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Results of Selective Biochemical Screening for Lysosomal Acid Lipase Deficiency and Sequencing of the *LIPA* Gene in the Risk Group Patients

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Aim: to study the prevalence of lysosomal acid lipase deficiency (Wolman disease and cholesteryl ester storage disease) among high-risk patients using selective biochemical screening.
Material and methods. Samples from 2805 patients are collected as dried blood spots on filter paper test forms. Biochemical study of the lysosomal acid lipase (LAL) enzyme activity was carried out according to Hamilton's protocol of, using 4-methylumbelliferyl palmitate as a substrate and LAL inhibitor Lalistat-2. Changes in fluorescence in the wells were recorded on Wallac 1420 Multilabel Counter analyzer at absorption wavelength of 355 nm and emission wavelength of 460 nm. Sequencing of the *LIPA* gene (NM_001127605) was carried out on an Illumina MiSeq device (Illumina, USA) from dried blood spots from patients with reduced LAL enzyme activity to define genetic variations.
Results. As a result of biochemical screening for LAL deficiency among patients from high-risk groups, 20 patients with reduced values of LAL enzyme activity were found. For 17 patients, search for mutations in the *LIPA* gene was carried out using NGS. In 9 patients, pathogenic genetic variants were found that led to decrease in LAL activity and the manifestation of clinical symptoms. In 100 % of detected cases, genetic mutations in the *LIPA* gene included single nucleotide substitution c.894G>A. Along with this mutation, two previously undescribed mutations (c.35dup and c.176A>G) were discovered in a compound heterozygous state.
Conclusions. The variety of clinical symptoms and wide range of ages at which symptoms may begin (in the case of cholesteryl ester storage disease) can lead to errors in diagnosis. The c.894G>A variant is the most common variant worldwide among patients with a confirmed diagnosis of LAL deficiency and was present in all confirmed cases in this study, suggesting that this variant is the predominant mutation in the *LIPA* gene in Russian population. Pathogenicity status of previously undescribed discovered mutations (c.35dup and c.176A>G) needs to be determined.
Keywords: lysosomal acid lipase deficiency, Wolman disease, cholesteryl ester storage disease, lysosomal storage diseases, NGS, *LIPA* gene
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Итоги селективного биохимического скрининга дефицита лизосомной кислой липазы и секвенирования гена *LIPA* у пациентов группы риска

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Цель исследования: изучить распространенность дефицита лизосомной кислой липазы (ЛКЛ) (болезни Вольмана и болезни накопления эфиров холестерина) и результаты секвенирования гена *LIPA* среди пациентов из групп высокого риска в ходе проведения селективного биохимического скрининга.
Материал и методы. Образцы 2805 пациентов представлены сухими пятнами крови на тест-бланках из фильтровальной бумаги. Биохимическое исследование активности фермента ЛКЛ проводили по протоколу Гамильтона с использованием 4-метилумбеллиферилпальмитата в качестве субстрата и ингибитора ЛКЛ

Lalistat-2. Для построения калибровочной кривой использовали значения серийных разведений 4-метилумбеллиферона. Изменения флуоресценции в лунках регистрировали при волне поглощения 355 нм и излучения 460 нм. Для проведения генетического исследования из сухих пятен крови пациентов со сниженной активностью фермента ЛКЛ проводили секвенирование гена *LIPA* (NM_001127605) на приборе Illumina MiSeq («Illumina», США).

Результаты. В результате проведенного биохимического скрининга на дефицит ЛКЛ среди пациентов из групп высокого риска было обнаружено 20 пациентов со сниженными значениями активности фермента ЛКЛ. Для 17 пациентов был проведен поиск вариантов в гене *LIPA* методом секвенирования нового поколения. У 9 пациентов были найдены патогенные генетические варианты, обуславливающие снижение активности ЛКЛ и проявление клинических симптомов. В 100 % обнаруженных случаев генетические нарушения в гене *LIPA* включали однонуклеотидную замену c.894G>A. Вместе с данным вариантом были обнаружены два ранее не описанных варианта (c.35dup и c.176A>G) в компаунд-гетерозиготном состоянии.

Выводы. Разнообразие клинических симптомов и широкий диапазон возраста проявления симптомов (в случае болезни накопления эфиров холестерина) обуславливают ошибки при постановке диагноза. Вариант c.894G>A является наиболее распространенным в мире среди пациентов с подтвержденным диагнозом дефицита ЛКЛ и присутствует во всех подтвержденных случаях данного исследования, что позволяет предположить, что данный вариант является превалирующим среди патогенных вариантов в гене *LIPA* в российской популяции. Статус патогенности обнаруженных ранее не описанных вариантов (c.35dup и c.176A>G) требует дополнительного исследования.

Ключевые слова: дефицит лизосомной кислой липазы, болезнь Вольмана, болезнь накопления эфиров холестерина, лизосомные болезни накопления, NGS, ген *LIPA*

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Introduction

Lysosomal acid lipase deficiency (OMIM 278000) is an orphan disease from lysosomal storage disorders. This disease is caused by a malfunction of the lysosomal acid lipase (LAL) enzyme due to mutations in the *LIPA* gene. LAL is involved in the breakdown of complex lipids and triglycerides; deficiency of this enzyme leads to their accumulation in cells and tissues [1]. The main clinical manifestations of LAL deficiency include hepatomegaly, liver fibrosis, dyslipidemia, and elevated serum transaminase levels [2]. Depending on the severity of the disease and the time of manifestation, LAL deficiency is usually divided into two forms: infantile LAL deficiency and cholesterol ester storage disease [3]. The infantile form of LAL deficiency, also known as Wolman disease, is characterized by the early onset of symptoms, typically within the first six months of life, and death due to rapidly progressing multi-organ failure before the age of one year [4]. Cholesterol ester storage disease is characterized by wide variability in both clinical symptoms and time of manifestation, which often complicates diagnosis [5]. The main symptoms of cholesterol ester storage disease include dyslipidemia and progressive liver damage [6].

The frequency of LAL deficiency varies and, according to various sources, lies between 1:40,000 and 1:300,000 [7]. The meta-analysis of the available data allowed clarifying the frequency of this disease, establishing that it corresponds to 1:177,000 [8]. No study has been conducted to establish the incidence of LAL deficiency in Russia; the expected frequency is determined as 1:100,000–1:150,000 [4, 6]. However, the analysis conducted to establish the frequency of the mutation carriage in the *LIPA* gene indicates a frequency of 1:67,600, which is twice as high as expected [9]. According to the latest data, the frequency of the major pathogenic variant c.894G>A (rs116928232) in Russia is estimated at approximately 0.001919 (http://ruseq.ru/#/variant/10-89222511-C-T) [10]. However, there is insufficient information on other variants. Therefore, the available data indicates the need for an expanded population study to establish the real frequency of the disease.

The disease is inherited in an autosomal recessive manner. The most common genetic defect of the *LIPA* gene, leading to disruption of LAL function, is a mutation in exon 8, affecting the splicing site (c.G894A, p.delS275_Q298). The splicing defect results in a shortened protein lacking enzymatic activity due to the absence of 24 amino acids. The detected residual activity of the LAL enzyme is associated with splicing errors of the "mutant" form [11]. This genetic variant in the *LIPA* gene is found in approximately 50 % of patients diagnosed with LAL deficiency [5].

This paper presents the interim results of selective screening for lysosomal acid lipase deficiency for 2019–2024.

Aim: to study the prevalence of lysosomal acid lipase deficiency (Wolman disease and cholesterol ester storage disease) among high-risk patients.

Materials and methods

Biological samples from patients

The selective screening program for LAL deficiency included patients with at least one of the following symptoms: enlarged liver/spleen; persistent diarrhea; malabsorption syndrome; underweight; growth retardation; elevated cholesterol; elevated alanine aminotransferase / aspartate aminotransferase, low-density lipoproteins, gamma-glutamyl transferase; decreased high-density lipoproteins; anemia; thrombocytopenia; elevated lactate dehydrogenase, ferritin; steatosis/fibrosis/cirrhosis of the liver; enlarged and calcified adrenal glands; history of non-viral liver disease. Samples from 2805 patients were presented as dried blood spots on filter paper test forms. Informed consent for the study was signed by all patients and/or their legal representatives.

LAL enzyme activity assay

Biochemical study of the LAL enzyme activity was carried out according to the protocol of J. Hamilton et al. [12] using 4-methylumbelliferyl palmitate (Sigma-Aldrich, USA) as a substrate and LAL inhibitor Lalistat-2 (Sigma-Aldrich, USA). To construct a calibration curve, the values of serial two-fold dilutions of 50 μM 4-methylumbelliferone were used (Sigma-Aldrich, USA). Changes in fluorescence in the wells were recorded on Wallac 1420 Multilabel Counter (Perkin Elmer, USA) at an absorption wavelength of 355 nm and an emission wavelength of 460 nm.

Genetic analysis of the LIPA gene using next-generation sequencing

To conduct a genetic study, genomic DNA was isolated from dried blood spots of patients with reduced LAL enzyme activity using the Blood DNA Mini Kit (Foregene, China) according to the manufacturer's protocol. Sample concentrations were measured using the Qubit dsDNA HS Assay Kit on a Qubit 3.0 fluorimeter (Thermo Fisher Scientific, USA). To prepare libraries for targeted sequencing, KAPA CustomPanel was used (Roche, Switzerland). The *LIPA* gene (NM_001127605) was sequenced on an Illumina MiSeq (Illumina, USA) using the V2 reagent kit (300 cycles). "The 1000 Genomes" (b37) human genome assembly was used as a reference for data analysis [13]. All samples were analyzed using bioinformatics processing based on BWA-MEM v.0.7.15-r1140, PicardTools v.2.2.2 (broadinstitute.github.io/picard/) and the genome analysis toolbox (Genome Analysis Tool kit, GATK) v. 3.5 (github.com/broadinstitute/gatk/releases) according to the GATK Best Practices (software.broadinstitute.org/gatk/best-practices/) [14] considering frequencies in RUSeq. Sequence enrichment metrics were obtained using Picard CalculateHsMetrics. All samples included in the dataset were genotyped using the GATK GenotypeGVCFs tool. Variants were filtered using the thresholds recommended by GATK. Variant annotation was performed using the SnpEff and SnpSift packages. The following resources and databases were used for variant annotation: dbSNP build 146, 1000 Genomes phase 3; Exome Aggregation Consortium r. 0.3.1; ClinVar v. 2018-04-01 и dbNSFP v. 2.9. NetGene2 server (cbs.dtu.dk/services/NetGene2) was used to detect splicing changes.

Results and discussion

Algorithm for the implementation of selective screening for LAL deficiency

The established algorithm for conducting a study to identify LAL deficiency is shown in Fig. 1.

At the initial stage, biological material and the necessary accompanying documents (referral for the study and informed consent) were collected. Then the biological material (dried blood spots) and referrals were sent to the laboratory, where a biochemical analysis of the activity of the LAL enzyme was carried out. The results of the biochemical analysis were processed and compared with the value ranges presented in Table 1, according to which a conclusion was made about the activity of the LAL enzyme.

Samples from patients with reduced enzyme activity were sent for genetic testing — searching for pathogenic variants in the *LIPA* gene using next-generation sequencing. At the same time, the material was re-sampled and a biochemical analysis of the activity of the LAL enzyme was performed. After genetic testing, conclusions were sent to the attending physicians.

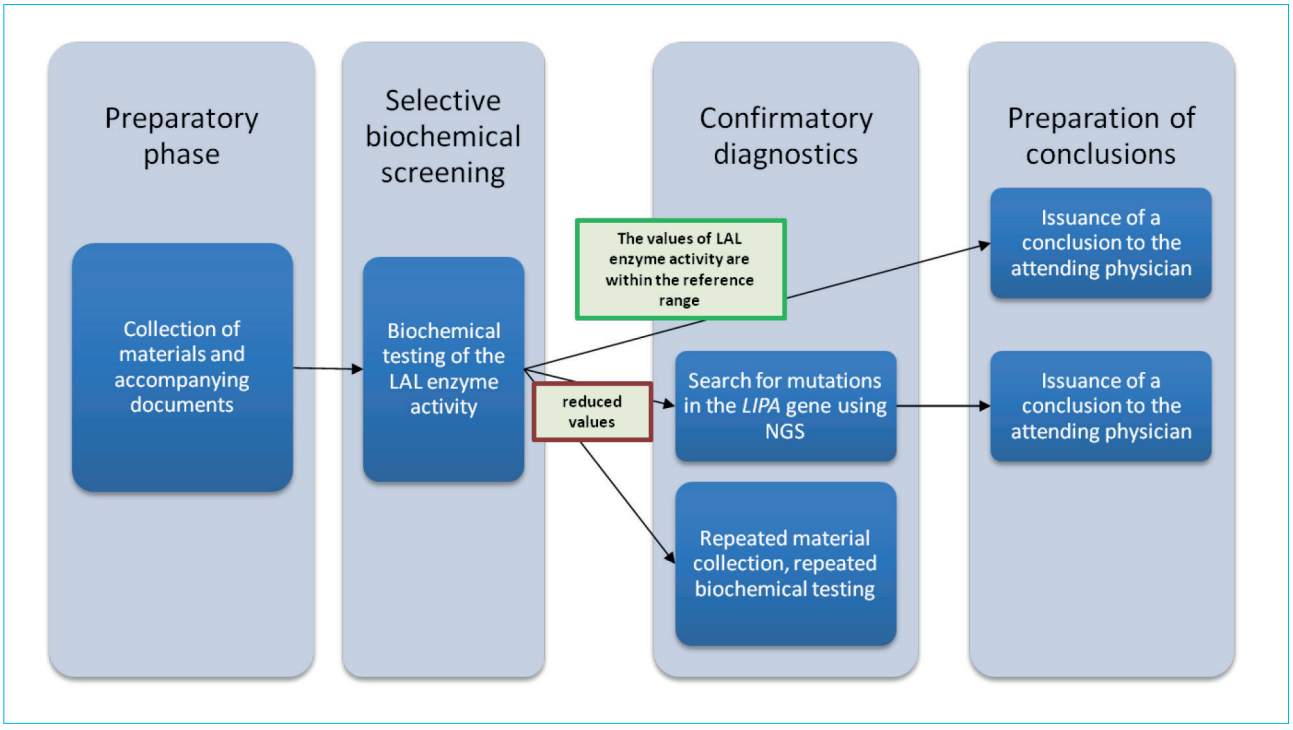

Figure 1. Algorithm for selective screening for LAL deficiency

Рисунок 1. Алгоритм проведения селективного скрининга на выявление дефицита ЛКЛ

Results of biochemical screening

During the selective biochemical screening, 2,805 samples were analyzed. The LAL activity in 2,785 samples corresponded to the established reference values, while decreased enzyme activity was recorded for 20 samples.

The majority of LAL activity values were determined in the range of 0.6–1.5 nmol/punch/hour. The average value of LAL activity was 1.22 ± 0.77 nmol/punch/hour, the median was 1.06 nmol/punch/hour.

Among the samples values of which did not correspond to the reference values for healthy individuals, the activity of the LAL enzyme was insignificantly reduced in 5 samples, decreased in 3 samples, and significantly reduced in 12 samples (Fig. 3). Some of the samples with reduced activity of the LAL enzyme were sent to search for mutations in the *LIPA* gene using next-generation sequencing as part of the confirmatory stage of diagnosis.

Results of genetic diagnostics

For patients whose LAL enzyme activity was within the ranges corresponding to reduced values suggesting pathology, a confirmatory genetic diagnosis was carried out – a search for pathogenic variants in the *LIPA* gene through sequencing. The search for variants in the *LIPA* gene was performed for all samples with significantly reduced enzyme activity. Since the end of 2023, it was decided to expand the selection criteria for confirmatory diagnostics by including samples with reduced and insignificantly reduced LAL activity into the analysis. Two samples with decreased activity and three samples with insignificantly decreased activity of the LAL enzyme were analyzed.

Table 1. Reference values for LAL activity and conclusions

Таблица 1. Референсные значения активности фермента ЛКЛ и заключения

Ranges of LAL enzyme activity values (nmol/punch/hour) ***Интервалы значений активности фермента ЛКЛ (нмоль/панч/час)***	**Conclusion on the activity of LAL enzyme** ***Заключение об активности фермента ЛКЛ***
0–0.061	Significantly reduced / *Резко снижена*
0.061–0.080	Reduced / *Снижена*
0.080–0.110	Insignificantly reduced / *Незначительно снижена*
> 0.110	Within reference values / *В пределах референсных значений*

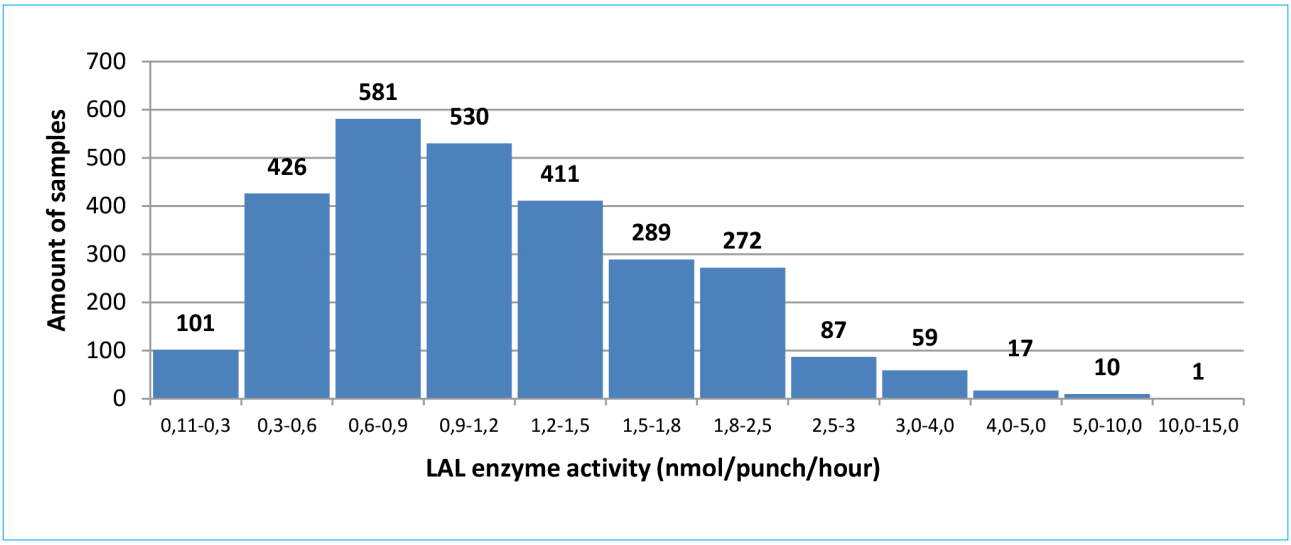

Figure 2. Distribution of LAL enzyme activity values among healthy individuals

Рисунок 2. Распределение значений активности фермента ЛКЛ среди здоровых индивидов

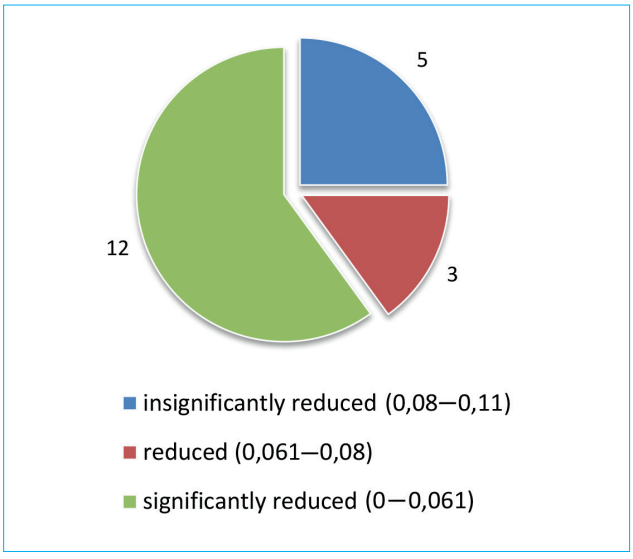

Figure 3. Number of samples with reduced LAL activity

Рисунок 3. Количество образцов со сниженной активностью фермента ЛКЛ

The results of the confirmatory diagnostic stage are presented in Table 2. In several cases, a sharp decrease in the activity of the LAL enzyme was registered, but there were no genetic abnormalities in the *LIPA* gene, which suggests the presence of other pathological processes affecting the activity of this enzyme. The most common abnormality in the *LIPA* gene leading to decreased LAL activity was the pathogenic variant c.894G>A. In 6 cases of confirmatory diagnostics, it was detected in the homozygous state, and in three more cases — in the compound heterozygous state. The c.796G>T variant, which is the second most common in patients with LAL deficiency, was detected in one patient [15]. It was previously reported that a patient with the c.796G>T variant had a significantly reduced activity of the LAL enzyme (0.030 nmol/punch/hour), which corresponds to the activity ranges for LAL deficiency and may cause a number of clinical manifestations of the disease [16]. Previously undescribed variants were detected — substitution c.176A>G (p.Tyr59Cys) and single nucleotide duplication c.35, leading to a shift in the reading frame during translation, in a compound heterozygous state with the variant c.894G>A. It has been previously noted that the presence of the c.894G>A variant in both homozygous and heterozygous states is associated with cholesterol ester storage disease and a milder phenotype of LAL deficiency in general [15].

Based on the clinical presentation, age of onset, and results of molecular genetic testing, 9 patients were suspected to have cholesterol ester storage disease. The age range of patients experiencing clinical symptoms was between 4 and 17 years old. Thus, the frequency of LAL deficiency among patients with clinical manifestations characteristic of the disease is 1:312, while the frequency of homozygous carriage of the pathogenic variant c.894G>A was 1:500 patients. The results of repeated biochemical diagnostics of three samples with significant reduced LAL enzyme activity, for which no genetic abnormalities in the *LIPA* gene were found, were within reference range, which suggests possible technical errors in the preparation of dried blood spots, leading to false-positive

Table 2. Results of confirmatory diagnostics in patients with reduced values of LAL activity
Таблица 2. Результаты подтверждающей диагностики у пациентов со сниженными значениями активности фермента ЛКЛ

Material *Материал*	Age (years) *Возраст (лет)*	LAL activity (nmol/punch/hour) *Активность ЛКЛ (нмоль/панч/час)*	Mutations in the *LIPA* gene *Мутации в гене LIPA*
Patient 1 *Пациент 1*	43	0	Not found / *Не обнаружены*
Patient 2 *Пациент 2*	3	0	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 3 *Пациент 3*	5	0	**c.894G>A/c.35dup**
Patient 4 *Пациент 4*	14	0	**c.894G>A/c.796G>T (p.G266*)**
Patient 5 *Пациент 5*	1	0.0010	Not found / *Не обнаружены*
Patient 6 *Пациент 6*	7	0.0080	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 7 *Пациент 7*	14	0.0100	Not found / *Не обнаружены*
Patient 8 *Пациент 8*	11	0.0288	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 9 *Пациент 9*	26	0.0378	Not found / *Не обнаружены*
Patient 10 *Пациент 10*	17	0.0400	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 11 *Пациент 11*	4	0.0430	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 12 *Пациент 12*	6	0.0510	**c.894G>A/c.176A>G (p.Y59C)**
Patient 13 *Пациент 13*	3	0.0640	Not found / *Не обнаружены*
Patient 14 *Пациент 14*	5	0.0645	**c.894G>A in a homozygous state** *c.894G>A в гомозиготном состоянии*
Patient 15 *Пациент 15*	1	0.09075	Not found / *Не обнаружены*
Patient 16 *Пациент 16*	46	0.1000	Not found / *Не обнаружены*
Patient 17 *Пациент 17*	11	0.1024	Not found / *Не обнаружены*

results [17]. To exclude the possibility of obtaining a false-positive result, it is recommended to conduct a further study of the activity of the control enzyme, β-galactosidase, in samples with reduced activity of the LAL enzyme [17]. No pathogenic variants affecting the *LIPA* gene were found in samples with insignificant reduced LAL enzyme activity (patients 15–17). This finding suggests the need to reconsider the ranges of enzyme activity levels indicating pathology.

Conclusion

Lysosomal acid lipase deficiency is a hereditary disease caused by pathogenic variants in the *LIPA* gene. The diversity of clinical symptoms and a wide range of ages of symptoms onset (in the case of cholesterol ester storage disease) lead to errors in diagnosis. Due to the lack of knowledge about the prevalence of LAL deficiency among Russian population and the availability of mathematically derived expected frequencies of LAL deficiency in Russia, a large-scale study is required. Variant c.894G>A is the most common variant worldwide among patients with confirmed diagnosis of LAL deficiency (cholesterol ester storage disease) and is present in all confirmed cases at this study, which suggests that this variant is also prevalent in the *LIPA* gene in the Russian population. The pathogenicity status of previously undescribed variants (c.35dup and c.176A>G) remains to be determined.

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