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Original Research

Reverse Cascade Genetic Screening for Revealing New Cases of Familial Hypercholesterolemia in Russia: Pilot Project

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Abstract

Background: Reverse cascade genetic screening, following initial lipid testing, is an effective strategy for the early diagnosis of familial hypercholesterolemia (FH) and related hereditary dyslipidemias. In this study, we present the results of a pilot project in Russia. **Methods:** This was a hybrid retrospective–prospective cross-sectional study. Analysis of 1897 lipid screenings of children referred to the main pediatric centers in St. Petersburg, Russia, demonstrated that 60 (3.2%) met the Simon Broome criteria for FH, defined as total cholesterol (TC) ≥6.5 mmol/L or low-density lipoprotein cholesterol (LDL-C) ≥4 mmol/L. All families were invited to undergo genetic testing, regardless of their history, with 35 (58%) families participating in the second stage of the study. Targeted sequencing was performed for children, and Sanger sequencing was performed for variant validation in children and their family members. **Results:** Sixteen children were shown to have causal variants in dyslipidemia-associated genes, including fourteen (40% of 35 tested children) with hereditary dyslipidemias: twelve FH cases (linked to *LDLR* and *APOB* genetic variants), one dysbetalipoproteinemia case (*APOE*), and one sitosterolemia case (*ABCG8*). Two children were heterozygous for sitosterolemia variants (one case with *ABCG5*, one case with *ABCG8*). Family history of FH or atherosclerotic cardiovascular disease (ASCVD) was reported in only 50% of cases, regardless of whether a causal variant was present. TC and LDL-C were higher in the causal variant-positive subgroup. Receiver operating characteristic curve analysis revealed that LDL-C >4.8 mmol/L acted as a diagnostic indicator of disease causing variant with 84% accuracy, 93% sensitivity, and 73% specificity. **Conclusions:** Reverse cascade genetic screening following selective lipid testing in children is an effective strategy to reveal new FH and other hereditary dyslipidemia cases, helping to mitigate future ASCVD risks and early mortality.

Keywords: dyslipidemias; hyperlipoproteinemia type II; familial hypercholesterolemia; reverse cascade screening; high-throughput nucleotide sequencing

1. Introduction

Cardiovascular diseases remain the leading cause of death in most countries, including Russia. Dyslipidemia, particularly familial hypercholesterolemia (FH), is a known risk factor for premature atherosclerotic cardiovascular disease (ASCVD). FH is an autosomal dominant inherited disorder of low-density lipoprotein (LDL) metabolism caused by mutations in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes [1,2]. FH is characterized by elevated plasma levels of total cholesterol (TC) and LDL cholesterol (LDL-C), along with the development of xanthomas (cholesterol deposits in the skin and tendons). The global prevalence of heterozygous FH (heFH) varies from 1 in 200

to 1 in 500 depending on the population, with estimates for Russia indicating a higher frequency of 1:173 [3]. Despite being the most common hereditary dyslipidemia, FH still remains largely underdiagnosed worldwide. Meanwhile, untreated FH usually leads to premature coronary artery or peripheral vascular disease [4]. Therefore, implementing screening programs across different risk groups that combine clinical criteria with genetic testing is necessary to improve detection rates for FH and other hereditary dyslipidemias, facilitating early treatment [5].

A 20-year follow-up study showed that starting statin therapy in childhood for FH significantly reduces adult cardiovascular risks. By age 39, patients treated early had a 1% incidence of cardiovascular events and 0% mortality, compared to 27% and 7%, respectively, in their untreated parents [6]. Therefore, identifying FH and other dyslipidemias during childhood is ideal for initiating hypolipidemic treatment, with most guidelines recommending beginning statin therapy by age 8 to 10 [7]. This strategy is expected to prevent premature ASCVD in adulthood. Therefore, combining universal or selective pediatric lipid screening with reverse cascade genetic screening is highly relevant. Reverse cascade screening leverages a child's confirmed genetic diagnosis to uncover hidden familial cases, aiming for earlier intervention and disease prevention in relatives [8]. The FH diagnostic algorithm involves three steps: (1) biochemical screening to identify children with abnormal cholesterol levels; (2) subsequent genetic testing; and (3) cascade screening of parents and siblings. It is worth noting that this approach allows the diagnosis of FH in parents before the onset of ASCVD symptoms, preventing severe disease. Thus, reverse cascade genetic screening efficiently and cost-effectively identifies new FH cases among parents, siblings, and second-degree relatives [9,10]. To ensure accurate differential diagnoses of rare, autosomal recessive dyslipidemias that mimic FH (e.g., sitosterolemia, lysosomal acid lipase deficiency), expanded next-generation sequencing (NGS) panels or whole genome sequencing (WGS) are the preferred methods [2,11,12].

Our previous study showed that 89% of children and adolescents with strict clinical FH (based on Simon Broome criteria, including history of hypercholesterolemia, and/or ASCVD) carried pathogenic variants in FH-associated genes [13]. While utilizing a strong family history as a diagnostic criterion identifies over 80% of monogenic dyslipidemia cases [14,15], this approach may miss a significant portion of genetic cases, as 30–50% of pediatric cases do not report a positive family history [16,17,18]. Decision making regarding genetic testing is further complicated by the mildness of symptoms in children and the lack of known lipid profiles or ASCVD in young patients [19,20].

In this study, we aimed to determine the prevalence of FH and other hereditary dyslipidemias among children with lipid abnormalities and to preliminarily assess the effectiveness and feasibility of a reverse cascade genetic screening program in Saint-Petersburg. To this end, we conducted a hybrid retrospective–prospective cross-sectional study as part of a pilot project, "Saint-Petersburg Reverse Genetic FH Screen". This approach combined the retrospective analysis of medical records for selective lipid screening in children from the two largest pediatric centers in St. Petersburg with reverse cascade genetic testing of families with dyslipidemia. From 2022 to 2024, 1897 lipid profiles were analyzed through a collaborative effort between the K.A. Rauhfus St. Petersburg Children's Municipal Multi-Specialty Clinical Center of High Medical Technology and the Consultative and Diagnostic Center for Children. Pavlov First Saint-Petersburg State Medical University provided genetic testing for children with suspected FH, prioritizing elevated lipid parameters regardless of family history. Genetic testing in children included targeted sequencing using our expanded custom NGS panel to differentiate between the types of hereditary dyslipidemia.

2. Materials and Methods

2.1 Patients and Study Design

The study was designed as a hybrid retrospective–prospective cross-sectional study. Initially, we conducted a retrospective review of electronic medical records for lipid screenings among children and adolescents (aged 3–18) who visited the K.A. Rauhfus Children Municipal Multi-Specialty Clinical Center of High Medical Technology and the Consultative and Diagnostic Center for Children between January 1, 2022 and October 23, 2023, and then lipid screenings were analyzed in real time until December 31, 2024 with the goal of immediately inviting patients for genetic testing. Summary 1897 lipid profiles were analyzed for children with various somatic pathologies, including constitutional obesity, chronic digestive disorders, vegetative–vascular dystonia, arterial hypertension, bronchial asthma, and allergic rhinitis. Children were examined by a gastroenterologist and an endocrinologist to exclude secondary dyslipidemia. Exclusion criteria were: syndromic obesity, diabetes mellitus, and thyroid pathology. Lipid profiles were analyzed for abnormalities according to Russian clinical recommendations. Pediatric dyslipidemia was defined as having two or more lipid abnormalities: total cholesterol (TC) $\geq$5.2 mmol/L; triglycerides (TGs) >1.3 mmol/L (under 10 years old) and $\geq$1.7 mmol/L ($\geq$10 years old); high-density lipoprotein cholesterol (HDL-C) $\leq$0.9 mmol/L (boys) and $\leq$1.03 mmol/L (girls); and LDL-C $\geq$3.0 mmol/L [21]. Families meeting the Simon Broome criteria [22] were offered genetic testing for hereditary dyslipidemia once secondary cases were ruled out, regardless of their family history. In the second step of the study, selected children were subjected to targeted NGS. Sanger sequencing was performed to validate potentially causal variants in all available family members (parents and siblings). Fig. 1 illustrates the study enrollment process and research progression.

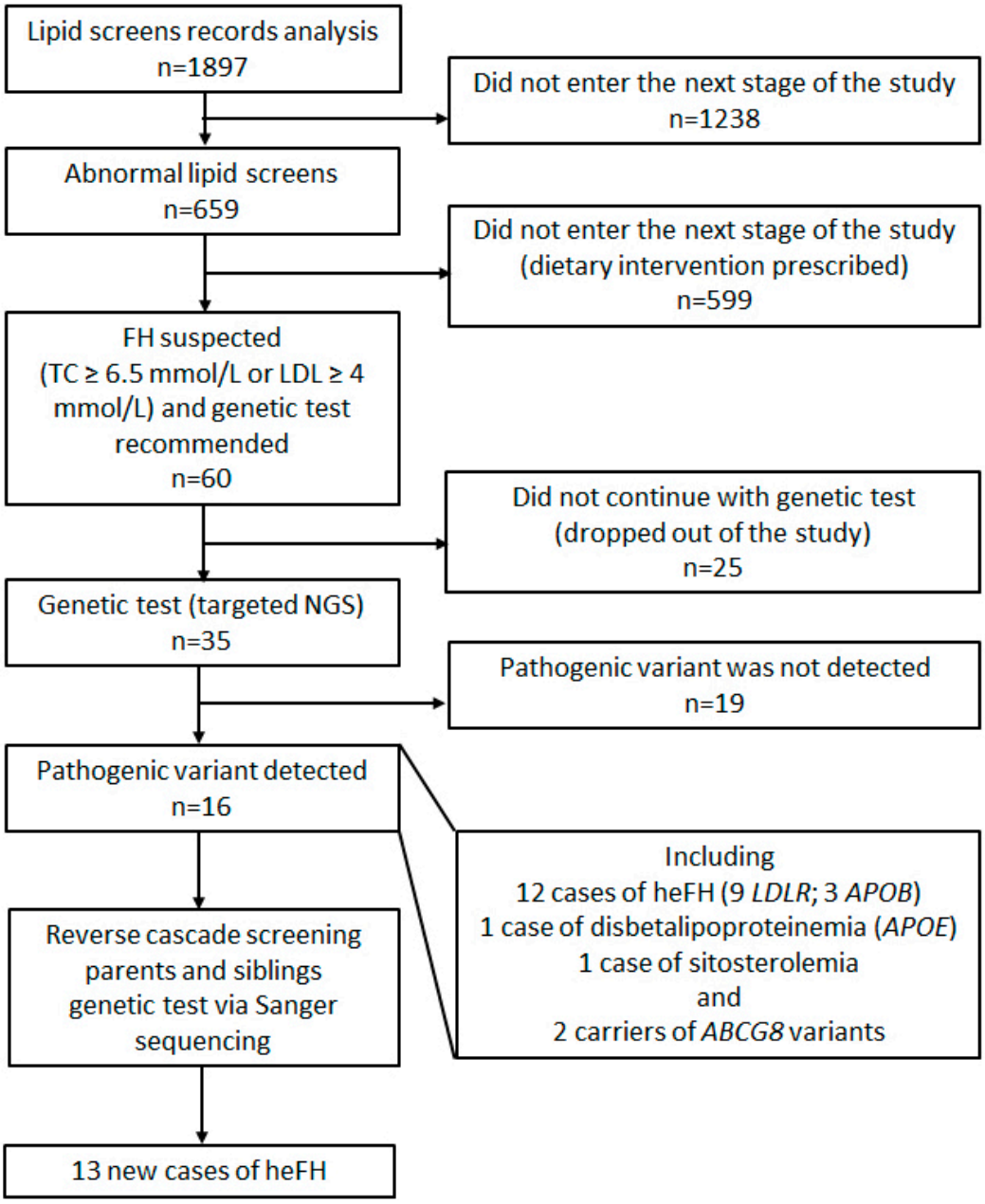

Fig. 1. Flow chart of study enrollment and research progression. FH, familial hypercholesterolemia; TC, total cholesterol; LDL, low-density lipoprotein; NGS, next-generation sequencing; heFH, heterozygous FH; *LDLR*, LDL receptor; *APOB*, apolipoprotein B; *APOE*, apolipoprotein E; *ABCG8*, ATP binding cassette subfamily G member 8.

2.2 Genetic Testing

Blood or saliva samples were taken from children, parents, and other available relatives. Deoxyribonucleic acid (DNA) was obtained via phenol–chloroform extraction. Libraries were prepared using an Illumina-compatible reagent kit (Prep&Seq U-target IL library kit; Parseq Lab Co., Saint-Petersburg, Russia) and our custom panel "Dyslipidemia and cardiovascular disease (CVD) risk" (VariFind LM assay v1.1.1, Parseq Lab Co., Saint-Petersburg, Russia) intended for differential diagnosis of hereditary dyslipidemias and targeting the following genes: *ABCA1*, *ABCG1*, *ABCG5*, *ABCG8*, *ANGPTL3*, *APOA1*, *APOA4*, *APOA5*, *APOB*, *APOC2*, *APOC3*, *APOE*, *CETP*, *CREB3L3*, *CYP27A1*, *CYP7A1*, *GCK*, *GPD1*, *GPIHBP1*, *HNF1A*, *LCAT*, *LDLR*, *LDLRAP1*, *LIPA*, *LIPC*, *LIPG*, *LMF1*, *LPL*, *LRP6*, *MTTP*, *MYLIP*, *NPC1L1*, *PCSK9*, *PNPLA5*, *SAR1B*, *SCARB1*, *SORT1*, *STAP1*, and *TTR* [10]. Paired-end sequencing (2 × 150 base pairs) was performed on the MiSeq System (Illumina, San Diego, CA, USA). Fastq files were analyzed using the manufacturer's Seq&Go Software (lm-pipeline-1-SP-1.3.2, Parseq Lab Co., Saint-Petersburg, Russia). The software includes standard FASTQ data processing and variant calling, and

Table 1. Demographic characteristics of the studied population and analysis of lipid screening results.

Parameter	
Male/Female, n	1062/835
Age, years	9 (3–18)
Abnormal analysis (at least one indicator is not normal), n (%)	659 (34.7%)
All cases of dyslipidemia, n (%)	250 (13.2%)
IIb (high TC, LDL-C, and TGs), n (%)	42 (2.2%)
IIa (high TC and LDL-C)	168 (8.9%)
Including clinical FH, n (%)	60 (3.2%)
Other variants	
High TG, low HDL-C, n (%)	30 (1.6%)
High LDL-C, low HDL-C, n (%)	10 (0.5%)

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol.

Table 2. Characteristics of the subgroup of children with suspected FH.

	All children	Causal variant-positive	Causal variant-negative
	n = 35 (100%)	n = 16 (45.7%)	n = 19 (54.3%)
Male/Female, n	18/17	9/7	9/10
Age, years	8 (3–17)	8 (5–16)	9 (3–17)
TC, mmol/L	7.00 (6.00–12.60)	7.50 (6.50–12.60)*	6.50 (6.00–12.20)
LDL-C, mmol/L	4.98 (4.00–9.60)	5.60 (4.11–9.60)**	4.55 (4.00–6.70)
HDL-C, mmol/L	1.74 (0.81–2.48)	1.57 (0.81–2.10)	1.75 (1.19–2.45)
TGs, mmol/L	0.84 (0.45–2.43)	0.84 (0.45–2.43)	1.02 (0.64–1.83)
Xanthomas	0	0	0
Positive family history of FH or ASCVD, n (%)	17 (48.6%)	8 (50%)	9 (47.4%)
Denied family history, n (%)	18 (51.4%)	8 (50%)	10 (52.6%)
Parents involved in genetic testing, n (%)	27 (77.1%)	14 (87.5%)	13 (68.4%)

*$p = 0.027$, **$p = 0.001$ compared to causal variant-negative subgroup. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides; ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia.

calculates quality metrics for each sample. The custom panel was designed to cover 117,584 base pairs; 500,000 reads per sample ensured at least 98% coverage of the target regions with high quality, samples with lower coverage were resequenced. The variants identified in the probands and their relatives were confirmed using polymerase chain reaction (PCR)-direct sequencing, utilizing the ABI BigDye Terminator 3.1 kit (4337456, Thermo Fisher Scientific, Waltham, MA, USA) with the Nanofor-05 instrument (Syntol, Moscow, Russia). Variant pathogenicity was assessed following American College of Medical Genetics and Genomics (ACMG) guidelines with modifications [23,24]. The following types of variants are reported in the article: pathogenic, likely pathogenic, and variant of unknown significance (VUS).

2.3 Statistical Analyses

Clinical and experimental data are presented as the median (min–max). The distribution of continuous variables was tested for normality using the Shapiro–Wilk test. For non-normally distributed variables, comparisons between two groups were performed using the Mann–Whitney U test. The predictive value of total and LDL-C as single criteria for genetic test assignment was assessed via receiver operating characteristic (ROC) curve analysis. The level of significance was set at $p < 0.05$.

3. Results

From 2022 to 2024, 1897 pediatric lipid screen records were analyzed from the two largest pediatric centers in St. Petersburg with the aim of confirming their diagnoses and receiving optimized therapy. The range of diagnoses included constitutional obesity, chronic digestive disorders, vegetative–vascular dystonia, arterial hypertension, bronchial asthma, and allergic rhinitis. Lipid spectrum analysis was performed to evaluate the prevalence of dyslipidemia; the results are presented in Table 1.

Abnormal lipid results were identified in 659 of the 1897 screened children (34.7%), requiring lifestyle interventions as a minimum measure, while 250 (13.2%) had dyslipidemia. Furthermore, 3.2% (60/1897) of children met the Simon Broome criteria for FH, defined by TC ≥6.5 mmol/L or LDL-C ≥4 mmol/L. Genetic testing was offered to these 60 children and their parents. Of the 35 families

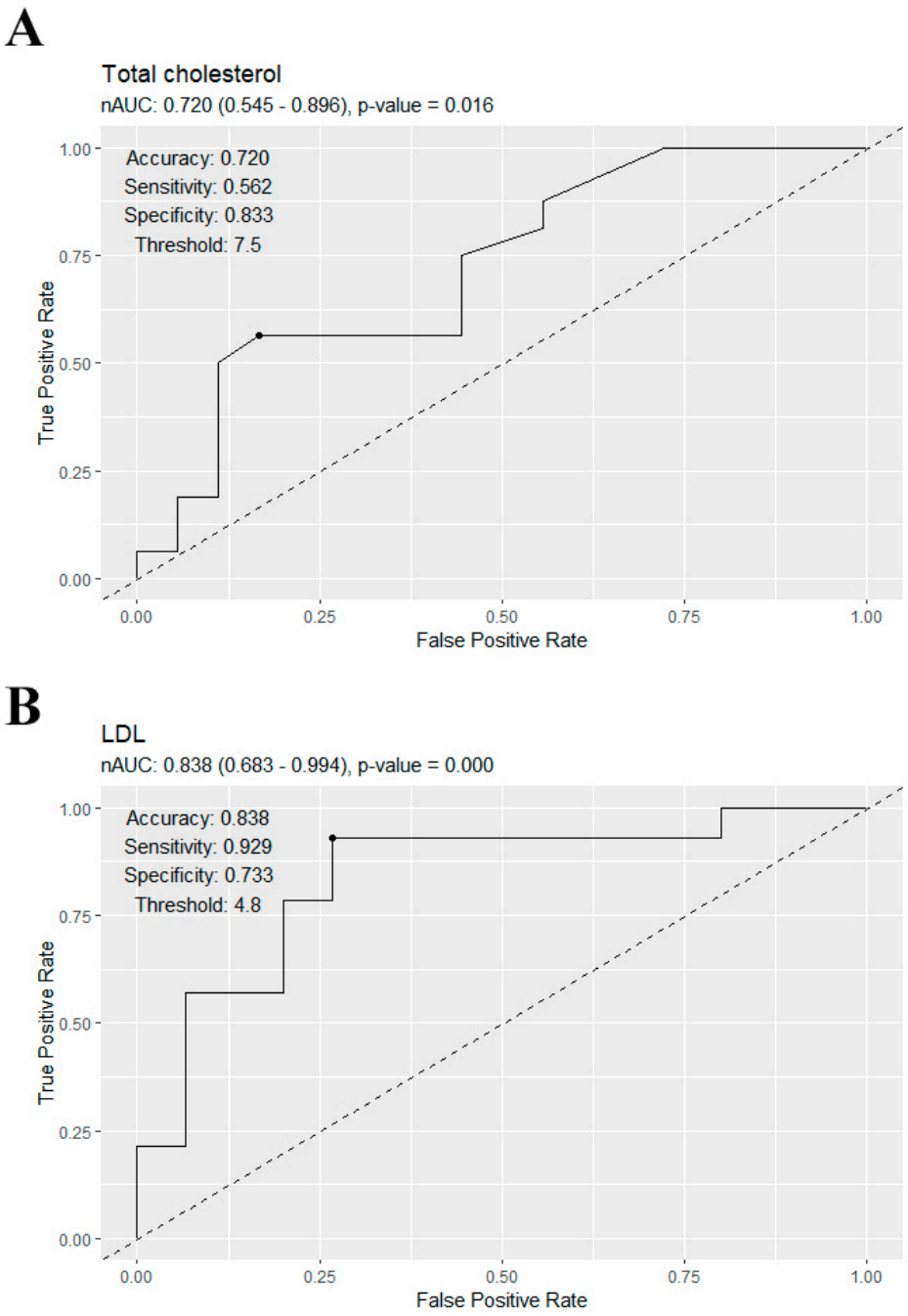

Fig. 2. Results of AUROC analysis for TC (A) and LDL-C (B) as standalone criteria for prediction of causal variant detection. AUROC, area under the receiver operating characteristic; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

who agreed to participate, 17 (48.6%) reported a positive family history, and potentially causal dyslipidemia variants were identified in 16 cases (45.7%). The characteristics of children with and without causal genetic variants are presented in Table 2.

Interestingly, none of the tested children or their parents had xanthomas. It is worth noting that the percentage of reported family history was similar between subgroups with and without causal FH variants. About 50% of families in both subgroups had a history of FH or ASCVD. TC and LDL-C were higher in the causal variant-positive subgroup. ROC curve analysis revealed that LDL-C >4.8 mmol/L predicted causal variant detection with 84% accuracy, 93% sensitivity, and 73% specificity (Fig. 2), making it a more reliable indicator for a positive genetic diagnosis than TC. Corresponding area under the ROC curve (AUROC) values were 0.720 ($p = 0.016$) and 0.838 ($p = 0.000$) for TC and LDL-C, respectively.

The detected causal variants are presented in Table 3. Hereditary dyslipidemias were diagnosed in 14 children (40%). Among them, 12 cases were genetically confirmed as FH: 9 involved *LDLR* gene mutations (7 pathogenic/

Table 3. Causal genetic variants detected in children and results of reverse cascade genetic screening.

Case number	Sex, age	TC, mmol/L	LDL-C, mmol/L	Family history	Causal variant	Genomic coordinate GRCh38	Pathogenicity classification	Detected relatives
					Familial Hypercholesterolemia			
1	F, 13	8.32	6.11	No	*LDLR* NM_000527.5:c.91G>A p.(Glu31Lys) rs776421777	chr19:11100246	VUS	Father
2	M, 7	7.00	5.08	No	*LDLR* NM_000527.5:c.223T>C p.(Cys75Arg)	chr19:11102696	Novel	*de novo*
3	M, 9	6.70	n/a	No	*LDLR* NM_000527.5:c.326G>A p.(Cys109Tyr) rs121908042	chr19:11105232	P/LP	Father
4	F, 5	7.85	5.80	No	*LDLR* NM_000527.5:c.514G>A p.(Asp172Asn) rs879254554	chr19:11105420	P/LP	Mother
5	F, 11	10.4	7.85	Yes	*LDLR* NM_000527.5:c.682G>A p.(Glu228Lys) rs121908029	chr19:11105588	P	Mother
6	M, 9	7.90	5.60	Yes	*LDLR* NM_000527.5:c.1202T>A p.(Leu401His) rs121908038	chr19:11113293	P	Father
7	F, 8	6.90	5.23	Yes	*LDLR* NM_000527.5:c.1202T>A p.(Leu401His) rs121908038	chr19:11113293	P	Mother
8	M, 7	7.00	5.70	No	*LDLR* NM_000527.5:c.2032C>T p.(Gln678Ter) rs879255114	chr19:11120414	P	Mother, two sisters
9	M, 8	7.54	4.88	Yes	*LDLR* NM_000527.5:c.2101G>A p.(Gly701Ser) rs368838866	chr19:11120483	VUS	Mother
10	M, 13	7.00	5.13	Yes	*APOB* NM_000384.3:c.10580G>A p.(Arg3527Gln) rs5742904	chr2:21006288	P/LP	Mother
11	M, 8	7.50	4.80	Yes	*APOB* NM_000384.3:c.10580G>A p.(Arg3527Gln) rs5742904	chr2:21006288	P/LP	Mother
12	F, 6	9.80	7.30	Yes	*APOB* NM_000384.3:c.10580G>A p.(Arg3527Gln) rs5742904	chr2:21006288	P/LP	Mother
					Dysbetalipoproteinemia			
13	F, 16	6.50	n/a	No	*APOE e2e2* p.(Cys130)/NM_000041.2:c.526C>T p.(Arg176Cys) rs7412	chr19:44908822	Risk factor	Parents did not take the test
					Sitosterolemia variants			
14	F, 6	12.60	9.60	No	*ABCG8* NM_022437.3:c.1534G>A p.(Gly512Arg) rs376069170	chr2:43875191	LP	Mother and sister were carriers
					ABCG8 NM_022437.3:c.1715T>C p.(Leu572Pro) rs769576789	chr2:43875372	P	Father was unavailable
15	M, 12	6.50	4.11	Yes	*ABCG8* NM_022437.3:c.1715T>C p.(Leu572Pro) rs769576789	chr2:43875372	P	Mother
16	F, 15	7.60	5.60	No	*ABCG5* NM_022436.3:c.-76C>T rs560839317	chr2:43838755	LP	Parents did not take the test

F, Female; LP, Likely pathogenic; M, Male; n/a, Not applicable; P, Pathogenic; VUS, Variant of unknown significance; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; *LDLR*, LDL receptor; *APOB*, apolipoprotein B; *APOE*, apolipoprotein E; *ABCG5*, ATP binding cassette subfamily G member 5; *ABCG8*, ATP binding cassette subfamily G member 8.

likely pathogenic, 2 VUS) and 3 had *APOB* variants. Thereafter, reverse cascade screening was performed in these families, and 13 new FH cases (11 parents and 2 siblings) were found. In one case, the novel *LDLR* substitution NM_000527.5: c.223T>C p.(Cys75Arg) was detected. Due to its absence in both parents, the variant was determined to be *de novo*. Structural modeling and in silico bioinformatic tools suggest that this variant is damaging [25]. A 16-year-old child was diagnosed with autosomal recessive dysbetalipoproteinemia, characterized by an *APOE e2e2* genotype and lipids of 6.5 mmol/L (TC) and 2 mmol/L (TGs). Additionally, as previously described, for one child we confirmed a diagnosis of autosomal recessive sitosterolemia, which was confirmed by biochemical analysis to be caused by compound heterozygous *ABCG8* pathogenic variants [11]. Two another children were identified as heterozygous carriers of sitosterolemia related pathogenic variants: one case with *ABCG5* and one case with *ABCG8*; however, their plasma plant sterol levels were not analyzed.

4. Discussion

Patients with genetically defined FH have a significantly elevated risk of ASCVD, specifically a greater than 10-fold higher risk compared to the general population and a 3-fold increased risk even at identical LDL-C levels [26]. Global identification rates for FH remain under 10%. Based on data from the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration, adults with FH are generally diagnosed in the age range of 40 to 49 years, often simultaneously with symptomatic ASCVD [27]. With approximately 450,000 children born with FH globally every year, this genetic condition remains vastly underdiagnosed and undertreated. Current diagnostic approaches, often adapted from adult criteria, fail to detect most cases, with only about 2% of patients diagnosed before the age of 18. Furthermore, registry data indicate a major treatment gap, as more than 70% of children diagnosed with FH are not receiving necessary lipid-lowering medication [27]. At the same time, children receiving treatment have a much lower cardiovascular risk in adulthood than their parents [6]. The National Heart, Lung, and Blood Institute and American Academy of Pediatrics recommend universal lipid screening for all children aged 9–11 and again at 17–21. Selective lipid screening for children aged 2–8 is advised for those with high-risk factors, including a family history of ASCVD/dyslipidemia, diabetes, hypertension, or elevated body mass index (BMI) [22]. However, family history alone is not a reliable indicator for pediatric FH [28,29].

Our study showed that lipid profile abnormalities are widespread among children referred to diagnostic centers, even when excluding cases of obesity, diabetes, and thyroid pathology. Notably, 34% of these children presented with at least one abnormal lipid parameter, 13.2% exhibited overt dyslipidemia, and 3.2% presented with suspected FH. Previous studies indicate that at least 20% of children under 18 experience dyslipidemia, including elevated TC, low HDL-C, and/or high non-HDL-C levels [30,31,32,33]. About 40% of abnormal results of lipid screening are associated with being overweight or obese [17,34,35]. Studies indicate that 30–50% of children with abnormal results have neither a positive family history nor elevated BMI [34]. Projections suggest that while targeted screening misses 30% to 60% of children with dyslipidemia, universal screening could identify 90% of FH cases in children aged 1 to 9 years, with a false-positive rate of less than 1% [36]. In the Coronary Artery Risk Detection in Appalachian Community (CARDIAC) Project, Ritchie et al. [37] screened 20,266 children, finding that FH was suspected in 1.2% of those with a family history and 1.7% of those without. Further studies that included genetic testing based on results of lipid screening demonstrated 30–55% of mutation-positive cases demonstrate a lack of family history [29,38]. Therefore, the design of our study supported genetic testing based solely on lipid screening results to increase detection rates and identify cases with unknown family history. This is also important because among children without family history recessive dyslipidemias might be detected (sitosterolemia, dysbetalipoproteinemia, lysosomal acid lipase deficiency) [11,13].

Our study found that 50% of causal genetic variants appeared in families lacking a history of dyslipidemia or ASCVD, underlining that relying on family history as a criterion for appointment of genetic testing may result in missed diagnoses. Overall, 16 children (45.7%) with LDL-C >4 mmol/L were identified as carriers of causal variants for FH and other dyslipidemias; 14 children (40%) received a definitive diagnosis of hereditary dyslipidemias. heFH was identified in 12 children, along with 11 parents and 2 siblings, with one novel variant suspected to be *de novo*. One child was diagnosed with autosomal recessive familial dysbetalipoproteinemia, confirmed by the *APOE e2e2* genotype. Familial dysbetalipoproteinemia is a highly atherogenic, genetically inherited lipid disorder with a prevalence that is often underestimated in clinical practice [39]. One child was diagnosed with autosomal recessive sitosterolemia as previously described [11]. Patients with sitosterolemia caused by biallelic pathogenic mutations in *ABCG5* or *ABCG8* is typically characterized by marked elevation of LDL-C. Previous reports have described familial cases with severe hyper-LDL cholesterolemia and elevated plant sterols in heterozygous *ABCG5/8* carriers, although data regarding a second mutation were not obtained [40]. Large population studies have demonstrated that heterozygous *ABCG5/8* variants are associated with altered lipid profiles and cardiovascular risk [41]. Still, most sitosterolemia and other rare hereditary autosomal recessive dyslipidemia cases remain underdiagnosed, similarly to FH, highlighting the need to develop screening programs. The high percentage of mutation-positive children without

family history highlights that universal lipid screening is preferable.

Beyond family history, a separate, key inclusion criterion for genetic testing is meeting specific threshold lipid levels following biochemical screening. Because physical characteristics of FH (like xanthomas) and symptomatic ASCVD are very rare for heFH in children, relying on lipid level is the most critical diagnostic approach, especially when family history is unavailable or denied. According to registry studies, children and adolescents with FH have a median LDL-C of 5.00 mmol/L (interquartile range [IQR] 4.05–6.08), and their unaffected siblings have an LDL-C of 3.20 mmol/L (IQR 2.70–3.60) [27]. Thus, we chose Simon Broome cut-offs for LDL-C (4 mmol/L) and TC (6.5 mmol/L) as an inclusion measure in our study. In the absence of xanthomas, elevated LDL-C and TC were the only clinical indicators for children without a documented family history. In our study, children with causal genetic variants had higher TC and LDL-C levels compared to mutation-negative patients. ROC curve analysis showed that TC >7.5 or LDL-C >4.8 mmol/L predicts a high probability of the presence of a causal genetic variant, regardless of family history. This criterion might be used if family history is unknown or unconfirmed. However, this approach still has its risks, as some pediatric cases demonstrating mild symptoms may be lost. For example, children carrying pathogenic genetic variants may have LDL-C levels under 4 mmol/L, causing them to be missed if their parents remain undiagnosed. Consequently, some studies recommend repeat biochemical testing and additional examination of parents when lipid levels fall into the borderline zone [14,29].

To summarize, inclusion criteria vary across studies; utilizing a positive family history as a selection criterion generally results in a higher mutation detection rate, often reaching 80–90% [13,42]. Relying solely on lipid parameters rather than family history results in a lower detection rate, yet it still identifies a high percentage of positive cases in patients without family history. Still family history is a crucial factor to consider when lipid levels fall within the borderline zone. Slovenia was the first country worldwide to implement universal pediatric screening for FH in 1995 [43]. Based on the Slovenian cohort, 813 children were selected for genetic screening using TC thresholds of >6 mmol/L (232 mg/dL) or 5–6 mmol/L (193–232 mg/dL) combined with positive family history [29,44]. Genetic analysis of this group revealed that 26.9% (219) carried pathogenic variants, 5.2% (42) were VUS heterozygotes, and 67.9% (552) tested negative [29]. A positive family history was only reported in 45.2% of positive cases. Based on a similar German pilot study, of 132 children with confirmed LDL-C levels >3.5 mmol/L (measured twice), 26 (19.7%) were classified as positive, 18 (13.6%) as VUS heterozygotes, and 88 (66.7%) as negative [29]. A positive family history was observed in 69.2% of positive cases. Pilot projects in Portugal, Italy, and Poland demonstrated 37%, 50%, and 57% mutation detection rates, respectively, in children with suspected FH according to Simon Broome criteria [38,42,45]. Consistent with our findings, 30–55% of mutation-positive cases lacked a documented family history.

National FH screening programs exist in several European countries and demonstrate different efficiencies depending on organization and duration [10,44]. For example, an estimated 90% of United Kingdom (UK) residents remain undiagnosed and consequently untreated [44]. Initiated in the 1990s, national FH screening programs in the Netherlands and Norway have successfully identified over 50% of their respective FH population [46]. A Chinese pilot study using first-tier WGS on newborn dried blood spots revealed that FH occurs at a frequency of approximately 1:170–1:195 [10]. The UK plans to perform WGS in 100,000 newborns during the Newborn Genomes Programme and screen 200 conditions, including FH. European strategies for FH detection are divided: countries like Slovenia, Germany, the UK, the Czech Republic, Estonia, Greece, and Slovakia are advancing universal pediatric lipid screening and genetic testing, whereas other European countries continue to use classical cascade screening [47]. Consequently, these programs are not universal or nationwide, and the overall effectiveness is not systematically assessed [10]. Moreover, the success and cost-efficiency of cascade screening depend on the structured involvement of relatives. Based on data from highly successful FH screening programs in the Netherlands and Norway, an effective approach involves testing an average of 5 relatives for every index case (proband), resulting in the identification of 2 to 2.5 genetically confirmed FH cases per index case [44]. Testing only 1–2 relatives may result in a lower success rating for the program [44]. While the UK identifies just 1.1 FH-positive relatives per index case, other regions show higher detection rates, with Norway, the Netherlands, and Northern Ireland identifying 2.1, 2.5, and 3.2, respectively [44]. In our study, 77.1% of parents consented to genetic testing prior to receiving the child's results. With sibling biomaterial available in multiple cases, the identified positive relatives averaged only 1.1 per index case.

Although national universal lipid screening has not yet been implemented in Russia, regional pilot studies in the Tatarstan district indicate that 35% children have elevated TC, suggesting a need for genetic testing [48]. These findings align with our Saint-Petersburg results, emphasizing that hypercholesterolemia is a significant problem in Russia. A substantial increase in the detection of childhood hypercholesterolemia is anticipated following implementation of the Russian Ministry of Health's Order No. 211n (as amended in April 2025) in September 2025, which mandates the express assessment of cholesterol levels in 6- to 10-year-old children within risk groups.

5. Limitations

The limitations of the study include a rather small sample size and a short pilot study period. Continuation of the project in the future may demonstrate the clinical and economic effectiveness of reverse cascade genetic screening and lead to improvements in existing FH screening programs in Russia, with potential expansion to all hereditary dyslipidemias. An additional limitation is that children with FH do not always demonstrate TC ≥6.5 mmol/L or LDL-C ≥4 mmol/L, which were the criteria for prescribing genetic diagnostics in our study. Consequently, these children may be missed during standard screening. Therefore, monitoring of families with documented lipid metabolism disorders should be established.

6. Conclusions

In conclusion, we demonstrate that reverse cascade genetic screening, initiated after pediatric lipid screening, is an effective strategy to identify new cases of FH and other hereditary dyslipidemias. This approach will reduce the future burden of ASCVD and early mortality associated with these conditions. However, implementing universal cholesterol screening coupled with genetic testing will likely increase the total number of diagnosed cases.

Abbreviations

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LP, likely pathogenic; NGS, next-generation sequencing; P, pathogenic; TC, total cholesterol; TGs, triglycerides; VUS, variant of unknown significance; WGS, whole genome sequencing.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

VVM, NNS and SNP designed the research; VVM, ADI, NNS, NBK, MNG, KVD, KOT, OSG performed the research and analyzed the data; SAU, SVL, AAP, KVL, ANK, IVI, TMI and LAK analyzed lipid records, recruited, examined and consulted patients and their parents; VVM, NNS and SNP wrote the original draft of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the local Ethics Committee of Pavlov First Saint Petersburg State Medical University (Protocol No. 275 of September 4, 2023) and was conducted with the informed consent of parents/legal representatives of children under 18 years of age. Retrospective analysis of the electronic medical records of previous period was approved by the local Ethics Committee (Protocol No. 277 of October 23, 2023) and was conducted with patient confidentiality protection and taking into account informed consent previously obtained for the medical examination and processing of personal data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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