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Epidemiology of Mucopolysaccharidosis Type II According to the Register of the Russian Federation

Natalia V. Buchinskaia[1,2], Ekaterina Yu. Zakharova[3], Yulia S. Koshevaya[2], Anastasia O. Vechkasova[2], Rostislav K. Skitchenko[4], Aleksandr M. Nikonov[5], Vera I. Kurilova[6], Yulia V. Maximova[7], Khasyanya F. Aksyanova[8], Elena G. Bakulina[9], Nina I. Kononenko[10], Elena V. Osipova[11], Mikhail M. Kostik[1,4], Sergei I. Kutsev[3]

[1]Saint-Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia
[2]Saint-Petersburg State Medical Diagnostic Center (Genetic Medical Center), Saint-Petersburg, Russian
[3]Federal State Budgetary Scientific Institution, Research Center for Medical Genetics, Moscow, Russia
[4]Almazov National Medical Research Centre, Saint-Petersburg, Russia
[5]KGBUZ Consulting and Diagnostic Center of the Altai Territory, Barnaul, Russia
[6]State Budgetary Institution of Health of the Perm Region, Regional Children's Clinical Hospital Perm, Russia
[7]Novosibirsk State Medical University, Novosibirsk, Russia
[8]Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod, Russia
[9]Stavropol Regional Clinical Consulting and Diagnostic Center, Stavropol, Russia
[10]Kursk Regional Clinical Hospital, Kursk, Russia
[11]Budgetary Healthcare Institution of the Udmurt Republic, The First Republican Clinical Hospital of the Ministry of Health of the Udmurt Republic, Izhevsk, Russia

What is already known on this topic?

MPSII is the most frequent type of the mucopolysacharidosis, the epidemiology of this disease is provided by the several countries.

What does this study add on this topic?

This is the first report about geographical and molecular epidemiology of MPS II in Russian Federation according the data of national MPS registry.

Corresponding author:
Mikhail M. Kostik
✉ kost-mikhail@yandex.ru, mikhail.kostik@gmail.com
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ABSTRACT

Objective: The study aimed to evaluate the epidemiological, clinical, and molecular data of mucopolysaccharidosis type II (MPS II) patients and their outcomes using the national registry of patients in the Russian Federation (RF).

Materials and Methods: In the retrospective cohort study, the authors included data from the Russian national registry of MPS II.

Results: The prevalence of MPS II in RF is 0.62 per 100 000 live births or 0.09 per 100 000 population with the majority of patients in the Central (n = 36) and the Volga Federal District (n = 35). Males were 157 (99.4%), positive MPS II family history had 47 (29.7%) patients. The median age of the first symptoms was 1.8 (0.8-2.6) years, ranging from 0.1 to 19 years, and the age of diagnosis was 4.0 (2.5; 5.9) years, ranging from 0.1 to 38.9 years. A genetic study was available for the analysis in 116 (73.4%) patients. Single nucleotide variants in the IDS gene were found in 98/116 (84.5%) patients, and 18 further patients (15.5%) had gross rearrangements. About 59/98 (60.2%) patients had missense, 15/98 (15.3%) had frame-shift variants, 12/98 (12.2%) had splice site, and 11/98 (11.2%) had nonsense variants. One (1.0%) patient out of 98 patients had a small deletion. Pathogenic, likely pathogenic variants, and variants with uncertain significance were found in 54 (55.1%), 36 (36.7%), and 8 (8.2%) patients, respectively. About 138 (87.3%) patients received enzyme replacement therapy.

Conclusion: The prevalence of MPS II in the RF is higher than that in some European countries and closer to the Asian population. The registry is a convenient tool for disease epidemiology and monitoring.

Keywords: Mucopolysaccharidosis type II, epidemiology, *IDS* gene, genotype-phenotype, Russian Federation

INTRODUCTION

Mucopolysaccharidosis type II (MPS II) or Hunter syndrome (OMIM 309900) is a rare lysosomal storage disease with an X-linked inheritance pattern, characterized by a progressive

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course and damage to multiple organs and tissues. The disease is caused by pathogenic variants in the *IDS* (iduronate sulfatase) gene, encoding an enzyme that breaks down the glycosaminoglycans dermatan sulfate and heparan sulfate.[1,2]

The European registry for MPS II, the Hunter Outcome Survey (HOS), started in 2005 when the first patient was enrolled. By 2006, it included 100 patients from 10 countries and, by 2021, 1322 patients from more than 16 countries.[3] The number of research papers from HOS today is approaching 20. The latest analytical snapshot of HOS data was carried out in July 2020. At that time, in 3 countries, 152 centers, and 1338 patients participated in the registry, and 86% of the patients received enzyme replacement therapy (ERT).[4]

The register of patients with MPS II in RF started in 2008, when the ERT was available in the RF, and was updated and expanded in 2022. The register includes patients diagnosed with MPS II, confirmed by biochemical and molecular genetic methods. Information about patients is entered by geneticists or attending physicians who closely monitor patients at their place of residence. In each region of the RF, a responsible physician maintains the information about the patients. All patients with MPS II are subject to inclusion in the register, regardless of age and therapy.

The study aimed to evaluate the epidemiological, clinical, and molecular data of MPS II patients and their outcomes using the national registry of patients in the RF.

MATERIALS AND METHODS

Register's Characteristics

In this study, the authors used data from the "Register of Patients with MPS II in the Russian Federation" provided by the Association of Medical Geneticists and the Federal State Budgetary Scientific Institution, Research Center for Medical Genetics named after Academician "N.P. Bochkov."

Participation in the registry was voluntary; the patient or his legal representative signed an informed consent to participate in the registry. The patient or his legal representative has given informed consent to participate in the registry.

Study Design

In the retrospective cohort study, the data about 158 patients with MPS II (November 2023) were extracted from the Russian national registry (2008–2023). The diagnosis was made on clinical phenotype with enzymatic and/or molecular confirmation.The study was approved by the Ethics Committee of Saint-Petersburg State Pediatric Medical University (protocol #1 from 19.01.2009). Written informed consent was obtained from the patients who agreed to take part in the study.

Assessments

From every patient, the authors extracted the following information:

- *Demography:* Demography includes age, sex, residence, family history of MPS II, the age of the first symptom(s), the age of the diagnosis, and time before the diagnosis. The age of the first symptom was determined retrospectively by the experienced physician, who included the patient in the registry according to personal opinion if this symptom could be related to MPS II or not.
- *Clinical features, related to the disease.* The neuronopathic form was determined if a patient has central nervous system involvement with at least one of the following symptoms: hydrocephalus, progressive intellectual disability, losing skills, and epilepsy. The main clinical symptoms were related to the time of diagnosis of MPS II.
- *Laboratory data:* Laboratory data include data of genetic analysis (sequencing by Sanger) and enzyme activity. The authors highlighted the significant changes at the *IDS* gene as deletions, recombinant events involving *IDS-IDS2*, and missense mutations leading to a severe phenotype of MPS II, according to the previously published data.[5]
- *Treatment:* Treatment category includes the number of patients being treated with ERT.
- *Outcomes:* Outcome catergory includes data on alive or dead.

STATISTICS

Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., Tulsa, Okla, USA). All continuous variables were checked for normality by the Kolmogorov–Smirnov test. All continuous variables are presented with median (Me), quartiles (Q1; Q3), range (minimum-maximum, min-max), and frequency and percentage for categorical variables. The chi-square test (if less than 20% of the cells have an expected count of less than 5) or Fisher's exact test (if more than 20% of the cells have an expected count of less than 5) was used to compare categorical variables. Two quantitative variables were compared using the Mann–Whitney *U*-test. For the calculation of the disease prevalence, the authors used the official statistical data from the Federal State Statistics Service: https://rosstat.gov.ru/.[6] The number of residents of the Russian Federation (RF) was taken from the Rosstat website based on the results of the 2020 population census.[6]

RESULTS

Demographic Characteristics of Patients with Mucopolysaccharidosis Type II

Now, in the registry, there are data about 158 patients with MPS II and 140 (88.6%) of them are currently alive. The patient cohort consisted of 157 males (99.4%) and 1 female (0.6%).

The disease was caused by a mutation in the *IDS* gene inherited from the mother and the presence of chromosome X of paternal origin, partially deleted in the long arm region—46, X, del(X)(q22.1).

The median age of the first symptoms was 1.8 (0.8-2.6) years, ranging from first months to 19 years.

The median time since the first symptom before genetic confirmation was 1.8 (0.6; 3.5) years ranging from 0.3 to 30.9 years. Among the clinical features, patients had cardiac involvement (n = 81; 51.6%), organomegaly (n = 100; 63.3%), and skeletal involvement (n = 130; 82.2%). According to the registry, the main manifestations of the disease included hepatomegaly (n = 100;

63.3%), ENT (ear, nose, and throat) involvement (n = 98; 62.4%), umbilical and inguinal hernias (n = 86; 54.8%), damage to the cardiovascular system (n = 81; 51.6%), with changes in the heart valves detected in 71 patients (45.2% of those examined), and multiple dysostosis (n = 62; 39.5%).

In the registry, there is a patient with a mild form of MPS, who experienced the first symptoms of the disease at the age of 19 and was diagnosed at 21 and has completed secondary education. The activity of the idursulfatase enzyme was low, and no molecular genetic analysis had been performed at the time. At the time of diagnosis, the patient's height was 136 cm and weight was 48 kg. The patient has a disproportionate physique, including macrocephaly, a short neck, prominent facial features, a chest deformity, hepatosplenomegaly, an umbilical hernia, joint stiffness, carpal tunnel syndrome, and mixed hearing loss. Echocardiography revealed regurgitation of the mitral, aortic, and tricuspid valves, as well as pulmonary artery stenosis and compensated heart failure. Since 2015, the patient has been receiving ERT with idursulfase (Elaprase®, Shire [a Takeda company], Lexington, Mass, USA) for 8 years.

The neuronopathic form to the last available visit was detected in 87/125 (69.6%), the non-neuronopathic form had 38/125 patients (30.4%) and there are no data in 33 (20.9%) patients. Severe intellectual disability had 28 (22.4%) and mild-to-moderate intellectual disability had 59 (47.2%) patients. Hydrocephalus was diagnosed in 60/123 (48.8%) patients, and epilepsy in 20/127 (15.8%). The median age of the diagnosis in neuronopathic form was 49.0 (35.0; 88.0) months, compared to non-neuronopathic 36.0 (26.0; 60.0) months (P = .059), and the time from the first symptoms to diagnosis was longer 29.0 (6.6; 58.3) months than in non-neuropathic 14.7 (6.8; 26.2) months (P = .022).

At the time of data collection, out of 158 patients, 139 (87.3%) had ever received ERT. By then, 140 people were still alive, of which 125 had received enzyme replacement treatment (89.3% of the surviving population), and 18 had died for various reasons. Out of these, 14 (77.8%) of the deceased had also received ERT (P = .158).

The main causes of death (n = 18; 11.4%) were progression of the underlying disease (n = 2), pneumonia (n = 3), acute heart failure (n = 5), accompanied by respiratory failure (n = 3), and multiple organ failure (n = 2). In 3 cases, the cause of death has not been noted. The median age of death in MPS II with and without cognitive deficiency was 15 years and 17 years, respectively. There are no differences in the mortality rates between neuronopathic form 8/87 (9.2%) and non-neuronopathic form 6/38 (15.8%), P = .282. The longest clinical follow-up is 16 years and the longest follow-up in the registry is 7 years. Detailed demographic characteristics of patients with MPS II according to the registry analysis as of November 2023 are presented in Table 1.

Family History of Patients with Mucopolysaccharidosis Type II

Forty-seven patients reported a positive family history of MPS II within their family. Most frequently, these were siblings (n = 18), accounting for 11.4% of all patients in the registry. Seven patients with MPS II had cousins with the same condition, accounting for 4.4% of all MPS II patients listed in the registry. Other familial cases were less common: 3 patients had a grandfather with MPS II (1.9%), 13 patients had an uncle with the same disease (8.2%), and 6 patients had other relatives with the diagnosis (3.8%). In some families, more than 2 relatives had MPS II, such as siblings and an uncle from the mother's side within the same family.

Regional Distribution of the Patients

On the territory of Russia, patients with MPS II are distributed unevenly: the majority of the patients live in the Central Federal District—36 (25.7%)—and in the Volga Federal District—35 (25.0%). The smallest number of patients was registered in the Far Eastern Federal District—6 (4.3%)—and in the North Caucasus Federal District—7 (5.0%) patients. The prevalence of MPS II in the RF is 0.09 per 100 000 population. The prevalence of MPS II is equal to Russia's average data in the Central and North-West Federal Districts, less in Far-Eastern, Southern, North-Caucasian and Ural Federal Districts, and the highest prevalence is observed in the Siberian and Volga Federal Districts. Data are in Table 2.

Table 1. Demographic and Clinical Characteristics of Registry Patients with Mucopolysaccharidosis Type II

Parameter	n	Results (n = 158), n (%) or Me (Q1; Q3)/min-max
Sex, male, n (%)	158	157 (99.4)
Sex, female*	1	1 (0.6)
Current age of the patient, years	140	13.5 (9.6; 18.9)/2.3-46.9
The age of the first symptom, years	115	1.8 (0.8; 2.6)/0-19
Age of genetic confirmation, years	109	4.3 (2.8; 7.7)/0.1-39.7
Age at diagnosis, years	133	4.0 (2.5; 5.9)/0.1-38.9
Time since first symptoms to genetic confirmation, years	109	1.8 (0.6; 3.5)/0.0-30.9
Ever received ERT, n (%)	138	138 (87.9)
Did not receive ERT, n (%)	20	20 (12.7)
Time since first symptoms of ERT, years	112	3.8 (2.0; 8.4)/0.25-40.4
Time since diagnosis to ERT, years,	104	0.8 (0.3; 4.1)/0.0-34.9
Patients with neuronopathic form, n (%)	125	87 (69.6)
Alive/died, n (%)	158	140 (88.6)/18 (11.4)
Age of death, years	18	18.7 (13.7; 21.7)/10.4-43.8

*Calculation for the number of the alive patients (n = 140).
ERT, enzyme replacement therapy; max, maximal; Me, median; min, minimal; Q1-Q3, quartiles.

Table 2. Prevalence of Mucopolysaccharidosis Type II in Federal Districts of the Russian Federation

Federal District	Number of Alive Patients with MPS II, n (%)	Number of Residents in the Federal District	Prevalence of MPS II in the Federal District per 100 000 Live Births
Central	36 (25.7)	40 334 532	0.09
Southern	10 (7.1)	16 746 442	0.06
Northwestern	12 (8.6)	13 917 197	0.09
Privolzhsky	35 (25.0)	28 943 264	0.12
Far-Eastern	6 (4.3)	7 975 762	0.075
North-Caucasian	7 (5.0)	10 171 434	0.07
Ural	8 (5.7)	12 300 793	0.065
Siberian	25 (17.9)	16 792 699	0.15

MPS II, Mucopolysaccharidosis Type II.

Molecular Genetic Assessment

Molecular genetic tests were performed in 123 patients (77.8%), but genetic data of 116/158 (73.4%) patients only were available for the analysis, in 7 (4.4%) patients data were not correct and could not be properly assessed, and information about genetic tests in 10 (6.3%) patients are missed and in the remaining 25 (15.8%) patients the diagnosis was established based on clinical data with biochemical confirmation. Single nucleotide variants in the *IDS* gene were found in 98/116 (84.5%) patients and gross rearrangements of the *IDS* gene were identified in 18/116 (15.5%) patients (Fig. 1 and Supplementary Table 1).

The following types of single nucleotide variants (n = 98) were identified: pathogenic (n = 54; 55.1%), likely pathogenic (37 variants) in 36 patients (36/98, 36.7%), variants with uncertain significance (n = 8; 8.2%). One of the patients (#20 in Supplementary Table 1) has 2 missense variants c.1411G>C (p.Asp471His) and c.1418C>T (p.Pro473Leu), both of which were likely pathogenic. He has the non-neuropathic form of MPS II. In the cohort 59/98 (60.2%) patients had 60 missense variants. The second major type was frame-shift mutations (15/98; 15.3%), followed by the nonsense mutations (11/98; 11.2%), splice sites mutations (12/98; 12.2%), and the least common were small deletion (1/98; 1%).

The most common mutations identified in the *IDS* gene during the analysis of the MPS registry in the RF were as follows: c.1122C>T (found in 5 unrelated patients from different regions of Russia), c.1402C>T, c.253G>A and c.257C>T. Each of these variants was detected in 4 unrelated patients from different parts of RF.

Missense mutations (54.2%, 32/59) and gross rearrangements (66.7%, 12/18) of *IDS/IDSP1* were the most common variants among patients with the neuropathic form who underwent genetic testing.

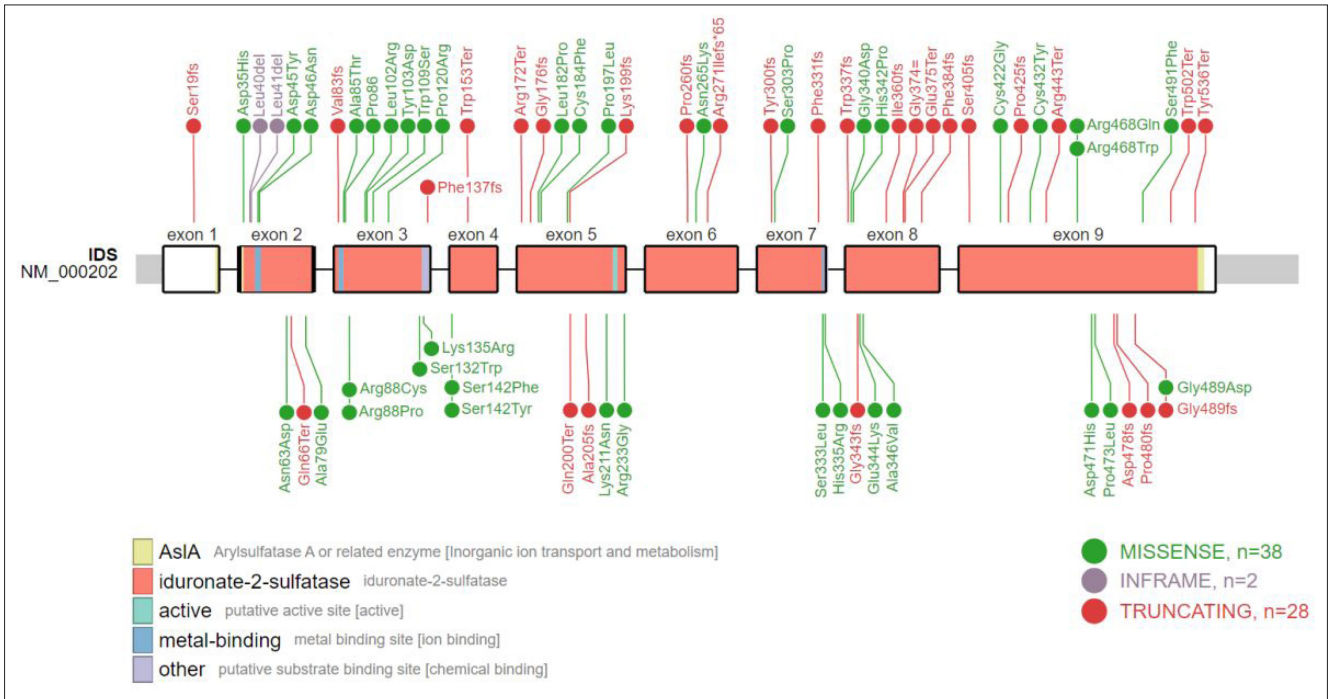

Figure 1. IDS gene variants localization and types. The figure shows the location of variants in the IDS gene and their types. The majority of variants are located in the iduronate 2-sulfatase domain and are missense variants; variants that result in a shorter version of the protein are the second most common.

The neuropathic form was found in 12 out of 13 patients in whom neurologic status was known (92.3%) of patients with gross rearrangements, in 32/55 (58.2%) with missense mutations, in 11/14 (78.6%) with frameshift mutations, in 6/11 (54.5%) with nonsense mutations, and in 5/12 (41.7%) with splicing mutations.

The large rearrangements of the *IDS* gene differed in structure. In 5 patients, recombination was detected between intron 7 and the distal part of exon 3 of the pseudogene *IDSP1*—this is the most common rearrangement in the sample. Two patients had an *IDS/IDSP1* inversion. Two patients had an extended deletion that affected exons 1-7 of the gene, one patient had the deletion of exons 3-7 of *IDS*, and one patient had the deletion of exons 4-7 of *IDS*. Two patients had a deletion of the entire *IDS* gene. Also, deletions of individual exons of the *IDS* gene were noted: 5 exons and 7 exons per patient. Detailed information about the genetic variants is in Supplementary Table S1.

In 8 patients (5%) with single nucleotide variants, enzyme activity was found to be 0. Four of these patients had pathogenic variants in the *IDS* gene, while 3 of them had likely pathogenic variants. One patient did not have any data on molecular genetic analysis available in the database. One patient with a large rearrangement (*IDS/IDSP1* inversion) had zero enzyme iduronate sulfatase activity.

DISCUSSION

The data about the clinical and molecular epidemiology of MPS II patients according to the national MPS registry have been provided.

Analysis of Disease Demography

Despite the rising awareness about MPS, the disease is still diagnosed with some delay. The median age of first symptoms and age of diagnosis were 1.8 (0.8; 2.6) and 4.0 (2.5; 5.9) years, respectively. The main symptoms of the disease include the combination of ENT involvement, which is the most common symptom being adenoid hypertrophy, the presence of hernia in the patient, either now or in the past, along with signs of skeletal dysplasia, such as multiple dysostosis with varying severity, and changes in heart valves as detected by echocardiography. These data correspond to the data of HOS, as well as the proportion of patients receiving ERT 87.9% in the Russian registry and 86% at HOS. Neuronopathic form had 87/128 (68.0%) patients, whose information was available and was very close to HOS 2021 data—66.6%. The neuronopathic form in patients with pathogenic missense mutations and extensive rearrangements was detected in 29/37 (78.4%) patients. Many disease-associated variants have been previously described.[7,8]

Analysis of Sex Distribution

Despite the X-linked recessive type of inheritance, there is 1 female patient in the registry. This case and similar cases have previously been described in the literature in the case of non-random inactivation of the X chromosome.[9,10]

Analysis of Deaths

According to the international HOS registry, patients with cognitive impairment have a shortened life expectancy of 11.7 years compared to patients without cognitive impairment, which is 14.1 years ($P = .024$).[11] In the registry, the median age of patients with cognitive impairment was 15.3 years, and 17 years in patients without cognitive impairment. The main reasons for deaths were respiratory (46%) and cardiac (16%) involvement and the reasons for the death were unknown in 23% of the patients.[11] In the registry, the majority of the deaths were related to heart failure (28%) and respiratory failure (33%), related to MPS progression. In several cases, patients with severe underlying MPS II course had an infection (usually pneumonia) that led to cardiopulmonary decompensation.

The Prevalence of Mucopolysaccharidosis Type II in the World

The data about MPS II epidemiology differs between countries and continents. In Japan, 176 patients were retrospectively identified over 18 years (1982-1999) and new 79 patients in 2003-2009 years. In Japan, the prevalence of all types of MPS during the study period was 1.53 per 100 000 live births, MPS II was 0.84 per 100 000 live births.[5] This type of MPS is the most prevalent in Japan, as in Russia.

In Russia, in 2008-2023 (15 years), 158 patients with MPS II were identified and included in the national register, containing 385 patients with different types of MPS, which amounted to 41%. The prevalence of MPS II in the RF during the study period was 0.62 per 100 000 live births (calculation of the total number of patients with MPS II per number of live births for the period 2008-2022) or 1 : 161 000 live births.

The Swiss National Registry of Patients with Lysosomal Storage Diseases working since 2009 contains information about 51 patients (from 1975 to 2008) with all types of MPS and 12 (23.5%) of them are MPS II patients.[5]

South Korean registry includes 147 patients (from 1994 to 2013) with all types of MPS, and MPS II is the most common type—54.6%. The overall incidence of MPS was 1.35 per 100 000 live births, while the incidence of MPS II was 0.74 per 100 000 live births.[12]

Over 6 years of diagnostics in China (2006-2012), 188 MPS patients were identified and 47.4% of them had MPS II.[13]

The distribution of patients with MPS is uneven across the country, which is primarily due to economic factors and early access to treatment in larger centers.[5,12,13-18] This uneven distribution can also be seen in other countries, such as Turkey.[19]

The register data does not accurately reflect the prevalence of MPS II in the RF. There are several factors that can affect the accuracy of the reported data. Firstly, there may be mild cases of the condition that are not diagnosed for a prolonged period or not diagnosed at all. Secondly, not completely recorded in the registry due to reluctance on the part of legal representatives or patients to participate in the registry (as mentioned in the Materials and Methods section).

According to neonatal screening data in Illinois, only 3 out of 339 269 newborns were diagnosed with MPS II, resulting in an incidence rate of 0.29 per 100 000 births, which is similar to the national average.[15,20] The results of neonatal screening for MPS I in the United States show a range of 0.45-2.81 cases per 100 000 live births, with significant variation in incidence among

Table 3. The Prevalence of Mucopolysaccharidosis Type II in the Russian Federation in Comparison with the Data of Other Countries of the World

Country	Selective Screening Period (years)	Number of Identified MPS Patients (Persons)	Incidence of MPS Per 100 000 Live Births	Number of Identified MPS II Patients (Persons)	Incidence of MPS II Per 100 000 Live Births
Japan[5]	18	331	1.53	176	0.84
Switzerland[5]	34	51	1.56	12	0.46
South Korea[12]	19	147	1.35	80	0.74
China[13]	6	188	–	89	–
Saudi Arabia[14]	26	28	–	0	–
USA[15]	10	–	1.2	–	0.29
Czech[16]	34	119	3.72		0.43
Poland[17]	40	392	1.81	99	0.46
Germany[18]	16	474	3.51	–	0.64
Russian Federation	15	385	1.5	158	0.62

MPS, Mucopolysaccharidosis.

states ranging from 0.22 (Idaho) to 3.14 (New Hampshire) per 100 000 live births. Pilot studies have reported higher incidence rates for MPS I based on neonatal screening data, ranging from 1.04 to 8.3 times.[15] However, it should be noted that during neonatal screening, diagnoses are made in the pre-symptomatic phase, and errors may occur due to pseudo-deficient conditions or during enzymatic testing as part of routine screening for children. In contrast, the registry analysis is limited to patients with a combination of clinical symptoms, biochemical data, and/or genetic confirmation.

Based on the data from national MPS registries, comparable results during the last 15-20 years of screening with similar disease prevalence were observed. More detailed comparative characteristics between counties are presented in Table 3.

Limitations

Our study has some limitations. The retrospective type of registry, missing data, personal opinion of the physician, absence of the exact data about the *IDS* gene analysis, and accuracy of the included in the registry data might influence the study results. Different times to diagnosis and treatment might influence the study's outcomes.

CONCLUSION

The prevalence of MPS II in the RF is higher than in some European countries, and closer to the Asian population. The register is a convenient and accessible tool for assessing the clinical features of the disease and creating algorithms for the early diagnosis of MPS. Analysis of register data makes it possible to assess the effectiveness of various methods of therapy and rehabilitation, continuous monitoring of all patients with this diagnosis, and accumulate and improve healthcare in the RF for MPS II patients.

Take home message: A nationwide registry for rare diseases is a useful tool for the assessment of the disease and the outcomes.

Availability of Data and Materials: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics Committee Approval: The study was approved by the Ethics Committee of Saint-Petersburg State Pediatric Medical University (approval number: #1; date:19.01.2009).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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Supplementary Table 1. Detailed information about genetic variants in patients with MPS type II.

	SNP/ rearrangements	Nucleotide; protein change found	rsID	Exons of IDS gene/9	Type of nucleotide change	Significance	Previously reported	
1	c.1403G>A	p.Arg468Gln	rs113993946	9	missense	Pathogenic	yes	Hsiang-Yu Lin et al., 2019
2	c.907T>C	p.Ser303Pro	-	7	missense	Likely pathogenic	no	
3	c.598C>T	p.Gln200Ter	-	5	nonsense	Pathogenic	yes	Semyachkina AN et al. 2021
4	c.257C>T	p.Pro86Leu	rs1557340280	3	missense	Pathogenic	yes	Alves S et al., 2006
5	c.1466G>A	p.Gly489Asp	-	9	missense	Likely pathogenic	yes	Lin HY et al, 2019
6	c.1122C>T	p.Gly374 =	rs113993948	8	splicing substitutions	Pathogenic	yes	Zhang W et al, 2019
7	c.1472C>T	p.Ser491Phe		9	missense	Likely pathogenic	yes	Vallance HD et al., 1999
8	c.458G>A	p.Trp153Ter		4	nonsense	Pathogenic	yes	Vafiadaki et al., 1999
9	c.1122C>T	p.Gly374 =	rs113993948	8	splicing substitutions	Pathogenic	yes	Zhang W et al, 2019
10	c.1123G>T	p.Glu375Ter		8	nonsense	Pathogenic	yes	Zhang W et al, 2019
11	c.257C>T	p.Pro86Leu	rs1557340280	3	missense	Pathogenic	yes	Alves S et al., 2006
12	c.1403G>A	p.Arg468Gln	rs113993946	9	missense	Pathogenic	yes	Hsiang-Yu Lin et al., 2019
13	c.263G>C	p.Arg88Pro	-	3	missense	Pathogenic	yes	Villani GR et al, 2000
14	c.1122C>T	p.Gly374 =	rs113993948	8	splicing substitutions	Pathogenic	yes	Zhang W et al, 2019
15	c.776_777dup	p.Pro260fs	-		frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
16	c.236C>A	p.Ala79Glu	-	2	missense	Likely pathogenic	yes	Saito S et al., 2016
17	c.359C>G	p.Pro120Arg	rs193302911	3	missense	Likely pathogenic	yes	Kosuga M et al. 2016
18	c.514C>T	p.Arg172Ter	rs104894860	5	nonsense	Pathogenic	yes	Chistiakov DA et al. 2014
19	c.305T>G	p.Leu102Arg	-	3	missense	Likely pathogenic	yes	Saito S et al., 2016
20	c.1411G>C	p.Asp471His	-	9	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
	c.1418C>T	p.Pro473Leu	-	9	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
21	c.1433delA	p.Asp478fs	-	9	frameshift mutations	Likely pathogenic	no	
22	c.545T>C	p.Leu182Pro	-	5	missense	Likely pathogenic	yes	Saito S et al., 2016
23	c.263G>C	p.Arg88Pro	-	3	missense	Pathogenic	yes	Chkioua L et al. 2011
24	c.136G>A	p.Asp46Asn	-	2	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
25	c.326G>C	p.Trp109Ser	-	3	missense	Likely pathogenic	no	
26	c.880-2del	-	-	intron 6	splicing substitutions	Pathogenic	yes	Semyachkina AN et al. 2021
27	c.1466delG	p.Gly489fs	-	9	frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
28	c.263G>C	p.Arg88Pro	-	3	missense	Pathogenic	yes	Villani GR et al, 2000
29	c.263G>C	p.Arg88Pro	-	3	missense	Pathogenic	yes	Villani GR et al, 2000
30	c.1402C>T	p.Arg468Trp	rs199422231	9	missense	Pathogenic	yes	Lin CY et al., 2020
31	c.121_123delCTC	p.Leu41del	-	2	small deltion	Likely pathogenic	yes	Semyachkina AN et al. 2021
32	c.697A>G	p.Arg233Gly	-	5	missense	VUS	yes	Chistiakov DA et al. 2014
33	c.697A>G	p.Arg233Gly	-	5	missense	VUS	yes	Chistiakov DA et al. 2014
34	c.795C>A	p.Asn265Lys	-	6	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
35	c.514C>T	p.Arg172Ter	rs104894860	5	nonsense	Pathogenic	yes	Chistiakov DA et al. 2014
36	c.1505G>A	p.Trp502Ter	-	9	nonsense	Pathogenic	yes	Zhang H et al., 2011
37	c.1028del	p.Gly343fs	-	8	frameshift mutations	Likely pathogenic	yes	Semyachkina AN et al. 2021

	SNP/ rearrangements	Nucleotide; protein change found	rsID	Exons of IDS gene/9	Type of nucleotide change	Significance	Previously reported	
38	c.1008delG	p.Trp337fs	-	8	frameshift mutations	Likely pathogenic	no	
39	c.1019G>A	p.Gly340Asp	-	8	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
40	c.1019G>A	p.Gly340Asp	-	8	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
41	c.1214_1220del	p.Ser405fs	-	9	frameshift mutations	Pathogenic	no	
42	c.1122C>T	p.Gly374 =	rs113993948	8	splicing substitutions	Pathogenic	yes	Zhang W et al, 2019
43	c.305T>G	p.Leu102Arg	-	3	missense	Likely pathogenic	yes	Saito S et al., 2016
44	c.1402C>T	p.Arg468Trp	rs199422231	9	missense	Pathogenic	yes	Lin CY et al., 2020
45	c.253G>A	p.Ala85Thr	rs113993949	3	missense	Pathogenic	yes	Sukegawa-Hayasaka K., et al. 2006
46	c.1327C>T	p.Arg443Ter	rs199422227	9	nonsense	Pathogenic	yes	Piña-Aguilar RE et al., 2012
47	c.404A>G	p.Lys135Arg	rs104894861	3	missense	Likely pathogenic	yes	Bunge S et al., 1992
48	c.410_411del	p.Phe137fs	-	3	frameshift mutations	Likely pathogenic	yes	Ebrahimi-Fakhari D et al., 2018
49	c.1438_1442del	p.Pro480fs	-	9	frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
50	c.1122C>T	p.Gly374 =	rs113993948	8	splicing substitutions	Pathogenic	yes	Zhang W et al, 2019
51	c.253G>A	p.Ala85Thr	rs113993949	3	missense	Pathogenic	yes	Sukegawa-Hayasaka K., et al. 2006
52	c.253G>A	p.Ala85Thr	rs113993949	3	missense	Pathogenic	yes	Sukegawa-Hayasaka K., et al. 2006
53	c.1025A>C	p.His342Pro	rs869025303	8	missense	Likely pathogenic	yes	Alcántara-Ortigoza MA et al., 2018
54	c.39_55dup	p.Ser19fs	-	1	frameshift mutations	Likely pathogenic	no	
55	c.103G>C	p.Asp35His	-	1	missense	VUS	yes	Semyachkina AN et al. 2021
56	c.103G>C	p.Asp35His	-	1	missense	VUS	yes	Semyachkina AN et al. 2021
57	c.1295G>A	p.Cys432Tyr	-	9	missense	Likely pathogenic	yes	Saito S et al., 2016
58	c.262C>T	p.Arg88Cys	rs398123249	3	missense	Pathogenic	yes	Lin HY et al, 2019
59	c.307T>G	p.Tyr103Asp	-	3	missense	Likely pathogenic	yes	Semyachkina AN et al. 2021
60	c.590C>T	p.Pro197Leu	-	5	missense	Pathogenic	yes	Semyachkina AN et al. 2021
61	c.590C>T	p.Pro197Leu	-	5	missense	Pathogenic	yes	Semyachkina AN et al. 2021
62	c.590C>T	p.Pro197Leu	-	5	missense	Pathogenic	yes	Semyachkina AN et al. 2021
63	c.248delT	p.Val83fs	-	3	frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
64	c.196C>T	p.Gln66Ter	rs1557340403	2	nonsense	Pathogenic	yes	Zhang H et al., 2011
65	c.1327C>T	p.Arg443Ter	rs199422227	9	nonsense	Pathogenic	yes	Piña-Aguilar RE et al., 2012
66	c.1608T>A	p.Tyr536Ter	-	9	nonsense	Likely pathogenic	yes	Ngu LH et al., 2017
67	c.241-9C>G	-	-	intron 2	splicing substitutions	VUS	yes	Semyachkina AN et al. 2021
68	c.241-9C>G	-	-	intron 2	splicing substitutions	VUS	yes	Semyachkina AN et al. 2021
69	c.1181-1G>A	-	rs864622777	intron 8	splicing substitutions	Pathogenic	yes	Amartino H et al., 2014
70	c.257C>T	p.Pro86Leu		3	missense	Likely pathogenic	yes	Alves S et al., 2006
71	c.1403G>A	p.Arg468Gln	rs113993946	9	missense	Pathogenic	yes	Hsiang-Yu Lin et al., 2019
72	c.1181-15C>A	-	-	intron 8	splicing substitutions	VUS	yes	Semyachkina AN et al. 2021
73	c.257C>T	p.Pro86Leu		3	missense	Likely pathogenic	yes	Alves S et al., 2006
74	c.998C>T	p.Ser333Leu	rs104894853	7	missense	Pathogenic	yes	Lin CY et al., 2020
75	c.613del	p.Ala205fs	-	5	frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
76	c.899_900del	p.Tyr300fs	-	7	frameshift mutations	Pathogenic	yes	Semyachkina AN et al. 2021
77	c.998C>T	p.Ser333Leu	rs104894853	7	missense	Pathogenic	yes	Lin CY et al., 2020

(*Continued*)

Supplementary Table 1. Detailed information about genetic variants in patients with MPS type II. (*Continued*)

	SNP/ rearrangements	Nucleotide; protein change found	rsID	Exons of IDS gene/9	Type of nucleotide change	Significance	Previously reported	
78	c.187A>G	p.Asn63Asp	rs193302909	2	missense	Pathogenic	yes	Zanetti A et al., 2019
79	c.187A>G	p.Asn63Asp	rs193302909	2	missense	Pathogenic	yes	Zanetti A et al., 2019
80	c.1403G>A	p.Arg468Gln	rs113993946	9	missense	Pathogenic	yes	Hsiang-Yu Lin et al., 2019
81	c.1004A>G	p.His335Arg	-	7	missense	Likely pathogenic	yes	Saito S et al., 2016
82	c.1030G>A	p.Glu344Lys	-	8	missense	Likely pathogenic	no	
83	c.551G>T	p.Cys184Phe	-	5	missense	VUS	yes	Saito S et al., 2016
84	c.425C>T	p.Ser142Phe	-	4	missense	Likely pathogenic	yes	Chistiakov DA et al. 2014
85	c.1037C>T	p.Ala346Val		8	missense	Likely pathogenic	yes	Maddox LO et al., 1998
86	c.425C>A	p.Ser142Tyr	rs193302908	4	missense	Likely pathogenic	yes	Saito S et al., 2016
87	c.596_599del	p.Lys199fs	-	5	frameshift mutations	Pathogenic	yes	Alcántara-Ortigoza MA et al., 2018
88	c.998C>T	p.Ser333Leu	rs104894853	7	missense	Pathogenic	yes	Lin CY et al., 2020
89	c.133G>T	p.Asp45Tyr	-	2	missense	Likely pathogenic	no	
90	c.395C>G	p.Ser132Trp	-	3	missense	Likely pathogenic	yes	Saito S et al., 2016
91	c.419-2A>G	-	-	intron 3	splicing substitutions	Pathogenic	no	
92	c.795C>G	p.Asn265Lys	-	6	missense	Pathogenic	yes	Saito S et al., 2016
93	c.262C>T	p.Arg88Cys	rs398123249	3	missense	Pathogenic	yes	Lin HY et al, 2019
94	c.1077delG	p.Ile360fs	-	8	frameshift mutations	Likely pathogenic	yes	Semyachkina AN et al. 2021
95	c.1327C>T	p.Arg443Ter	rs199422227	9	nonsense	Pathogenic	yes	Piña-Aguilar RE et al., 2012
96	c.1273del	p.Pro425fs	-	9	frameshift mutations	Likely pathogenic	no	
97	c.1264T>G	p.Cys422Gly	rs199422229	9	missense	Pathogenic	yes	Bunge S et al., 1992
98	c.1006+2T>G	-	-	intron 7	splicing substitutions	Pathogenic	yes	Semyachkina AN et al. 2021
99	IDS\IDSP1 in IDS gene						yes	Alcántara-Ortigoza MA et al., 2016
100	Recombination IDS/ps IDS2 ex3/ int7						yes	Bondeson ML et al., 1995
101	CP973598/ Recomb. between in. 7 and seq. distal of ex. 3 in IDS-2 without exons deletion						yes	Semyachkina AN et al. 2021
102	Recombination IDS/ps IDS2 ex3/ int7						yes	Bondeson ML et al., 1995
103	inv IDS/IDSP1						yes	Alcántara-Ortigoza MA et al., 2016
104	NM_0000202.5, ex.4-7del.						no exact coordinates	Semyachkina AN et al. 2021
105	Recombination IDS/ps IDS2 ex3/ int7						yes	Bondeson ML et al., 1995

	SNP/ rearrangements	Nucleotide; protein change found	rsID	Exons of IDS gene/9	Type of nucleotide change	Significance	Previously reported	
106	Recombination IDS/ps IDS2 ex3/ int7						yes	Bondeson ML et al., 1995
107	del exon 3-7 IDS gene						no exact coordinates	Semyachkina AN et al. 2021
108	del exon 7						no exact coordinates	Semyachkina AN et al. 2021
109	gene IDS deletion						no exact coordinates	Froissart, R et al., 1993
110	del exon 1-7 IDS						no exact coordinates	Zanetti A et al., 2014
111	del exon 1-9 IDS						no exact coordinates	Semyachkina AN et al. 2021
112	DEL:chrX:148 294 415-148 657 098 (362.7kb, Del: HSFX3, IDS, CXorf40A, LINC00893)						no	
113	Recombination IDS/ps IDS2 ex3/ int7						yes	Bondeson ML et al., 1995
114	Recombination IDS/ps IDS2 ex3/ int5						yes	Semyachkina AN et al. 2021
115	del exon 1-7 IDS						no exact coordinates	Zanetti A et al., 2014
116	ex.5del						no exact coordinates	Semyachkina AN et al. 2021