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Real-World Experience from Türkiye: Genetic and Therapeutic Insights in Pediatric Heterozygous Familial Hypercholesterolemia

Havva Yazıcı[1], Esra Er[2], Fehime Erdem[1], Ayşe Yüksel Yanbolu[1], Sakina Mammadova[1], Sedef Alpdoğan[1], Merve Yoldaş Çelik[1], Yasemin Atik Altınok[3], Ebru Canda[1], Ayça Aykut[4], Haluk Akın[4], Sema Kalkan Uçar[1], Mahmut Çoker[1]

[1]Ege University Faculty of Medicine, Department of Pediatrics, Division of Metabolism and Nutrition, İzmir, Türkiye
[2]University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatrics, Division of Metabolism and Nutrition, İzmir, Türkiye
[3]İzmir Tınaztepe University Faculty of Health Sciences, Department of Nutrition and Dietetics, İzmir, Türkiye
[4]Ege University Faculty of Medicine, Department of Medical Genetics, İzmir, Türkiye

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What is already known on this topic?

Familial hypercholesterolemia (FH) is a common inherited lipid disorder that increases atherosclerotic risk from childhood.

What this study adds?

This is the first comprehensive Turkish cohort analysing both genetic and therapeutic aspects of pediatric heterozygous FH. The study found major shortcomings in early screening, treatment acceptance, and follow-up. The study also identified three novel *LDLR* variants.

ABSTRACT

Objective: Familial hypercholesterolemia (FH) is an inherited metabolic disorder that increases cardiovascular risk from childhood. Despite its frequency, pediatric diagnosis and treatment remain limited, particularly in developing countries.

Corresponding Author: Assoc. Prof. Ebru Canda, Ege University Faculty of Medicine, Department of Pediatrics, Division of Metabolism and Nutrition, İzmir, Türkiye
E-mail: ebru.canda@ege.edu.tr **ORCID:** orcid.org/0000-0002-9175-1998
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Methods: Retrospective analysis of pediatric patients with genetically confirmed heterozygous FH (HeFH). Genetic testing included sequencing of the genes *LDLR*, *APOB*, and *PCSK9*. Clinical features, treatment responses, statin use, and adverse events were assessed and a comparative analysis was conducted between different statin types.

Results: Among the cohort of 124 patients only 28.2% of patients were diagnosed via routine lipid screening, though 90.3% had a positive family history. After diagnosis, 16.1% declined treatment and 41.1% were lost to follow-up. Most genetic diagnoses involved pathogenic *LDLR* variants; only a few cases involved *APOB* and *PCSK9*. Three novel *LDLR* variants were identified. Among treated patients, atorvastatin led to a greater median low density lipoprotein-cholesterol (LDL-C) reduction. A higher (though not statistically significant) proportion of pitavastatin users achieved LDL-C targets. LDL-C reduction was positively correlated with baseline LDL-C levels. For the majority of patients, statins were well tolerated; five patients had transient creatine kinase elevations that resolved with treatment interruption.

Conclusion: This is the first large pediatric HeFH cohort study from Türkiye and provides data on both genetic background and treatment outcome. Despite genetic confirmation, significant gaps remain in early diagnosis, treatment acceptance, and long-term follow-up. Both atorvastatin and pitavastatin proved to be safe and effective. These results suggest a need for national screening programmes, family education, dietary counselling, and consistent follow-up.

Keywords: DNA sequencing, heterozygous familial hypercholesterolemia, *APOB, LDLR, PCSK9,* paediatrics

Introduction

Familial hypercholesterolemia (FH) is attributed to mutations in genes that are critical for the receptor-mediated endocytosis of low-density lipoprotein cholesterol (LDL-C). This impairment compromises the body's ability to effectively clear LDL-C from the circulation, resulting in hyperlipidemia that significantly elevates the risk of premature cardiovascular disease (CVD). As such, early identification and prompt initiation of therapeutic interventions are of paramount importance (1).

FH occurs in two distinct clinical forms: heterozygous FH (HeFH) and homozygous FH. HeFH is associated with monoallelic mutations in the autosomal semi-dominant genes *LDLR*, *APOB*, and *PCSK9*. *LDLR* gene variants are most commonly found in patients with FH, while variants in *APOB* and *PCSK9* genes are less frequently observed (2,3). Scientific organisations, including the European Atherosclerosis Society (EAS) Consensus Panel, Simon Broome Register Group, and Dutch Lipid Clinic Network, have established well known diagnostic criteria based on scores assigned to family history and laboratory parameters (4,5,6,7).

Current guidelines recommend universal lipid screening for pediatric patients aged 9 to 11 years and 17 to 21 years. For those outside these age ranges, a selective screening approach is preferred, which involves screening individuals who have risk factors or a family history of early CVD (8,9,10). The EAS Familial Hypercholesterolemia Studies Collaboration has indicated that approximately 450,000 children are born annually worldwide with FH. Nevertheless, only 2.1% of adults affected by this condition receive a diagnosis before the age of 18 years (11). Despite these international insights, data on the national burden of FH have been scarce. A recent large-scale study from Türkiye, using electronic health records of over 83 million citizens, revealed a notably high FH prevalence of 0.63% among adults (~1/159) and 0.37% (~1/270) among children and adolescents. Despite its inherited nature, the lower prevalence of FH observed in childhood compared to adulthood suggests a significant gap in early diagnosis during the pediatric period in Türkiye (12).

In the absence of sufficient lipid-lowering therapy (LLT), individuals with HeFH, which affects an estimated 1 in 100 to 1 in 500 people, face a 20-fold increased risk of developing CVD when their LDL-C levels exceed 5.5 mmol/L, compared to unaffected individuals with LDL-C levels below 3.5 mmol/L (13). In terms of treatment for FH in children, conflicting opinions remain among healthcare professionals about when to initiate LLT, particularly at what age, at what lipid thresholds and what the target lipid levels should be. Statins and ezetimibe are conventional LLTS. A widely acceptedpublished approach recommends initiating statin therapy in pediatric patients with LDL-C levels of 160 mg/dL or higher, particularly when additional risk factors or comorbidities are present. Moreover, treatment is also advised for children with LDL-C levels exceeding 190 mg/dL, even without other risk factors (14). Current treatment recommendations suggest achieving LDL-C reduction of at least 50% and targeting an LDL-C level below 130 mg/dL in children and adolescents with FH, although aiming for levels below 100 mg/dL may offer greater protection against CVD over the lifespan (14,15). Moreover, the earlier the initiation of treatment, the more favourable the long-term prognosis tends to be (1).

All commercially available statins are FDA-approved (16) and are generally well-tolerated in children, with adverse events being rare, mild, and typically reversible without requiring discontinuation (17). Multiple randomised controlled trials, Cochrane reviews, and long-term studies, including a 20-year follow-up in children with FH (18), have confirmed statins' short- and long-term safety in the pediatric population (16,19,20,21). Though uncommon, potential adverse effects include liver enzyme elevations and muscle symptoms (22).

Therefore, this study aimed to present comprehensive data on the identification of FH, underlying molecular defects, and treatment approaches in a large pediatric patient cohort from Türkiye, where such data are limited when compared to developed countries in Europe and North America.

Methods

Study Population

Our research adopted a retrospective cohort design, focusing on patients under 18 years of age. A total of 450 patients who were referred to a tertiary centre for evaluation of FH were initially assessed. After excluding secondary causes of hypercholesterolemia, patients with confirmed heterozygous mutations in the *LDLR*, *APOB*, or *PCSK9* genes were included in the study. The baseline for the study was established at the point when a clinical diagnosis of HeFH was made.

Lifestyle change recommendations were made, focusing on reducing eating frequency outside the home, snacking habits, and unhealthy food choices while encouraging physical activity. In all cases, lifestyle modifications were implemented, starting with the CHILD-1 diet, followed by a gradual transition to the CHILD-2 diet (8). The study was approved by the Medical Research Ethics Committee of Ege University Faculty of Medicine (approval number: E.2371714, date: 28.03.2025).

When statins were prescribed, adherence was assessed based on information obtained from patients and their families regarding the regular intake of statin therapy. The target LDL-C level was defined as 130 mg/dL (14,15).

Sequencing of FH-related Genes

DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. The concentration of the extracted DNA was quantified using the Qubit™ double-stranded DNA (dsDNA) HS Assay Kit on the Qubit 2.0 Fluorimeter (Thermo Fisher Scientific, Waltham, MA, USA). This approach provides high sensitivity and accuracy in quantifying dsDNA, ensuring reliable results for downstream applications.

First, *LDLR* was analysed using Sanger sequencing. Only after confirming negative results for *LDLR*, a targeted next-generation sequencing (NGS) panel was used to analyse the following genes: *ABCA1*, *ABCG5*, *ABCG8*, *ACTA2*, *ACVRL1*, *AGL*, *ALMS1*, *ANGPTL3*, *APOA1*, *APOA5*, *APOB*, *APOC2*, *APOE*, *BMPR1B*, *BMPR2*, *CAV1*, *CBS*, *CETP*, *COL3A1*, *CREB3L3*, *CYP27A1*, *ENG*, *FBN1*, *FBN2*, *GHR*, *KCNK3*, *LCAT*, *LDLR*, *LDLRAP1*, *LIPA*, *LIPC*, *LMF1*, *LPA*, *LPL*, *MYH11*, *PCSK9*, *SCARB1*, *SLC2A10*, *SMAD2*, *SMAD3*, *SMAD9*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*, *USF1*, and *GPIHBP1*. The study was conducted based on the analysis of these genes. The use of NGS allowed simultaneous analysis of multiple genes with high precision, enabling the identification of a broad spectrum of genetic variants.

Identification of Disease-Causing Variants

Detected variants were classified for their pathogenicity following the guidelines of the American College of Medical Genetics and Genomics (ACMG), ensuring that the interpretation was clinically relevant and accurate. The minor allele frequencies of the variants were assessed using publicly available databases, such as National Center for Biotechnology Information dbSNP and the Genome Aggregation Database (gnomAD). Disease-associated variant information was retrieved from databases, including ClinVar, which provides insights into genetic variants linked to diseases, and Online Mendelian Inheritance in Man, a detailed resource for genetic disorders and traits.

Novel variants identified during NGS were systematically analysed for their pathogenicity, mode of inheritance, and association with clinical phenotypes. Variants were examined for their potential impact on protein function, focusing on missense variants affecting evolutionarily conserved amino acid residues within critical protein domains.

To confirm the accuracy of candidate pathogenic variants identified through NGS, Sanger sequencing was employed using the Applied Biosystems, Inc. PRISM 3500 DNA Analyzer (Applied Biosystems, Foster City, CA, USA). This gold-standard method provided reliable verification of the identified variants. Furthermore, segregation analyses were performed, where applicable, to determine the inheritance patterns of the variants within affected families, strengthening the link between the variants and observed clinical phenotypes.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables, including baseline LDL-C, LDL-C reduction (mg/dL), statin initiation age, treatment duration of statin, and age at the last visit, were assessed for normality using visual inspection and tested for distribution. Since most variables were not normally distributed, results are presented as medians with interquartile ranges (IQR, 25^{th}-75^{th} percentiles). Comparisons between atorvastatin and pitavastatin groups were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, such as LDL target achievement, statin dose adjustment, and statin adherence. Correlations between baseline LDL-C and absolute LDL-C reduction were evaluated using Spearman's rank correlation coefficient for the total cohort and within each treatment subgroup. A two-sided p value <0.05 was considered statistically significant.

Results

Patient Demographics and Clinical Characteristics

A total of 124/450 (27.5%) patients were included in the study, with 45.2% (n=56) female and 54.8% (n=68) male. The median age at diagnosis was 7.9 (4.8-11.0) years. The most common reason for referral was family screening (46.0%, n=57), followed by routine screening (28.2%, n=35) and other causes (25.0%, n=31). Xanthoma was noted in only one patient (0.8%). A positive family history of hypercholesterolemia was present in 90.3% (n=112) of cases, and 32.3% (n=40) had a family history of premature CVD. The median body mass index standard deviation score at diagnosis was 0.22 (-0.79 to 1.0) kg/m^2, and the median LDL-C level at diagnosis was 234.5 (197.5-270.8) mg/dL. At the time of analysis, 29.0% (n=36) were on pitavastatin, 26.6% (n=33) on atorvastatin, 28.2% (n=35) had not yet started statin treatment, and 16.1% (n=20) had declined treatment. The median age at the last follow-up visit was 13.0 (8.6-15.7) years) (Table 1). In terms of follow-up, 42.7% (n=53) of patients remained under regular follow-up, 7.3% (n=9) were poorly compliant, 8.1% (n=10) had transitioned to adult care, 41.1% (n=51) were lost to follow-up, and 0.8% (n=1) were followed at another centre.

Clinical Characteristics of Patients under Statin Treatment

Lifestyle modifications and dietary interventions were implemented in all cases, beginning with the CHILD-1 diet and transitioning to the CHILD-2 diet as needed. Statin therapy was initiated in patients who did not achieve adequate lipid control through these measures. Among the 69 patients receiving statin therapy, 53.3% (n=36) were treated with pitavastatin and 46.7% (n=33) with atorvastatin. Although other statin preparations are available in Türkiye, these two remained consistently accessible and were continuously provided to the cohort throughout the study period. The median age at statin initiation was 11.3 (8.3-12.4) years, with no difference between the pitavastatin group [11.0 (7.9-12.0) years] and the atorvastatin group [11.3 (9.5-13.3) years; p=0.216]. Median baseline LDL-C level at statin initiation was significantly higher in the atorvastatin group [274.0 (247.0-298.0) mg/dL] compared to the pitavastatin group [225.5 (202.8-262.0) mg/dL; p<0.001]. The overall duration of statin treatment was 2.6 (1.4-3.4) years, with no difference between groups (p=0.263). The median age at the last follow-up was significantly older in the atorvastatin group [15.2 (13.3-16.4) years] than in the pitavastatin group [13.0 (10.8-15.9) years; p=0.037]. Overall adherence to statin therapy was 46.4% (n=32), with higher rates observed in the pitavastatin group (55.6%, n=20) compared to the atorvastatin group (36.4%, n=12) (Table 2). There was no significant difference between the atorvastatin and pitavastatin groups regarding the requirement for dose adjustment or statin adherencece (chi-square test, p=1.0; Mann-Whitney U test, p=0.148, respectively).

Firstly, when evaluating the treatment response to atorvastatin in terms of dosage, the median drop in LDL-C levels were: for 5 mg/day (n=17), 0.345 (0.294-0.476); for 10 mg/day (n=23), 0.494 (0.332-0.538); and for 20 mg/day (n=4), 0.369 (0.224-0.476). The number of cases in the 20 mg/day group was limited, and one of these patients had poor statin adherence. Similarly, when evaluating the treatment response to pitavastatin in terms of dosage, the median values were: for 1 mg/day (n=25), 0.450 (0.307-0.517); for 2 mg/day (n=19), 0.508 (0.315-0.578); and for 4 mg/day (n=2), 0.314 (0.307-0.321). Both patients in the 4 mg/day group had poor statin adherence.

The median absolute reduction in LDL-C was significantly greater in the atorvastatin group compared to the pitavastatin group (133.0 mg vs. 101.0 mg; p=0.048) (Figure 1A), while no difference was found in percentage LDL-C reduction between the groups (53.8% vs. 43.4%; p=0.778). Since the atorvastatin group had higher baseline LDL-C levels, the observed difference in absolute LDL-C reduction was affected by these initial values.

Table 1. Overview of patient demographics and baseline characteristics

Gender, % (n)	
Female	45.2% (56)
Male	54.8% (68)
Diagnosis age (y), median (IQR)	7.9 (4.8-11)
Reason for examination, % (n)	
Family screening	46.0% (57)
Screening	28.2% (35)
Others	25.0% (31)
Xanthoma	0.8% (1)
Hypercholesterolemia in family	
Yes	90.3% (112)
No	9.7% (12)
Premature CVD in family, % (n)	
Yes	32.3% (40)
No	67.7% (84)
BMI SDS at diagnosis, median (IQR)	0.22 (-0.79-1.0)
LDL-C at diagnosis, median (IQR), mg/dL	234.5 (197.5-270.8)
Statin, % (n)	
Pitavastatin	29.0% (36)
Atorvastatin	26.6% (33)
Not started yet	28.2% (35)
Declined	16.1% (20)
Age at last visit (y), median (IQR)	13 (8.6-15.7)

y: years, IQR: interquartile range, CVD: cardiovascular disease, BMI: body mass index, SDS: standard deviation score, LDL-C: low density lipoprotein-cholesterol

Table 2. Overview of clinical characteristics of patients undergoing statin treatment

	Overall 100% (69)	Pitavastatin 53.3% (36)	Atorvastatin 46.7% (33)	p*
Starting age of statin (y), median (IQR)	11.3 (8.3-12.4)	11.0 (7.9-12.0)	11.3 (9.5 -13.3)	0.216[m]
LDL-C at initiating statin, median (IQR)	247.0 mg/dL (217.0-285.0)	225.5 mg/dL (202.8-262.0)	274 mg/dL (247.0-298)	0.001[m]
Treatment duration under statin, median (IQR)	31.0 m (17.2-41)	31.0 m (13.5-38.2)	31.5 m (18.8-67.2)	0.263[m]
Age at last visit (y), median (IQR)	14.3 (12.2-16.4)	13.0 (10.8-15.9)	15.2 (13.3-16.4)	0.037[m]
Adherence with statin, % (n)	46.4% (32/69)	55.6% (20/36)	36.4% (12/33)	0.148[m]

*p values refer to comparison between statin sub-groups; [m]Mann-Whitney U test, y: years, IQR: interquartile range, LDL-C: low density lipoprotein-cholesterol

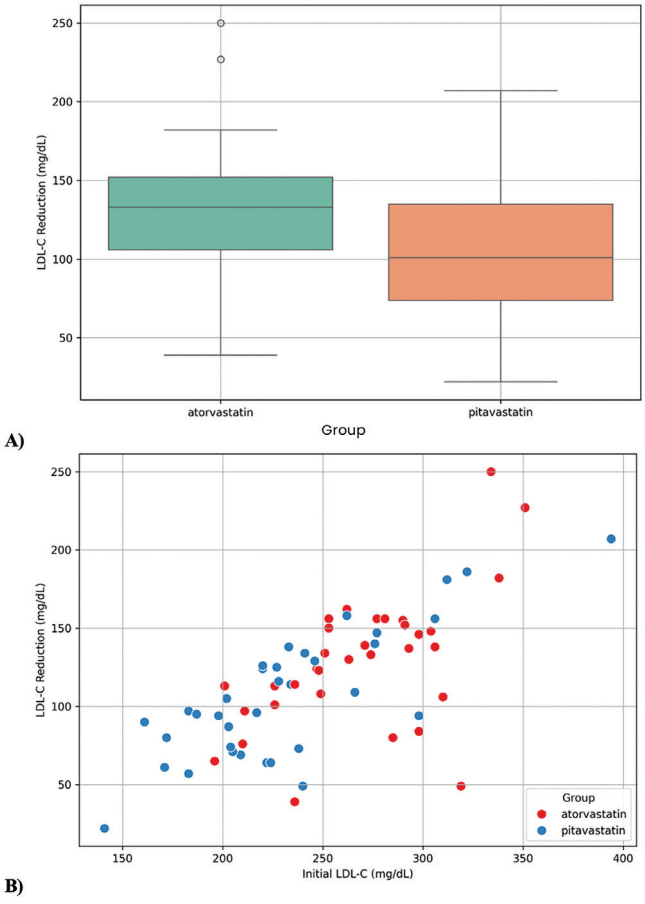

Figure 1. A) Comparison of absolute LDL-C reduction (mg/dL) between atorvastatin and pitavastatin groups. Each box represents the median and interquartile range (IQR) of LDL-C reduction. The atorvastatin group showed a greater median reduction compared to the pitavastatin group (p=0.048). **B)** Correlation between baseline LDL-C and absolute LDL-C reduction in patients receiving atorvastatin or pitavastatin. Each dot represents an individual patient. A significant positive correlation was observed in the total cohort (p=0.675, p<0.0001), as well as in both treatment subgroups (atorvastatin: p=0.502, p=0.003; pitavastatin: p=0.709, p<0.0001)
LDL-C: low density lipoprotein-cholesterol

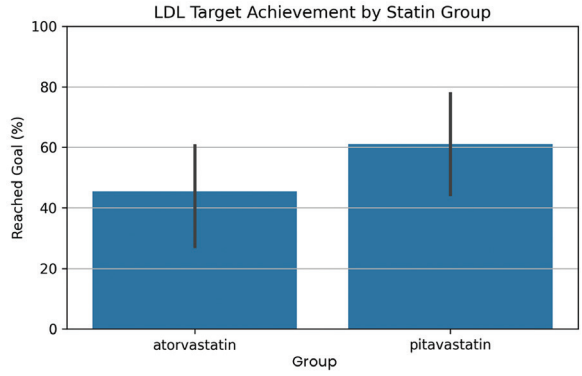

Figure 2. Comparison of LDL-C target achievement rates between atorvastatin and pitavastatin groups. The percentage of patients who reached their LDL-C goal was higher in the pitavastatin group (61.1%) compared to the atorvastatin group (45.5%), though the difference was not significant (p=0.231). Error bars represent 95% confidence intervals
LDL-C: low density lipoprotein-cholesterol

A correlation analysis was performed between initial LDL-C and the absolute LDL-C reduction following statin therapy to investigate whether baseline LDL-C levels influenced treatment response. A significant positive correlation was observed in the total cohort (p=0.675, p<0.0001), indicating that patients with higher baseline LDL-C tended to experience greater absolute reductions. This association remained significant within both treatment subgroups; for atorvastatin (p=0.502, p=0.003) and for pitavastatin (p=0.709, p<0.0001) (Figure 1B).

While a higher proportion of patients in the pitavastatin group achieved LDL-C targets compared to the atorvastatin group (61.1% vs. 45.5%), the difference was not significant (p=0.2318) (Figure 2). Regarding atorvastatin treatment, among the patients receiving 5 mg/day (n=17), 5 (29.4%) patients achieved the target. In the 10 mg/day group (n=23), 9 (39.1%) patients reached the target, while in the 20 mg/day group (n=4), only 1 (25%) patient met the target. As for pitavastatin, 11 (44%) out of 25 patients receiving 1 mg/day achieved the target. In the 2 mg/day group (n=19), 11 (57.9%) patients reached the target. In contrast, neither (0%) of the 2 patients on 4 mg/day achieved the target.

Adverse Events during Statin Therapy

Elevated creatine kinase (CK) levels were observed in five statin therapy patients (Table 3). One male patient (P1) on atorvastatin 10 mg/day developed two separate CK elevations at ages 17.5 and 18 years, with CK levels reaching 1631 U/L and 1262 U/L, respectively. Before statin initiation, his CK level was 73 U/L, which rose to 154 and 227 U/L after discontinuation. The remaining four cases occurred in patients receiving pitavastatin 2 mg/day. CK elevations ranged from 504 U/L to 5105 U/L, and all patients showed increases relative to baseline values. In these patients, pre-statin CK levels ranged from 65 to 184 U/L, while levels measured after statin discontinuation ranged from 118 to 149 U/L. Notably, the highest CK elevation (5105 U/L) occurred on pitavastatin in a male patient (P3). No adverse effects on growth or pubertal development were observed in any of the patients within the statin-treated cohort.

Molecular Results

Genetic analysis identified a wide spectrum of variants, predominantly in the *LDLR* gene, with additional variants detected in *APOB* and *PCSK9*. A total of 59 distinct *LDLR* variants were found, most of which were classified as pathogenic based on ACMG criteria. Three novel *LDLR* variants were identified, including c.1551delC (p.Lys518Serfs30)*, c.1528A>C (p.Thr510Pro), and c.1749del (p.Ser584ProfsTer81), all of which were considered likely pathogenic. A notable finding was that none of these novel detected variants were present in the gnomAD database, highlighting their rarity or novelty within the general population. In addition, novel variants were also found in *APOB* (c.9217A>G, p.Asn3073Asp and c.10238C>A, p.Thr3413Asn) and were interpreted as variants of uncertain significance (VUS).

Among the pathogenic variants in *LDLR*, c.1729T>C (p.Trp577Arg) was the most frequently observed (n=13), followed by c.1646G>A (p.Gly549Asp) (n=6), and c.1432G>A (p.Gly478Arg) and c.81C>G (p.Cys27Trp) (each n=5). Large rearrangements were also detected, consistent with structural mutations (exon 1-2 and exon 1-18 deletions). One pathogenic variant was identified in *PCSK9* (c.286C>T, p.Arg96Cys), a known mutation associated with autosomal dominant hypercholesterolemia.

The molecular diagnosis confirmed a high proportion of pathogenic or likely pathogenic variants, supporting the clinical diagnosis and justifying the initiation or continuation of LLT in this cohort (Table 4).

Discussion

This study presents an overview of the diagnostic approach and molecular characteristics of a large pediatric Turkish population diagnosed with HeFH. The findings support that initiating statin therapy at an early age is safe and effective, with no severe adverse effects observed. Despite growing awareness, published data on statin use in children and adolescents remain limited. To the best of our knowledge, this study represents the largest pediatric HeFH cohort from Türkiye to systematically investigate the etiology, clinical follow-up, and treatment course.

Screening Gaps

Only 28.2% of patients in our cohort were diagnosed through lipid screening, indicating that routine or opportunistic screening for FH in children is still underutilised. Although a large proportion of patients had a family history of hypercholesterolemia, less than half were diagnosed through family screening, and only a minority were identified through routine lipid screening. This suggests that both cascade and opportunistic lipid screening remain underutilised in the Turkish pediatric population, despite clear familial risk aligned with the previous reports (23,24). Global registry data from the EAS Familial Hypercholesterolemia Studies Collaboration showed that only 2% of participants were diagnosed before the age of 18 years (25). Furthermore, only 3.6% of individuals under 18 registered in the same cohort were from non-high-income countries (11). The observed gap highlights missed opportunities for early diagnosis and timely intervention, particularly in non-high-income countries, such as Türkiye.

Table 3. Clinical characteristics of patients with elevated CK levels under statin therapy

Number	Gender	Statin	Age at initiation of statin (y)	Event			CK before statin	CK off statin
				Statin dose	Age (y)	CK		
P1	Male	Atorvastatin	9.6	10 mg/day	17.5	1631 U/L	73 U/L	154 U/L
				10 mg/day	18	1262 U/L	73 U/L	227 U/L
P2	Female	Pitavastatin	8.6	2 mg/day	9.1	569 U/L	184 U/L	126 U/L
P3	Male	Pitavastatin	12.0	2 mg/day	14.9	5105 U/L	120 U/L	137 U/L
P4	Male	Pitavastatin	11.5	2 mg/day	15.8	504 U/L	65 U/L	149 U/L
P5	Female	Pitavastatin	5.8	2 mg/day	7.3	562 U/L	98 U/L	118 U/L

y: years, CK: creatine kinase

Table 4. Characterization of detected genetic variants by gene, DNA, and protein changes

Gene	DNA	Protein	Novelty	ACMG	n
LDLR	c.1729T>C	p.Trp577Arg	Known	Pathogenic	13
LDLR	c.1646G>A	p.Gly549Asp	Known	Pathogenic	6
LDLR	c.1432G>A	p.Gly478Arg	Known	Pathogenic	5
LDLR	c.81C>G	p.Cys27Trp	Known	Pathogenic	5
LDLR	c.1730G>C	p.Trp577Ser	Known	Pathogenic	4
LDLR	c.858C>A	p.Ser286Arg	Known	Pathogenic	4
LDLR	c.1678A>T	p.Ile560Phe	Known	Pathogenic	4
LDLR	c.1048C>T	p.Arg350*	Known	Pathogenic	3
LDLR	c.1551delC	p.Lys518Serfs*30	Novel	Likely pathogenic	3
LDLR	c.157C>T	p.Gln53*	Known	Pathogenic	3
LDLR	c.415G>A	p.Asp139Asn	Known	Pathogenic	3
LDLR	c.1061C>A	p.Asp354Gly	Known	Pathogenic	2
LDLR	c.1246C>T	p.Arg416Trp	Known	Pathogenic	2
LDLR	c.1151A>C	p.Gln384Pro	Known	Pathogenic	2
LDLR	c.1324T>C	p.Tyr442His	Known	Pathogenic	2
LDLR	c.1463T>C	p.Ile488Thr	Known	Pathogenic	2
LDLR	c.1807A>T	p.Lys603*	Known	Pathogenic	2
LDLR	c.2311+1G>A		Known	Pathogenic	2
LDLR	c.2389+5G>T		Known	VUS (PM2 PP3 BP6)	2
LDLR	c.2389G>A	p.Val797Met	Known	Pathogenic	2
LDLR	c.339_343delGTTTC	p.Phe114Leufs*14	Known	Pathogenic	2
LDLR	c.378delC	p.Phe126fs	Known	Pathogenic	2
LDLR	c.530C>G	p.Ser177Trp	Known	Likely pathogenic	2
LDLR	c.664T>C	p.Cys222Arg	Known	Pathogenic	2
LDLR	c.682G>C	p.Glu228Gln	Known	Pathogenic	2
LDLR	c.761A>C	p.Gln254Pro	Known	Pathogenic	2
LDLR	Exon 7-12 del		Known	Pathogenic	2
APOB	c.9217A>G	p.Asn3073Asp	Novel	VUS (PM2 BP4)	2
APOB	c.10238C>A	p.Thr3413Asn	Novel	VUS (PM2)	1
LDLR	c.1135T>C	p.Cys379Arg	Known	Pathogenic	1
LDLR	c.1195G>A	p.Ala399Thr	Known	Pathogenic	1
LDLR	c.1216C>T	p.Arg406Trp	Known	Pathogenic	1
LDLR	c.1285G>A	p.Val429Met	Known	Pathogenic	1
LDLR	c.1322T>A	p.Ile441Asn	Known	Pathogenic	1
LDLR	c.1478_1479delCT	p.Ser493Cysfs*42	Known	Pathogenic	1
LDLR	c.1528A>C	p.Thr510Pro	Novel	Likely pathogenic	1
LDLR	c.1567G>A	p.Val523Ile	Known	Pathogenic	1
LDLR	c.1601C>A	p.Thr534Asn	Known	Pathogenic	1
LDLR	c.1664_1674delTGGTGACTGAAinsCC	p.Leu555_Glu558delinsPro	Novel	Likely pathogenic	1
LDLR	c.1720C>T	p.Arg574Cys	Known	Likely pathogenic	1
LDLR	c.1747C>T	p.His583Tyr	Known	Pathogenic	1
LDLR	c.1749del	p.Ser584ProfsTer81	Novel	Likely pathogenic	1

Table 4. Continued

Gene	DNA	Protein	Novelty	ACMG	n
LDLR	c.1775G>A	p.Gly592Glu	Known	Pathogenic	1
LDLR	c.1823C>T	p.Pro608Leu	Known	Pathogenic	1
LDLR	c.1898G>A	p.Arg633His	Known	Pathogenic	1
LDLR	c.1946C>T	p.Pro649Leu	Known	Likely pathogenic	1
LDLR	c.2093G>T	p.Cys698Phe	Known	Pathogenic	1
LDLR	c.268G>A	p.Asp90Asn	Known	Pathogenic	1
LDLR	c.40dupT	p.Leu14Phefs*38	Known	Pathogenic	1
LDLR	c.41dup	p.Leu14fs	Known	Pathogenic	1
LDLR	c.460C>T	p.Gln154Ter	Known	Pathogenic	1
LDLR	c.502delG	p.Asp168Thrfs*38	Novel	Likely pathogenic	1
LDLR	c.506delA	p.Asn169Thrfs*37	Novel	Likely pathogenic	1
LDLR	c.694+2T>C		Known	Pathogenic	1
LDLR	c.763T>G	p.Cys255Gly	Known	Pathogenic	1
LDLR	c.796G>A	p.Asp139Asn	Known	Pathogenic	1
LDLR	c.846C>A	p.Phe282Leu	Known	Pathogenic	1
LDLR	c.859G>A	p.Gly287Ser	Known	Likely pathogenic	1
LDLR	c.888C>A	p.Cys296Ter	Known	Pathogenic	1
APOB	c.9068C>T	p.Ala3023Val	Novel	VUS (PM2)	1
LDLR	c.977C>G	p.Ser326Cys	Known	Pathogenic	1
LDLR	c.97C>T	p.Gln33*	Known	Pathogenic	1
LDLR	Exon 1-2 del		Known	Pathogenic	1
LDLR	Exon 1-18 del		Known	Pathogenic	1
PCSK9	c.286C>T	p.Arg96Cys	Known	Pathogenic	1

ACMG: American Journal of Medical Genetics, VUS: variant unknown significance

Parental Treatment Refusal

In addition to the gaps in early diagnosis, our study also identified barriers to treatment initiation. In 16.1% of cases within the study cohort, statin therapy was recommended, but the parents refused to initiate statin treatment in their children. Unfortunately, the retrospective study design did not permit investigation of the reasons behind parental refusal of statin therapy. However, numerous previous studies have explored and highlighted parental concerns regarding the use of statins in children. These studies consistently report that parents' concerns primarily revolve around the potential side effects and long-term safety of statin therapy, the perceived medicalization of childhood, and the uncertainty regarding the necessity of early treatment initiation (26,27,28). Despite the availability of long-term data demonstrating the safety of statin therapy in pediatric populations, parental hesitation and concerns remain a persistent barrier to treatment initiation. A nationwide study based on electronic health records reported LLT coverage as low as 1.5% among Turkish pediatric patients (12).

One of the strengths of this study was the relatively long and carefully monitored follow-up period. The median age at diagnosis was 7.9 years, with statin therapy initiated at a median age of 11.3 years and the last follow-up recorded at 13.0 years. These findings highlight the continuity of care and the structured long-term monitoring of the cohort, which allowed for a more comprehensive assessment of treatment response and disease progression. Statin therapy was introduced in cases where dietary and lifestyle interventions did not lead to sufficient lipid control. However, due to limitations in the consistency and completeness of lifestyle-related data collected from families and patients, these findings were not included in the analysis.

A comparative analysis of atorvastatin and pitavastatin was performed to evaluate differences in lipid-lowering efficacy and target attainment. The atorvastatin group showed a significantly greater median absolute reduction in LDL-C levels. In contrast, a higher proportion of patients in the pitavastatin group achieved their LDL-C targets, although this difference was not significant. This trend may suggest a difference in pharmacologic response rather than adherence, as no significant differences

were observed in adherence or the need for dose adjustments. Although not significant, the higher rate of target attainment in the pitavastatin group may still be clinically relevant, as even modest improvements in LDL-C goal achievement during childhood could contribute to reduced lifetime cardiovascular risk. This observation warrants confirmation in larger, prospective pediatric studies.

Differences in LDL-C reduction between the two statins may reflect their pharmacodynamic profiles, baseline LDL-C levels, or differential metabolism in pediatric patients. Further prospective studies are warranted to confirm these trends and inform statin selection.

A correlation analysis was performed to further investigate factors influencing treatment response between baseline LDL-C levels and the absolute LDL-C reduction. A significant positive correlation was observed across the total cohort indicating that higher initial LDL-C levels were associated with greater absolute reductions in both treatment groups. Our findings suggest that baseline LDL-C may be a key determinant of statin response, regardless of the statin type used. Both atorvastatin and pitavastatin have efficacy in the treatment of FH in children (14,15,18,29). In addition, it has been consistently reported that higher baseline LDL-C levels are associated with greater absolute reductions, indicating that starting lipid levels may significantly influence the therapeutic response (15).

A total of six adverse events were observed in five patients during statin therapy, with one patient experiencing two separate episodes. All events were muscle-related and asymptomatic, consistent with previous reports (30,31). In each case, statin treatment was temporarily interrupted and re-initiated after CK levels normalized. Although the literature suggests that muscular symptoms, when present, typically resolve spontaneously without requiring discontinuation of therapy (30,31), treatment was paused in our cases due to parental concerns. During follow-up visits, adverse events should be actively assessed, and even in asymptomatic cases, organ-specific markers should be monitored to detect subclinical effects and guide clinical decision-making.

In this cohort, the majority of molecular diagnoses were associated with pathogenic or likely pathogenic variants in the *LDLR* gene, consistent with previous studies identifying *LDLR* as the most commonly affected gene in FH 2 and in Turkish patients (32). The high frequency of c.1729T>C (p.Trp577Arg), c.1646G>A (p.Gly549Asp), and c.1432G>A (p.Gly478Arg) variants aligns with earlier findings from Turkish (32,33,34,35) and Mediterranean populations (36), supporting the notion of population-specific founder mutations.

Importantly, three novel *LDLR* variants were identified, all predicted to be pathogenic, expanding the mutational spectrum of FH and contributing to the understanding of genetic heterogeneity in this condition. Detecting structural rearrangements, such as exon deletions, further highlights the need for comprehensive molecular testing that includes sequencing and Multiplex Ligation-dependent Probe Amplification. Although *APOB* and *PCSK9* variants were less frequent, their identification highlights the importance of including these genes in genetic testing panels, especially for cases with a negative or inconclusive *LDLR* result. The two novel *APOB* variants, currently classified as VUS, warrant functional validation studies to clarify their role in LDL-C metabolism.

Overall, the high diagnostic yield of molecular testing in this study reinforces the utility of genetic analysis in guiding clinical decision-making, cascade screening, and risk stratification in pediatric FH populations.

Study Limitations

This retrospective study design may have limited the completeness and consistency of clinical and lifestyle data. Treatment adherence was based on self-reports and could not be objectively verified. Moreover, functional validation of the novel genetic variants identified in this study was not performed, and therefore their pathogenicity could not be conclusively established. This gap should be addressed in future studies using *in vitro* or *in vivo* assays to confirm variant effects. The high rate of loss to follow-up may have introduced bias in treatment outcome estimates and limits the generalizability of our findings. In addition, long-term follow-up data into adulthood were lacking, underscoring the need for future studies to evaluate treatment continuity and cardiovascular outcomes beyond childhood.

Conclusion

This study presented the diagnostic, genetic, and therapeutic characteristics of the first and largest pediatric HeFH cohort reported from Türkiye. Despite confirmed diagnoses, substantial gaps persist in early detection, treatment acceptance, and long-term follow-up. Both atorvastatin and pitavastatin were safe and effective, underscoring the importance of national screening, family education, and sustained care to reduce lifelong cardiovascular risk.

Ethics

Ethics Committee Approval: The study was approved by the Medical Research Ethics Committee of Ege University Faculty of Medicine (approval number: E.2371714, date: 28.03.2025).

Informed Consent: Our research adopted a retrospective cohort design, focusing on patients under 18 years of age.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Havva Yazıcı, Esra Er, Fehime Erdem, Ayşe Yüksel Yanbolu, Sakina Mammadova, Sedef Alpdoğan, Merve Yoldaş Çelik, Concept: Havva Yazıcı, Design: Havva Yazıcı, Ebru Canda, Data Collection or Processing: Yasemin Atik Altınok, Mahmut Çoker, Analysis or Interpretation: Ayça Aykut, Haluk Akın, Literature Search: Ebru Canda, Sema Kalkan Uçar, Writing: Havva Yazıcı, Ebru Canda.

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