AD	5	3.44	26.99	20–25
23	308100	Ichthyosis, X-linked	XL	9	12.37	15.01	10–50
24	PS305100	Ectodermal dysplasia	XL	3	4.12	2.24	0.1–1
Hereditary skeletal disorders							
25	100800	Achondroplasia	AD	14	9.62	5.43	
26	146000	Hypochondroplasia	AD	6	4.12	3.35	
27	185900	Syndactyly 1	AD	5	3.44	6.55	10–50
28	PS166200	Osteogenesis imperfecta	AD	9	6.18	7.51	10–50
29	181800	Scoliosis, idiopathic	AD	22	15.11	7.35	10–25
30	PS136760	Frontonasal dysplasia	AD	7	4.81	3.35	n/d
31	226900	Epiphyseal dysplasia, multiple, 4	AR	5	3.44	0.8	n/d
Hereditary syndromes							
32 33	PS130000	Ehlers–Danlos syndrome	AD AR	145 5	99.62 3.44	44.56 2.56	52
34	PS309510	Intellectual developmental disorder, X-linked syndromic	XL	12	16.49	3.83	n/d
35	PS119530	Orofacial cleft syndrome	AD	6	4.12	1.6	10–50
36	300624	Fragile X syndrome	XL	7	9.62	5.43	10–50
37	113477	Brachydactyly E syndrome, amelogenesis, growth retardation, intellectual developmental disorder (BOD syndrome)	AD	9	6.18	n/d	n/d
38	143500	Gilbert syndrome	AR	9	6.18	3.03	n/d
39	PS118100	Klippel–Feil syndrome	AD	6	4.12	2.4	
40	PS163950	Noonan syndrome	AD	5	3.44	4.95	10–50
41	PS180849	Rubinstein–Taybi syndrome	AD	5	3.44	1.92	
42	185300	Sturge–Weber syndrome	AD	5	3.44	4.31	1–9
43	312750	Rett syndrome	XL	6	8.24	4.15	1–9

Table 5. Ending

Other hereditary diseases							
44	PS220290	Deafness, autosomal recessive	AR	103	70.76	61.97	20–50
45	274400	Thyroid dyshormonogenesis 1	AR	25	17.18	11.34	
46	261600	Phenylketonuria	AR	40	24.94	22.02	
47	PS173900	Polycystic kidney disease 1	AD	20	13.74	4.63	10–50
48	PS262400	Growth hormone deficiency, isolated	AR	10	6.87	5.91	1–9
49	230400	Galactosemia	AR	12	8.24	2.56	n/d
50	219700	Cystic fibrosis	AR	12	8.24	7.35	10–50
51	201910	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency	AR	11	7.56	3.51	1–9
52	201810	Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency	AR	9	6.18	n/d	< 0.1
53	PS203200	Albinism, oculocutaneous, type II	AR	6	4.12	2.4	1–9
54	PS203100	Albinism, oculocutaneous, type IA	AR	5	3.44	5.59	1–9
55	608644	Thalassemia, beta	AR	5	3.44	0.8	n/d
56	306700	Hemophilia A	XL	9	12.37	12.14	1–9
57	306900	Hemophilia B	XL	3	4.12	1.92	1–9

Note: No. OMIM — numbers of diseases according to the international OMIM catalog by Dr. Victor A. McKusick; PS — phenotypic series of the diseases of heterogeneous group according to OMIM; I/T — inheritance type; N/P — number of patients; RNO-A — Republic of North Ossetia–Alania; ER — average disease prevalence values according to the genetic and epidemiological studies of pediatric population in European Russia; n/d — no data; the prevalence of X-linked diseases is represented by the number of boys.

was found in children living in rural areas of 17 subpopulations. Such a situation is observed in all seven pediatric populations previously surveyed in the Russian Federation [17–20].

The average OHD prevalence (1 : 117) in children of the RNO-A (Table 3 and Figure) obtained in this study is similar to the data on cumulative prevalence in the previously assessed regions of the Russian Federation (the values range between 1 : 200 in the Chuvash Republic and 1 : 99 in Karachay-Cherkessia). It is important to note that the average prevalence among children is 1 : 130, i.e. 1% of children are diagnosed with OHDs, which is consistent with the data provided in the reports of foreign colleagues [2, 3]. It is important for scientists, practical healthcare, and the society to emphasize that it is children, who constitute the share of the total number of patients with OHDs in the population: 58.62% of all patients identified in the Republic. The same situation is observed in other regions. The average share of pediatric patients with OHDs among all the patients identified in eight surveyed constituent territories of the Russian Federation was 43.5% (from 35% in the Kirov Region to 58% in the RNO-A), although the share of children in the surveyed regions varies between 17.80% in the Kirov Region and 26.77% in the RNO-A. Such a situation is due to the high mortality rate and decreased genotype fitness associated with a number of common OHDs [2, 3, 17–20].

The diversity of OHDs is made up of 241 diseases (109 AD, 102 AR, and 30 XL ones). The largest number of affected individuals (n = 880, 70.91%) is reported for the group of common (with the prevalence exceeding 1 : 30.000) OHD disease entities: 57 (23.65%). We have analyzed the spectrum of common OHDs and their prevalence in the RNO-A (Table 5); a comparison with the prevalence in seven previously surveyed regions of European Russia (ER) and the data deposited in the international Orphanet database has been conducted [6, 17–20].

High prevalence (per 100,000 children) of 11 diseases, three of which have not been previously reported in our studies (type 12 congenital myasthenia (GFPT1 gene) — 3.44 (1 : 29,112); the rare form found globally in 1% of patients with congenital adrenal cortex dysfunction (3-beta-hydroxysteroid dehydrogenase 2 deficiency — HSD3B2 gene) — 6.18 (1 : 16,173); brachydactyly E–amelogenesis–mental retardation–nanism syndrome — 11.28 (has not been mapped)), is the feature of the surveyed population.

We identified type 1 congenital myotonic dystrophy — 6.87 (1 : 14.556), associated with the trinucleotide repeat expansion in the DMPK gene, Duchenne muscular dystrophy — 37.10 (1 : 2696 boys), type I neurofibromatosis — 18.06 (1 : 7661), congenital X-linked ichthyosis — 12.37 (1 : 8087 boys), fragile X syndrome — 9.62 (1 : 10,327 boys), Rett syndrome — 9.62 (1 : 12,130 boys), achondroplasia — 9.62 (1 : 10,397), AR deafness — 70.76/100,000 (1 : 1413) showing high prevalence among children. All patients with the above diseases have been genotyped, the locus and allelic heterogeneity have been determined.

CONCLUSIONS

The population of the Republic of North Ossetia–Alania (RNO-A) is characterized by a specific spectrum of OHDs caused by rare mutations, some of which do not occur or are significantly less common in other populations of the world and the Russian Federation. The higher prevalence of this spectrum of diseases in rural populations attracts attention. The findings suggest the need to develop customized region-specific programs for the prevention of childhood disability. Given the fact that hereditary diseases in children are characterized by severe course and often lead to premature death, the development of methods to prevent such diseases constitutes the obligatory direction of reducing child mortality. In general, the data obtained during this study are important in practical terms; these also contribute to global science and fundamental epidemiological studies of OHDs.

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