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Spectrum of genetic variants detected in children tested for long QT syndrome

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Abstract

Background Long QT syndrome (LQTS) is one of the most common inherited cardiac arrhythmias associated with sudden cardiac death worldwide. Despite the widespread implementation of next-generation sequencing, its diagnostic value remains limited due to challenges in interpreting the clinical significance of the identified variants. Since LQTS is rare and underreported in Baltic region, studies on small populations are valuable for expanding current knowledge on this rare cardiac channelopathy. Our aim was to evaluate the diagnostic yield of genetic testing and clinical manifestations of the disease in paediatric patients assessed for LQTS in Lithuania.

Results The phenotypic spectrum of LQTS among the cohort was notably heterogeneous, with more than half of the asymptomatic patients at the time of genetic testing. The overall diagnostic yield was 22%. The majority of pathogenic or likely pathogenic variants were detected in the *KCNQ1* gene, with 17% of these categorised as high-risk for arrhythmic events. Individuals harbouring pathogenic or likely pathogenic variants showed significantly prolonged corrected QT (QTc) intervals in comparison to those without such variants.

Conclusions Less stringent referral criteria may reduce the diagnostic yield of genetic testing for LQTS. In our cohort, 17% of patients with 1 type LQTS had genetic variants located in regions associated with elevated arrhythmic risk. This knowledge should be considered as part of their individualised care plans. Furthermore, the identification of multiple variants of uncertain significance highlights the ongoing need for enhanced interpretive frameworks to integrate complex genetic findings into routine clinical decision-making.

Keywords Long QT syndrome, Sudden cardiac death, Children, Genetic testing, Clinical presentation

Background

Continuous research on cardiac channelopathies has significantly advanced our understanding of these conditions, leading to many numerous essential discoveries in the field [1]. Among them, the most common inherited cardiac arrhythmia is long QT syndrome (LQTS), which involves 14 minor LQTS susceptible genes, and three major genes – *KCNQ1*, *KCNH2*, and *SCN5A* – for which there is definite evidence of causing LQTS [2]. Over the past decade, comprehensive genetic testing has enabled the identification of numerous biologically plausible genes and their encoded proteins. However, the strength of evidence linking them to LQTS varies widely [3]. As a rule, rare and newly reported gene variants without further evidence receive the label of variant of uncertain significance (VUS), which can obscure the understanding and interpretation of their role in rare diseases [3]. LQTS is also described as a genetic disease highly influenced by incomplete penetrance phenomena, when

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patients with the same pathogenic variant exhibit different disease severity [4]. The individuality of human body structure and genome plays a vital role in understanding this concept, along with modifier genes that may encode determinants of the primary cellular substrate for abnormal cardiomyocyte excitability, proteins responsible for inward and outward ion currents, and other proteins involved in trafficking cellular and membrane proteins [5]. However, less attention has been given to the functional consequences of these variants [1, 6]. Recently, research has focused on functional risk alleles that can alter function or electrical signalling of cardiac ion channels in either primary LQTS-causing genes or modifier genes, thereby modulating the clinical manifestation of LQTS [1]. Crotti L et al. concluded that integrating functional information about disease-causing variants and modifying genetic variants, which act in conjunction with disease-causing variants but do not necessarily worsen the phenotype, is essential to determine the actual risk of LQTS [1]. The prevalence of LQTS is 1 in 2500, often diagnosed during the teenage years [7]. Risk stratification and management strategy planning play a crucial role in managing the syndrome. For example, misinterpretation of VUS previously resulted in overdiagnosis and overtreatment with late initiation or missed initiation of predictive family members' screening for LQTS [3]. However, genetic noise from minor susceptible genes complicates this task. While our understanding of the polygenic nature of LQTS continues to evolve, data collection could benefit future research. Countries with small populations, like ours (Lithuania), face challenges in gathering large enough samples of patients to draw meaningful conclusions. However, the data we characterise is valuable when compared to the literature. Our research aimed to determine the clinical phenotype and diagnostic yield of genetic testing in our children's cohort of LQTS patients.

Methods

Study design

This is a single-centre retrospective study conducted at a tertiary care centre. The study protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee of Lithuania, with a waiver of informed consent from the patients due to the study's retrospective nature. The analysis included in this study was performed on anonymised patient data.

Study subjects

Inclusion criteria were as follows: (1) suspected LQTS, including diagnoses recorded with the International Classification of Diseases 10th Revision, Clinical Modification (ICD-10-CM) codes, (2) underwent next-generation sequencing for long QT syndrome-associated genes between January 2020 and December 2023. Patients were referred to our tertiary care centre due to clinical symptoms suggestive of LQTS or incidental abnormal ECG findings. Before genetic testing, they were evaluated by a paediatric cardiologist. Anonymous patient data were extracted from electronic medical records. The extracted data included demographics, clinical manifestations, family history, instrumental testing results, and genetic data. Information required to access the Schwartz score was collected as needed [8] and recalculated manually by one of the investigators.

Genetic analysis

Sequence variants were identified in the patients using exome sequencing by employing a virtual cardiovascular gene panel (which incorporates arrhythmia genes) in clinical diagnostic settings. Virtual gene panels were compiled in-house by reviewing the literature, databases such as OMIM [8] and Orphanet [9], as well as publicly available commercial panels. The panel was continuously updated during the study period and the latest version contains 599 genes. All identified variants were revised using freely available online software tool Varsome to evaluate pathogenicity. The pathogenicity of the identified variants was established according to American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria [10]. The Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/) was used to verify the presence of these variants in control populations. Diagnostic yield was defined as the percentage of pathogenic or likely pathogenic (P/LP) variants considered to cause the LQTS phenotype. The novelty of the identified variants was determined according to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) database. Patients with P/LP variants were considered genotype positive. Genetic variants were classified as missense or non-missense (nonsense, frameshift, and splice site).

Statistical analysis

Statistical data analysis was performed using IBM SPSS Statistics 20. Quantitative data were expressed as frequencies and means or medians. Features of qualitative variables within groups were analysed using the Chi-square test of independence. The normality of the variables was tested using the Shapiro-Wilk test and by comparing histograms of the sample data. To assess the strength and direction of the relationship between continuous numerical and binomial variables, the Mann-Whitney U test was applied.

Results

We analysed data from 172 unrelated probands who underwent genetic testing for LQTS. The patients were equally distributed by sex, with more than half of them (67%, 116/172) being of adolescent age (Table 1). A broad spectrum of clinical presentations characterised the cohort. The most common clinical symptom was syncope without stress (17%, 29/172), followed by heart palpitations (16%, 28/172), and chest pain (12%, 20/172), while other non-cardiovascular symptoms were present less frequently. In addition, 2% (3/172) experienced cardiac-respiratory arrest, of which one patient was found carrying a pathogentic variant (c.477+1G>A) in *KCNQ1*. Symptomatic patients accounted for 45% (77/172) of the sample. No statistically significant difference was found between patients in the genetic positive and negative groups in terms of their symptoms. The mean QTc interval was 491 ± 29 ms for patients with P/LP variants and 477 ± 21 ms for those with negative genetical testing result or VUS. The distribution of QTc interval was statistically significantly different between the two groups ($p < 0.001$) (Table 1). A total of 22% (37/172) of the patients carried P/LP variant, as shown in Fig. 1-A.

Table 1 Baseline characteristics of the patients presented in the study

	Count (%) or average +/- SD [min; max]
Proband with positive genetic testing result	37/172 (22%)
Male	81/172 (47%)
Age at first evaluation	
< 10 yo	57/172 (33%)
10–21 yo	115/172 (67%)
Schwartz score	
Positive genetic testing result	3.12 ± 1.15 [0;6]
Negative genetic testing result	2.09 ± 1.42 [0;5]
QTc*	
Positive genetic testing result	491 ± 29 ms
Negative genetic testing result	477 ± 21 ms
Symptomatic	77/172 (45%)
Asymptomatic	95/172 (55%)
Symptoms among all patients	
Tiredness	8/172 (5%)
Cardialgia	20/172 (12%)
Dyspnea	7/172 (4%)
Palpitations	28/172 (16%)
Syncope without stress	29/172 (17%)
Headspinning	11/172 (6%)
Headache	5/172 (3%)
Cardiac-respiratory arrest	3/172 (2%)

*$p < 0.001$

The percentage of P/LP variants present in our study is displayed in Fig. 1-B. In our cohort, four patients out of 37 (11%) with P/LP variants and LQTS phenotype were found to carry single variants not associated with LQTS in the *FBN1*, *ACTA1*, *TTN* and *FLNC* genes. Additionally, we specified the risk for arrhythmic events in patients with LQTS type 1, according to the methodology described by Schwartz PJ et al., as it is the most common type of LQTS found in our sample and elsewhere [11]. 17% (4/23) of our patients carry a high-risk variant in *KCNQ1*, which could lead to significant arrhythmic events (see Table 2). VUS found during the study comprised 9% (15/172) of our patients sample and are listed in Table 3.

Discussion

The literature contains numerous reports on the clinical variability of LQTS, which differs according to its subtype, age of the individual and other factors. Nonetheless, some patients diagnosed with congenital LQTS exhibit a negative phenotype – an observation now attributed to the phenomenon of incomplete penetrance or the presence of modifying genetic variants alongside the disease-causing variant [5, 12]. As the syndrome is closely linked to individual cardiac tissue development and ion channel function, studying its unique characteristics – even in small patient cohorts – may provide valuable insights into its underlying mechanisms. Overall, our patient sample was similarly distributed by age and sex, which results are consistent with the literature [13–15]. As for the clinical manifestation of the syndrome, more than half of our patients carrying the P/LP variant (62%) were asymptomatic when tested, which is higher than the prevalence reported in the literature: 49% [13], 20% [14], and 25% [15]. Syncopal and other complaints in our cohort were similarly distributed compared to reports elsewhere, with no life-threatening arrhythmias reported in our sample [13]. The mean Schwarz score of the patients referred for genetic testing was lower in our cohort compared to the literature: 3.1 ± 1 SD (ours) vs. 4.5 vs. 5.6 ± 1.2 SD [14]. This may partially explain our cohort's lower yield of genetic testing, as the criteria for referring patients for genetic counselling may not have been consistently stringent.

Genetic findings

In the present study, genetic testing confirmed the diagnosis of LQTS in 22% of the patients. According to the literature, the yield of genetic testing in LQTS ranges from 30 to 70%. Our findings align with a recent study, which identified a diagnosis in 15.4% of LQTS cases [16]. Authors of this recent study hypothesise that less stringent referral criteria and free-of-charge genetic testing for the patients lower the yield of genetic testing.

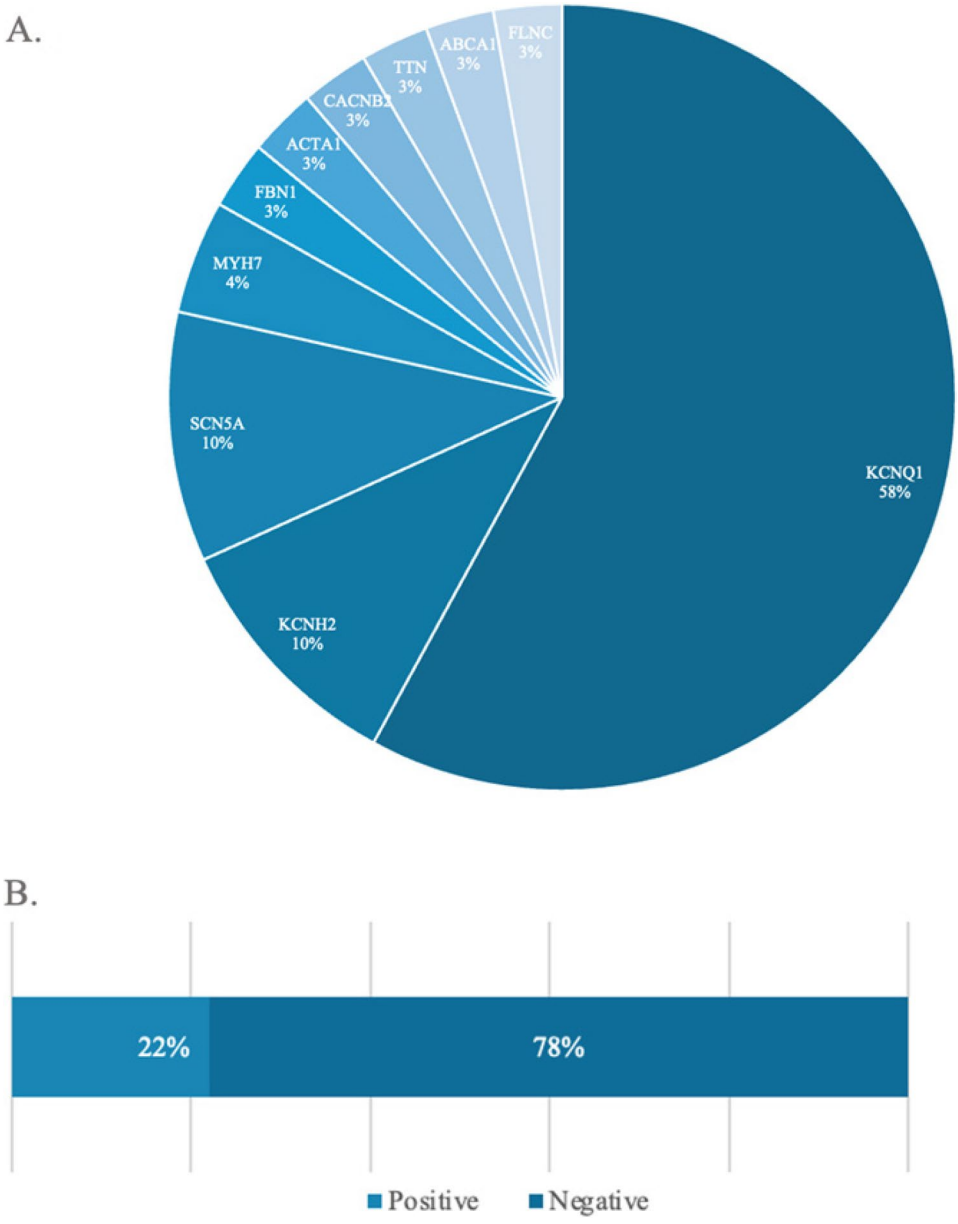

Fig. 1 Frequencies of genotypes. A – Frequency of pathogenic/likely pathogenic (P/LP) variants detected by gene among patients in the current study who had positive genetic testing for LQTS. B – Diagnostic yield of genetic testing in the present study

This may partly explain the yield observed in our study, as genetic testing is increasingly implemented early in the diagnostic pathway. Genetic testing can confirm the diagnosis of LQTS and help stratify arrhythmia risk, as well as inform genotype-focused clinical management of the patients. However, healthcare professionals should be aware that genotype negative LQTS patients require the same clinical management as those carrying disease-causing variants. At the same time, the arrhythmic risk is similar between these groups [17]. Speaking of LQTS types distribution, in our sample, LQTS type 1 accounted for 62% (23/37) of genetically positive cases, which is consistent with frequencies reported in other European studies [11, 18]. However, 11% (4/37) had variants in genes not linked to LQTS, so they cannot be classified as genetically positive. These genes are associated with structural cardiac diseases, which may affect the QT interval and warrant further investigation. Furthermore, a splice site pathogenic variant c.477 + 1G > A in the *KCNQ1* gene was identified in slightly more than half of our cohort's LQTS type 1 cases. This finding suggests a local variant prevalence, although c.477 + 1G > A is considered a rare pathogenic variant of *KCNQ1* in the general population, with an allelic frequency of 0.00001% in the NFE population according to the gnomAD database. *KCNH2* and *SCN5A* variants, each, were responsible for

Table 2 Variants detected in *KCNQ1* (NM_000218.3) and risk for symptomatic clinical presentation according to the variant topology [11]

Number of patients*	cDNA variant	Protein variant	ACMG classification[a]	GnomAD NFE MAF (%)	CADD score	Location	Risk [Schwartz et al. (10)][b]
1	c.643G>A	p.(Val215Met)	P	0.000009920	24.6	S3, transmembrane	High risk for arrhythmic events by variant location, 31%
1	c.590C>T	p.(Pro197Leu)	P	0.00003351	29.3	S2-S3, transmembrane	High risk for arrhythmic events by variant location, 31%
1	c.701A>C	p.(Gln234Pro)	LP	6.200e-7	24.6	S4, transmembrane	High risk for arrhythmic events by variant location, 31%
14	c.477+1G>A	p.(?)	P	0.00001055	33	S2, intron 2, non missense	Low risk for arrhythmic events by variant location, 13%
1	c.513C>G	p.(Tyr171Ter)	P	0.000001860	36	S2-S3 C loop, missense	Low risk for arrhythmic events by variant location, 15%
1	c.940G>A	p.(Gly314Ser)	P	-	27.9	Pore, transmembrane	High risk for arrhythmic events by variant location, 31%
1	c.1265delA	p.(Lys422Serfs*10)	P	0.000008679	32	C term, non missense	Low risk for arrhythmic events by variant location, 13%
1	c.1051_1065del	p.(Phe351_Val355del)	P	-	-	C terminus non missense	Low risk for arrhythmic events by variant location, 13%
1	c.355G>A	p.(Gly119Arg)	P	-	14.42	Before S1, N terminus	Low risk for arrhythmic events by variant location, 5%
1	c.1621G>A	p.(Val541Ile)	LP	0.00003375	17.89	After S6, missense C terminus	Low risk for arrhythmic events by variant location, 13%

Abbreviations * a total number of probands with a genetic variant in *KCNQ1*,[a] Varsome accessed on August 8, 2024, *CADD* Combined Annotation Dependent Depletion, *MAF* Minor Allele Frequency, *NFE* European (non-Finnish), *L* Pathogenic, *LP* Likely pathogenic, [b] 4/23, 17% – high risk – 31%; 19/23, 83% – low risk – <13%

Table 3 Overview of the variants of unknown significance (VUS) identified in this study

No.	Gene	RefSeq ID	cDNA variant	Protein variant	ACMG classification[a]	GnomAD NFE MAF (%)	CADD score
1	*KCNJ5*	NM_000890.5	c.817C>T	p.(Pro273Ser)	VUS5	-	24,9
	MYH11	NM_002474.3	c.502G>A	p.(Asp168Asn)	VUS4	-	33
	ANK2	NM_001148.6	c.3392C>T	p.(Pro1131Leu)	VUS	0.000008674	24,9
2	*FLNC*	NM_001458.5	c.6968G>C	p.(Gly2323Ala)	VUS	-	26,6
3	*TMEM43*	NM_024334.3	c.578C>T	p.(Ser193Leu)	VUS	0.00002354	29,5
4	*SCN4B*	NM_174934.4	c.155C>G	p.(Thr211Arg)	VUS	-	28
5	*RYR2*	NM_001035.3	c.908G>A	p.(Gly303Glu)	VUS5	0.000008056	27,5
6	*KCNH2*	NM_000238.4	c.379C>T	p.(Leu127Phe)	VUS5	-	27,3
7	*CACNA1C*	NC_000012.12(NM_000719.7)	g.(?_189852807)_(189963485_?)dup	-	VUS	-	-
8	*KCNH2*	NM_000238.4	c.3089C>T	p.(Pro1030Leu)	VUS	0.0001419	20,8
9	*KCNJ2*	NM_000891.3	c.1240G>A	p.(Asn410Ser)	VUS	-	21,7
10	*KCNQ1*	NM_000218.3	c.217C>A	p.(Pro73Thr)	VUS	0.0002021	3,82
11	*ANK2*	NM_001148.6	c.397C>G	p.(Pro133Ala)	VUS	0.000003760	26,1
12	*KCNJ2*	NM_000891.3	c.1240G>A	p.(Asn410Ser)	VUS	-	21,7
13	*CACNA1C*	NM_000719.7	c.5162C>A	p.(Thr1721Asn)	VUS	-	23,5
14	*NOS1AP*	NM_014697.3	c.815_817del	p.(Ser276del)	VUS	0.0002763	14,1
15	*ANK2*	NM_001148.6	c.3051G>A	p.(Met1017Ile)	VUS	-	26,4
	KCNQ1	NM_000218.3	c.641G>A	p.(Cys214Tyr)	VUS4	0.000003100	25,9

Abbreviations [a] Varsome accessed on August 12, 2024

11% of the cases. Among the patients in whom genetic testing revealed alterations, 17% (9/52) had two or more variants identified. While the clinical significance of these findings remains uncertain in the absence of functional studies, and some variants may represent VUS, the presence of multiple variants raises the possibility of a polygenic contribution to disease expression. This may suggest a potential role of gene-gene interactions in modulating disease expression. It is worth considering that such variants could potentially influence the phenotype through mechanisms similar to those described for modifier genes, as discussed in the context of sudden cardiac death by Schwartz et al. [5]. Approximately a quarter (17%) of the patients with LQTS type 1 in our study carried high arrhythmia-risk variants, compared to 32% in the study by Schwartz et al. However, since our patient sample was significantly smaller than that of the aforementioned study, these results may be subject to bias.

Variants of unknown significance

In this cohort, VUS were identified in 9% (15/172) of patients, involving 18 different genes. Among these patients, 79% were asymptomatic. However, 21% had a clinical presentation similar to that of genetically positive patients, highlighting an area of uncertainty in the interpretation of genetic testing results in LQTS. To determine the deleterious effects of VUS, various methods are employed, including patch-clamp electrophysiology studies, protein expression and trafficking assays, in silico prediction tools, and cardiac action potential simulations. Functional analyses of these variants are crucial for understanding their impact on cardiac electrophysiology and their possible role in the pathogenesis of LQTS. Despite this, research in this area is often underfunded and deprioritised, particularly for rarer conditions such as LQTS. Additionally, reanalysis of VUS is not part of routine clinical practice at our centre, which may influence the number of genetically positive LQTS cases identified in our cohort. As VUS may be linked to ion channel dysfunction but remain of uncertain clinical significance, their integration into patient management strategies remains challenging.

This study was retrospective in nature, which may have led to incomplete or inconsistent data. We relied on available electrocardiogram (ECG) reports rather than original tracings, which limited the accuracy of QTc evaluation. Referral criteria for genetic testing may not have been consistent, which could possibly have affected the diagnostic yield. The relatively small sample size and single-centre setting may also limit the broader applicability of our findings.

Conclusions

In conclusion, this study provides new insights into the genetic backgrounds of LQTS patients in Lithuania, thereby enhancing the current understanding of geographically specific genetic diversity and its potential implications for diagnosis and treatment. In addition, we have identified a possible founder variant (NM_000218.3(KCNQ1):c.477+1G>C) in our cohort. We also demonstrate a 22% diagnostic yield for genetic testing, which may reflect less stringent selection criteria for patients with suspected LQTS in our country. patients with suspected LQTS in our country. Additionally, our data revealed that 17% of patients with 1 type LQTS had genetic variants located in regions associated with elevated arrhythmic risk. This knowledge should be considered as part of their individualized care plans, such as more frequent follow-ups. Detection of multiple genetic variants together with a great number of VUS and a possible founder variant, in such a small cohort of Lithuanian patients, highlights areas that warrant further investigation to understand the pathogenesis of LQTS better. Our results can be biased due to the small patient sample. However, they are still meaningful, as they highlight additional areas for investigation in the small cohort of LQTS patients in Lithuania.

Abbreviations

LQTS	Long QT syndrome
VUS	Variant of unknown significance
ACMG/AMP	American college of medical genetics and genomics/ association for molecular pathology
gnomAD	The genome aggregation database
P	Pathogenic
LP	Likely pathogenic
CADD	Combined annotation dependent depletion
MAF	Minor allele frequency
NFE	European (non–Finnish)
ECG	Electrocardiogram

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Authors' contributions

A.K. was responsible for conceptualization, data analysis, and drafting the manuscript. B.B. contributed to conceptualization, supervision, and manuscript writing. R.M. reviewed and contributed to the presentation of genetic data. A.U. reviewed the manuscript. All authors edited and approved the final version of the manuscript.

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Data availability

Data associated with this study are available upon justified request from the corresponding author. The dataset used in the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the Vilnius Regional Biomedical Research Ethics Committee of Lithuania (Approval No. 2024/1-1564-1025). The need for

written informed consent was waived by the ethics committee, as the study involved no intervention and used anonymized group-level data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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