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Disorders of Lipid Metabolismin Children with Clinical Phenotypic Features Based on Second Generation Sequencing

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ABSTRACT This study aimed to explore pathogenic genes associated with pediatric dyslipidemia using second-generation sequencing and analyse their correlation with clinical phenotypes. The researchers retrospectively analysed clinical and genetic data from 20 pediatric patients. Skin xanthoma (60%) and hypercholesterolemia (55%) were common presentations. Second-generation sequencing targeting lipid metabolism genes was performed. Causative mutations were identified in 14 of 18 tested patients, involving genes such as LDLR, LPL, ABCG5, ABCA1, and HFE2. Distinct genotype-phenotype correlations were observed, for example, ABCG5, HFE2, LDLR, and ABCA1 mutations were associated with xanthomas, while LPL and LDLR mutations were linked to hypertriglyceridemia and hypercholesterolemia patterns, respectively. These findings suggest that pediatric dyslipidemia presents with diverse clinical phenotypes that are strongly associated with mutations in specific genes. Molecular genetic diagnosis based on sequencing significantly improves clinical assessment and deepens the understanding of these disorders, offering valuable guidance for early detection and precision medicine.

INTRODUCTION

Disorders of lipid metabolism, also known as dyslipidemias, are a group of disorders characterised by dysregulation of lipid and lipoprotein metabolism, which may be caused by heredity or a variety of acquired factors. These disorders are asymptomatic in the early stages and are occasionally detected in blood tests (Wang et al. 2022; Wazir et al. 2023). Disorders of lipid metabolism can be medically classified into two main groups according to their causes, that is, primary and secondary. In terms of presentation morphology, they can be subdivided into hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, and low HDL (Yu et al. 2024). Although lipid concentrations have a limited range of variability in normal individuals, environmental and genetic factors may lead to various abnormalities in lipid levels. Various studies and epidemiological investigations have shown (Yi et al. 2023; Foster 2024; Burger et al. 2024) that it has been increasingly recognised that elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and non-HDL cholesterol, as well as declining levels of HDL cholesterol, are key indicators of increased risk of cardiovascular disease. The impact of abnormal lipid metabolism in childhood, as a core component of metabolic diseases in children, cannot be ignored, especially as it is of particular importance as a major potential risk factor for early-onset heart disease (Yu et al. 2024). There are many types of dyslipidemia, each with its own unique clinical manifestations, and most patients do not have obvious symptoms in the early stages and need to be recognised by blood tests (Jin et al. 2023). As the disease progresses, clinical manifestations such as cutaneous xanthomas, corneal arches, and pancreatitis may occur. Although the age of onset of disorders of lipid metabolism varies, cutaneous xanthomas often appear as the first symptom (Wang et al. 2023). Prevention and treatment of disorders of lipid metabolism require consideration of the interaction of multiple genetic and environmental factors. Genetic polymorphisms and their interaction with the environment play an important role in the development of dyslipidemia. Studies have shown (Yan et al. 2022) that there is a genetic association between polymorphisms in the LPL gene and hyperlipidemia and coronary heart

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disease. Improvement of lipid levels by physical activity showed differences in different genotypes of the population, suggesting that the influence of environmental factors on lipid levels is also influenced by genetic background. Disorders of lipid metabolism not only affect aesthetics, but may also lead to chronic diseases such as fatty liver and cardiovascular disease. For patients who have developed severe cardiovascular disease, current medications are difficult to effectively reverse the condition. Studies have shown that patients with familial hypercholesterolemia (FH) are difficult to treat, and the risk of coronary events within one year of hospital discharge is twice as high in patients with FH as in those without FH. This highlights the critical importance of genetic factors in the disease process. Therefore, early identification and screening of patients with high risk and dyslipidemia is essential for the prevention and treatment of dyslipidemia (Yan et al. 2024). Next generation sequencing (NGS) technology has obvious advantages in the molecular diagnosis of childhood inborn disorders of metabolism, providing a new direction for diagnosis and treatment (Ozalp and Anlas 2024). However, pediatric dyslipidemia exhibits considerable heterogeneity, with clinical phenotypes ranging from xanthomas to severe hyperlipidemia, while genotype-phenotype correlations remain inadequately characterised. Previous studies have often been constrained by limited sample sizes or the absence of molecular confirmation, highlighting the need for investigations that integrate genetic sequencing with clinical features to enhance diagnostic accuracy and enable earlier intervention.

Objectives

This study aimed to investigate pathogenic gene mutations associated with pediatric dyslipidemia using second-generation sequencing and to analyse their correlations with clinical phenotypic features, thereby providing evidence for accurate diagnosis and early management.

MATERIAL AND METHODS

General Data

The researchers retrospectively analysed the clinical data and genetic test results of 20 cases of children with dyslipidemia admitted to the hospital from July 2022 to September 2023, focusing on the correlation between disease-causing genes related to lipid metabolism disorders in children and clinical phenotypic features. In collecting the initial medical data from the patients, the researchers focused on the following information, that is, the patient's medical record number, name, gender, age, emergency contact person and their contact information, and the time of the initial consultation. In addition, the researchers also recorded in detail the patient's lifestyle habits including diet, exercise, and other daily activities, the family medical history (for example, a family history of sudden death, cardiac disease, diabetes mellitus, hypertension, etc.), and the corresponding treatments, and the blood fat level test results. To ensure that the patient receives continuous attention and care, a liaison mechanism of regular outpatient reviews and telephone callbacks is established to keep abreast of changes in the patient's condition and response to treatment, focusing on the following indicators of the appearance or change of yellow tumors of the skin, and the presence of other members of the family with similar medical conditions. Fasting lipid levels are tracked in real time to monitor the child's low-fat diet. Comparison of clinical manifestations between hypercholesterolemic and hypertriglyceridemic patients. The study was reviewed and approved by the Ethics Committee of the hospital and the children and their families were informed about the experiment and signed an informed consent form.

Inclusion and Exclusion Criteria

Inclusion Criteria

According to the 2007 Expert Consensus on the Classification of Dyslipidemia in Populations (Zhou et al., 2024), dyslipidemia was defined as follows: triglyceride levels ?1.70 mmol/L (150 mg/dL) were categorized as hypertriglyceridemia, total cholesterol levels ?5.18 mmol/L (200 mg/dL) as hypercholesterolemia, low-density lipoprotein cholesterol (LDL-C) levels ?3.17 mmol/L (130 mg/dL) as hyper-LDL-Cemia, and high-density lipoprotein cholesterol (HDL-C) levels <1.04 mmol/L (40 mg/dL) as hypo-HDL-Cemia. Cut-off values were established based on results from at least two independent tests to ensure diagnostic reliability.

Exclusion Criteria

The exclusion criteria included any secondary lipid metabolism disorder caused by other diseases such as diabetes, hypertension, obesity, renal or hepatic diseases, and other factors that may affect the lipid level, such as dietary habits, physical activity, psychological stress and emotional changes.

Detection of Blood Lipids and Other Biochemicals

In the course of the study, all participants had venous blood samples collected in the morning on an empty stomach after fasting for 8 hours at night. Plasma was separated and sent to the hospital testing centre for testing. Total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C) and high density lipoprotein (HDL-) were measured by professional technicians using a fully automated biochemistry analyser according to established standard procedures. The levels of lipid components such as triglyceride (TG), low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C) were measured. To ensure the quality of the tests, blood collection is carried out by senior nurses, while biochemical analysis is performed by certified laboratory specialists, and the entire testing process strictly follows the laboratory's standardised operating procedures.

Detection of Genes

2 ml of peripheral venous blood was collected using a vacuum blood collection tube with anticoagulant with EDTA and stored at -80°C. The sample is sent to Goldcorp for second-generation sequencing (Panel) of specific genes, which focuses on the detection of abnormalities in lipid metabolism. DNA is extracted from the blood samples using the "column method", and the Panel includes the exon regions of 21 genes, including LDLR, LDLRAPI, PCSK9, ABCG5, ABCG8, ABCA1, LIPA, APOB, LPL, APOA5, APOA1, LIPI, USF1, APOE, LIPI, USF1, APOE, and LIPI, USF1, APOE, LIPC, LCAT, HAMP, HFE, HFE2, SLC40A1, and TFR2. The sequences of these genes were comparatively analysed. Second-generation sequencing revealed potential gene variants, which were validated using first-generation DNA sequencing in the affected children.

Statistical Analysis

SPSS22.0 software was used for statistical analysis, and in data processing, the measurement data such as blood biochemical indexes were expressed in the form of ($x \pm s$), and t-test was used to compare the blood biochemical indexes and the age at diagnosis between the two groups. The difference was considered statistically significant at $P<0.05$.

RESULTS

Clinical Data of Children

Of the 20 patients, 11 (55%) were male and 9 (45%) were female. The age distribution of the cohort comprised 8 (40%) patients were aged 0-1 years, 2 (10%) were aged 2-5 years, 6 (30%) were aged 6-9 years, and 4 (20%) were aged 10-13 years. Of the initial symptoms, 12 (60%) patients presented with skin xanthomas, and 7 (35%) exhibited changes in the colour of the blood. Regarding clinical manifestations, 11 (55%) patients were diagnosed with hypercholesterolemia, 8 (40%) with mixed hyperlipidemia, and 1 (5%) with hypertriglyceridemia. These findings demonstrate the heterogeneity of clinical presentations in pediatric dyslipidemia. (See Table 1).

Comparison of Results Between Hypercholesterolemia and Mixed Hyperlipidemia Groups

The patients were divided into three groups, wherein 11 (55%) had hypercholesterolemia, 1 (5%) had hypertriglyceridemia, and 8 (40%) had mixed hyperlipidemia. The triglyceride (TG) levels in the mixed hyperlipidemia group were significantly higher than those in the hypercholesterolemia group ($P<0.05$), suggesting that dyslipidemia with mixed lipid abnormalities is associated with more severe metabolic disruption. In contrast, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels did not show statistically significant differences between the groups ($P>0.05$). This suggests that while TG is a prominent marker in mixed hyperlipidemia, the other lipid components may remain within similar ranges across the different dyslipidemia

Table 1: Comparison of clinical data of patients (n (%))

Particulars	*Number*		*%*
Gender	Male	11	55.00
	Female	9	45.00
Age	0-1 years old	8	40.00
	2-5 years old	2	10.00
	6-9 years old	6	30.00
	10-13 years old	4	20.00
Initial Symptom	xanthoma of the skin	12	60.00
	blood colour change	7	35.00
Clinical Performance	hypercholesterolemia	11	55.00
	mixed hyperlipidemia	8	40.00
	hypertriglyceridemia	1	5.00

subtypes. The lipid profile comparisons between groups are presented in Table 2.

Sequencing Results in Children

Two patients (16 and 19) did not undergo second-generation sequencing due to parental opposition. For the remaining 18 children, second-generation sequencing targeting lipid metabolism genes was performed, and the mutated loci were validated using first-generation sequencing. Causative mutations were identified in 14 patients (77.78%), including mutations in key lipid metabolism genes: c.628G>A (Val210Ser) and c.356C>T (Thr119Ile) in the LPL gene (patients 9 and 11, respectively), c.1058C>T (Pro353Leu) and c.685C>T (His685Asp) mutations in the LDLR gene (patients 3 and 16), c.854G>A (Cys285Tyr) and c.452C>T (Ser151Leu) mutations in the HFE2 gene (patients 13 and 10), and mutations in the ABCG5 gene in patients 1, 4, 5, and 12. Furthermore, patients 2, 7, 14, and 18 had variants in the ABCA1 gene, including two mutations in patient 2: c.2002C>T (Leu668Phe) and c.3121C>G (Leu1041Val). No pathogenic mutations were found in five patients (6, 8, 15, 17 and 20). This data highlights the significant role of genetic mutations in the pathogenesis of dyslipidemia, particularly in the ABCG5, LPL, LDLR, HFE2, and ABCA1 genes, which are critical for lipid metabolism regulation (See Table 3).

Table 2: Comparison of lipid test results between the two groups of patients

Group	*N*	*TC(mmol/l)*	*TG(mmol/l)*	*LDL-C(mmol/l)*	*HDL-C(mmol/l)*
Hypercholesterolemia group	11	13.64±3.19	1.07±0.42	11.23±4.20	1.73±0.62
Mixed hyperlipidemia group	8	8.75±2.68	21.85±15.33	10.28±3.54	1.92±0.12
t		0.630	4.318	0.510	0.849
P		0.538	0.001	0.617	0.408

Table 3: Results of gene sequencing variants in 14 children with lipid metabolism disorders

Serial number	*Mutant gene*	*Mutant*	*Placement*	*cDNA*	*Proteins*
1	*ABCG5*	nonsense mutation	Exon3	c.659 C>G	p.(Tyr 220*)
10	*HFE2*	missense mutation	Exon4	c.452 C>T	p.(Ser 151 Leu)
13	*HFE2*	missense mutation	Exon3	c.854G>A	p.(Cys 285Tyr)
9	*LPL*	missense mutation	Exon6	c.628G>A	p.(Val 210Ser)
11	*LPL*	missense mutation	Exon5	c.356C>T	p.(Thr 119Ile)
3	*LDLR*	missense mutation	Exon12	c.1058C>T	p.(Pro353Leu)
16	*LDLR*	missense mutation	Exon10	c.685C>T	p.(His685Asp)
4	*ABCG5*	missense mutation	Exon8	c.1166G>A	p.(Arg389His)
2	*ABCA1*	missense mutation	Exon29	c.2002C>T	p.(Leu 668Phe)
		missense mutation	Exon16	c.3121C>G	p.(Leu1041Val)
5	*ABCG5*	missense mutation	Exon5	c.749C>T	p.(Ser250Phe)
12	*ABCG5*	missense mutation	Exon6	c.298C>T	p.(Pro 100Leu)
7	*ABCA1*	missense mutation	Exon18	c.265C>G	p.(Leu 89 Val)
18	*ABCA1*	missense mutation	Exon14	c.965G>A	p.(Arg322 His)
14	*ABCA1*	missense mutation	Exon6	c.458G>A	p.(Ser 153Lys)

Correlation Analysis of Dyslipidemia-related Pathogenic Genes and Clinical Phenotypic Features

Among the 18 children, 14 (77.78%) were found to have mutations in genes associated with lipid metabolism disorders, specifically in ABCG5, HFE2, LPL, LDLR, and ABCA1. Genotype-phenotype correlations were observed as follows, wherein mutations in ABCG5 and HFE2 were associated with skin xanthomas, and HFE2 mutations were also linked to high cholesterol levels. ABCA1 mutations were characterised by elevated sitosterol levels, while LPL and LDLR mutations were associated with mixed lipid profiles, including type I and type II hyperlipidemia. These findings underscore the diversity of clinical manifestations in pediatric dyslipidemia and the importance of genetic testing in diagnosing specific lipid metabolism disorders. The correlation between gene mutations and clinical phenotypes provides a better understanding of the underlying molecular mechanisms and could inform personalised treatment strategies for affected children (See Table 4).

DISCUSSION

Disorders of lipid metabolism in children, including conditions like hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipidemia, are multifactorial diseases influenced by both genetic and environmental factors. In this study, the researchers identified significant genetic mutations in genes such as ABCG5, HFE2, LPL, LDLR, and ABCA1, which were associated with various clinical phenotypic features, including skin xanthomas and elevated cholesterol levels.

The findings of this study corroborate prior research that has established a link between ABCG5 mutations and sitosterolemia, a disorder characterised by the accumulation of plant sterols (Nghiem-Rao and Patel 2013; Zein et al. 2019; Jiang et al. 2023). Similarly, the identified LDLR mutations (for example, p.Pro353Leu) are well-documented to cause familial hypercholesterolemia (FH) and are strongly associated with severe hypercholesterolemia and xanthoma formation (Kamar et al. 2021; Harada-Shiba et al. 2023). Furthermore, the researchers' observations regarding HFE2 and ABCA1 mutations align with their known biological roles in iron metabolism/cholesterol regulation and cellular cholesterol efflux, respectively, suggesting their potential contribution to the dyslipidemic phenotypes observed in the cohort (Oram 2000; Piperno 2020; Hernández et al. 2021; Barbosa-Gouveia et al. 2023).

The use of second-generation sequencing technology in this study enabled the identification of multiple pathogenic genetic variants, offering a more comprehensive molecular diagnosis compared to traditional methods. This approach has been increasingly recognised for its utility in diagnosing inherited metabolic disorders in pediatric populations, where symptoms may be subtle or absent in the early stages. Despite these insights, the study has several limitations. The relatively small sample size from a single centre may limit the generalisability of the findings. Moreover, the retrospective design precluded the systematic collection of data on environmental influences and lifestyle habits, which are known modifiers of lipid phenotypes. Therefore, the observed genotype-phenotype correlations should be interpreted with caution.

Table 4: Correlation analysis between pathogenic genes associated with lipid metabolism disorders and clinical phenotypic features

Number of people	*Mutant gene*	*Xanthoma*	*Typing*
2	*ABCG5*	Yes	type I/mixed
2	*ABCG5*	Yes	anabolic steroids
2	*HFE2*	Yes	high cholesterol
2	*LPL*	No	type I/mixed
2	*LDLR*	Yes	type II/mixed
4	*ABCA1*	Yes	anabolic steroids
2	negativity	No	high cholesterol
1	negativity	No	type I/mixed
1	negativity	No	type II/mixed
1	untested	No	high cholesterol
1	untested	No	hypertriglyceridemia

Future studies should address these limitations by expanding the sample size, including diverse populations, and incorporating both genetic and environmental factors to offer a more holistic understanding of lipid metabolism disorders in children. Additionally, further research into the mechanisms by which these genetic mutations influence lipid metabolism will be crucial in developing targeted therapies and improving early diagnosis.

CONCLUSION

In conclusion, this study identified a spectrum of pathogenic mutations in genes such as ABCG5, HFE2, LPL, LDLR, and ABCA1 in a cohort of Chinese children with dyslipidemia, which were associated with specific clinical features. These findings provide a better understanding of the genetic basis of these disorders and emphasise the importance of genetic testing in improving clinical diagnosis and treatment strategies for pediatric patients. The findings underscore the clinical utility of second-generation sequencing in achieving a precise molecular diagnosis for complex pediatric dyslipidemias, which is a prerequisite for early intervention and personalised management.

RECOMMENDATIONS

Based on the findings, the researchers recommend that next-generation sequencing should be considered as a part of the standard diagnostic workflow for children with suspected inherited dyslipidemia, particularly those with early-onset symptoms or a family history. Early identification of genetic mutations can lead to more accurate diagnoses and enable the development of personalised treatment strategies. Additionally, future studies should expand the sample size and explore the role of environmental factors in the development of these disorders to provide a more comprehensive understanding and improve patient outcomes.

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IRB APPROVAL

The study was approved by the Ethics Committee of The Fourth Affiliated Hospital of Nanjing Medical University.

ETHICAL STATEMENT

The authors declare no conflicts of interest.

CONSENT FOR PUBLICATION

Manuscript is approved by all authors for publication.

AUTHOR CONTRIBUTIONS

Weiyuan Wang was responsible for the study conceptualisation, data collection, formal analysis, investigation, and writing of the original draft. Tingting Yu supervised the project, provided resources, administered the project, validated the results, and reviewed and edited the manuscript.

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