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Spectrum of LDLR gene variants in patients with familial hypercholesterolaemia

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Abstract

Background: Familial Hypercholesterolaemia (FH) is an inherited disorder characterised by lifelong elevation of low-density lipoprotein cholesterol and increased risk of premature atherosclerotic cardiovascular disease. Pathogenic variants in the LDLR gene account for most genetically confirmed cases, but the spectrum of variants and their relationship with clinical phenotype vary considerably. **Objective:** This study characterised the spectrum of LDLR variants in patients with clinically diagnosed FH and examined associations between variant functional class and disease phenotype. **Methods:** In 180 adults with clinically diagnosed FH, LDLR was analysed by sequencing of coding exons and flanking intronic regions with additional assessment for large rearrangements. Detected variants were classified according to variant type, receptor domain, functional class, and pathogenicity and were related to clinical diagnostic certainty and phenotype. **Results:** An LDLR variant was detected in 120 of 180 patients (66.7%). Among the detected variants, 69 (57.5%) were classified as pathogenic, 29 (24.2%) as likely pathogenic, and 22 (18.3%) as variants of uncertain significance. Missense variants predominated (55.8%), while 40 (33.3%) were classified as null and 80 (66.7%) as defective. Null variants were associated with higher untreated LDL cholesterol and greater frequencies of tendon xanthomas and premature coronary disease than defective variants. **Conclusion:** LDLR variant analysis identified a genetic variant in two-thirds of clinically diagnosed patients, with detection increasing according to clinical diagnostic certainty. Functional variant class was associated with differences in biochemical and clinical phenotype, supporting the complementary role of molecular characterisation in familial hypercholesterolaemia.

Keywords: *Familial hypercholesterolaemia, LDLR gene, Variant spectrum, Null variant, Genotype-phenotype correlation, LDL cholesterol, Genetic testing, Dutch Lipid Clinic Network*

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1. Introduction

Familial hypercholesterolaemia is among the commonest of the monogenic disorders, affecting roughly one

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person in three hundred, and it is characterised by a lifelong elevation of low-density lipoprotein cholesterol that, if untreated, produces atherosclerotic cardiovascular disease decades earlier than in the general population (Nordestgaard *et al.*, 2013; Defesche *et al.*, 2017; Beheshti *et al.*, 2020). The disorder is inherited in an autosomal dominant fashion, and although it is common and its treatment effective, it remains substantially underdiagnosed, so that most affected individuals are identified late, after the vascular damage has begun.

The molecular basis of the disorder is well understood. In the great majority of cases it arises from a variant in the LDLR gene, which encodes the low-density lipoprotein receptor, the cell-surface protein that clears low-density lipoprotein from the circulation by receptor-mediated endocytosis (Goldstein and Brown, 2009; Hobbs *et al.*, 1992). A variant that impairs the number or the function of these receptors reduces the clearance of low-density lipoprotein, and the cholesterol accumulates in the blood. The receptor is a modular protein, its polypeptide folded into distinct domains, a ligand-binding domain that grips the lipoprotein, an epidermal-growth-factor-precursor homology domain that governs the release of the ligand and the recycling of the receptor, and further domains that anchor and traffic it, and a variant may fall in any of these and disturb a different step of the receptor's work (Galicia-Garcia *et al.*, 2020).

The variants of the LDLR gene are correspondingly numerous and diverse, more than two thousand having been catalogued, and they differ in kind (Usifo *et al.*, 2012; Leigh *et al.*, 2017). Some are missense variants that substitute a single amino acid and leave a receptor that is made but works imperfectly; others are nonsense, frameshift or large rearrangement variants that abolish the production of a functional receptor altogether; and still others disturb the splicing of the messenger. On the basis of their effect on the receptor the variants are grouped into functional classes, the distinction of greatest clinical weight being that between the null variants, which yield no functional receptor, and the defective variants, which yield a receptor of reduced activity (Benito-Vicente *et al.*, 2018).

This distinction matters because it relates to the severity of the disease. Patients carrying a null variant, with no functional receptor from that allele, tend to have higher cholesterol and a greater burden of atherosclerosis than those carrying a defective variant, and the identification of the variant therefore carries prognostic as well as diagnostic information (Sanchez-Hernandez *et al.*, 2016; Guo *et al.*, 2022; Trinder *et al.*, 2019). The confirmation of a pathogenic variant also secures a diagnosis that clinical criteria alone leave uncertain, and it is the key that permits the cascade screening of relatives, the most efficient means of finding the many undiagnosed (Sturm *et al.*, 2018; Iacocca and Hegele, 2017; Wald *et al.*, 2016). Characterising which variants are present, and how they distribute across the receptor and its functional classes, is thus of direct clinical value.

The present study was undertaken to characterise the spectrum of LDLR variants in a cohort of patients with a clinical diagnosis of familial hypercholesterolaemia. Its objectives were to determine the yield of genetic analysis and how it varied with the certainty of the clinical diagnosis; to describe the spectrum of the variants detected, by their type, their position within the receptor and its domains, their functional class and their pathogenicity; and to relate the functional class of the variant, the distinction between null and defective, to the biochemical and clinical severity of the disease.

2. Materials and methods

2.1. Participants

This cross-sectional molecular study examined 180 unrelated adults with a clinical diagnosis of familial hypercholesterolaemia. Reporting follows the recommendations for observational studies (Vandenbroucke *et al.*, 2007). The clinical diagnosis was made and graded by the Dutch Lipid Clinic Network criteria, which combine the personal and family history of hypercholesterolaemia and premature vascular disease, the physical signs, and the untreated low-density lipoprotein cholesterol into a score that classifies the diagnosis as definite, probable or possible. Patients with a secondary cause of hypercholesterolaemia were excluded.

2.2. Genetic analysis and variant classification

Genomic DNA was extracted from a peripheral blood sample, and the coding exons and the flanking intronic regions of the LDLR gene were analysed by sequencing, with a method for the detection of the large rearrangements that sequencing does not capture. The variants detected were characterised in four respects. Variants were grouped into functional classes according to their predicted or established effect on LDLR

function. Variants expected to result in loss of receptor production or function, including qualifying nonsense, frameshift, and large-rearrangement variants, were classified as null, whereas variants associated with residual receptor activity, predominantly missense variants, were classified as defective. Where available, published functional evidence was considered during classification (Richards *et al.*, 2015; Chora *et al.*, 2022).

2.3. Statistical analysis

Categorical variables are summarised as counts and percentages and continuous variables as mean with standard deviation. The yield of variant detection was compared across the categories of the clinical diagnosis by the chi-square test with a test for trend. The biochemical and clinical features were compared between the carriers of null and defective variants by the t test for the low-density lipoprotein cholesterol and by the chi-square or Fisher exact test for the clinical signs. A probability below 0.05 was accepted as significant.

2.4. Ethical considerations

The study was approved by the Institutional Ethics Committee before commencement and was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

3.1. Cohort and gene detection yield

The study included 180 patients with clinically diagnosed familial hypercholesterolaemia, with a mean age of 43 ± 13 years. According to the Dutch Lipid Clinic Network criteria, 59 patients (32.8%) had definite FH, 57 (31.7%) had probable FH, and 64 (35.6%) had possible FH. An LDLR variant was detected in 120 patients (66.7%). The detection yield increased significantly with clinical diagnostic certainty, from 34% among patients with possible FH to 79% among those with probable FH and 90% among those with definite FH. Among the 120 detected variants, 69 (57.5%) were classified as pathogenic, 29 (24.2%) as likely pathogenic, and 22 (18.3%) as variants of uncertain significance.

Table 1: Characteristics of the 180 patients with clinically diagnosed familial hypercholesterolaemia

Characteristic	n (%)/Mean ± SD
Demographic characteristics	
Age (years)	43 ± 13
Female	102 (56.7)
Clinical diagnostic category	
Definite FH (DLCN >8)	59 (32.8)
Probable FH (DLCN 6–8)	57 (31.7)
Possible FH (DLCN 3–5)	64 (35.6)
Clinical features	
Tendon xanthomas	53 (29.4)
Corneal arcus	39 (21.7)
Premature coronary disease	43 (23.9)
Biochemical characteristic	
Untreated LDL-C (mmol/L)	7.7 ± 1.4
Molecular finding	
LDLR variant detected	120 (66.7)

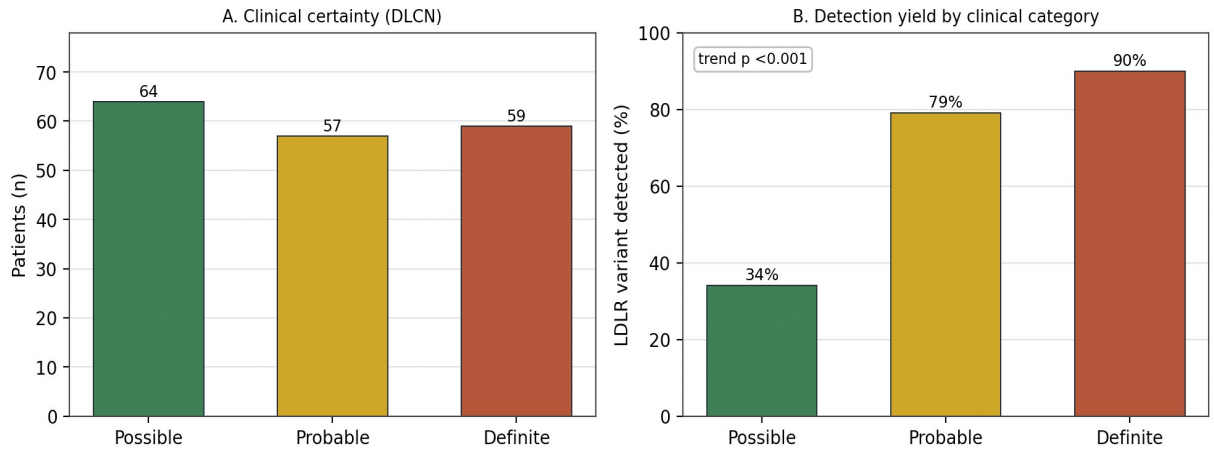


Figure 1: Clinical diagnostic categories (A) and LDLR variant detection yield by category (B)

3.2. Spectrum of LDLR variants

Among the 120 detected LDLR variants, missense variants were the most common, accounting for 67 (55.8%), followed by nonsense variants (15, 12.5%), splice-site variants (12, 10.0%), frameshift variants (11, 9.2%), large rearrangements (9, 7.5%), and in-frame insertions or deletions (6, 5.0%). Based on functional classification, 40 variants (33.3%) were classified as null and 80 (66.7%) as defective. The variants were distributed mainly across the ligand-binding domain (46, 38.3%) and epidermal-growth-factor-precursor homology domain (54, 45.0%), while 20 (16.7%) occurred in other receptor regions. According to ACMG/AMP classification, 69 variants (57.5%) were pathogenic, 29 (24.2%) were likely pathogenic, and 22 (18.3%) were variants of uncertain significance. Eighteen variants (15.0%) were reported as previously unreported.

Table 2: Spectrum of the LDLR variants detected: type, functional class, domain and pathogenicity

Category	**n**	**%**
Variant type	n	%
Missense	67	55.8
Nonsense	15	12.5
Frameshift	11	9.2
Splice-site	12	10.0
Large rearrangement	9	7.5
In-frame indel	6	5.0
Functional class		
Null (loss-of-function)	40	33.3
Defective (reduced function)	80	66.7
Domain		
Ligand-binding (exons 2-6)	46	38.3
EGF-precursor (exons 7-14)	54	45.0
Other (exons 1,15-18)	20	16.7
ACMG classification		
Pathogenic	69	57.5
Likely pathogenic	29	24.2
VUS	22	18.3

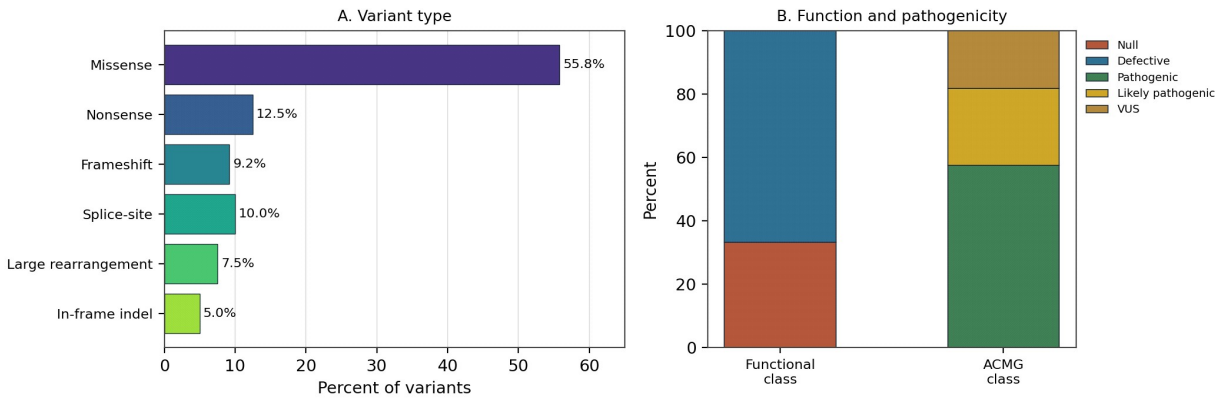


Figure 2: Distribution of LDLR variant types (A) and their functional class and pathogenicity (B)

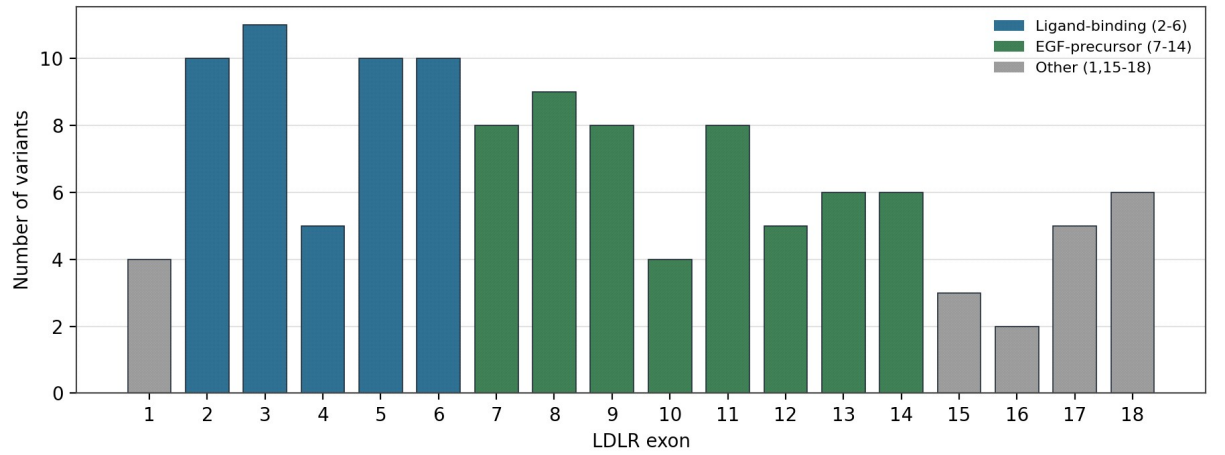


Figure 3: Distribution of the variants across the exons and functional domains of the LDLR gene

3.3. Genotype-phenotype correlation

The functional class of the LDLR variant was associated with differences in biochemical and clinical phenotype. Untreated LDL-C was significantly higher among carriers of null variants than among carriers of defective variants (9.4 ± 0.9 vs 7.7 ± 1.1 mmol/L; p<0.001). Tendon xanthomas were also more frequent among null-variant carriers (70% vs 31%; p<0.001), as was premature coronary disease (52% vs 24%; p=0.002). In contrast, the frequency of corneal arcus did not differ significantly between the two groups (30% vs 24%; p=0.510). Overall, null-variant carriers demonstrated a more severe observed biochemical and clinical phenotype in this cohort.

Table 3: Biochemical and clinical features by variant functional class (null versus defective)

Feature	Null variant	Defective variant	p
Untreated LDL-C (mmol/L)	9.4 ± 0.9	7.7 ± 1.1	<0.001
Tendon xanthomas	70%	31%	<0.001
Corneal arcus	30%	24%	0.510
Premature coronary disease	52%	24%	0.002

4. Discussion

This study characterised the spectrum of LDLR variants in a clinically defined cohort of patients with familial hypercholesterolaemia and examined their relationship with clinical diagnostic certainty and phenotype.

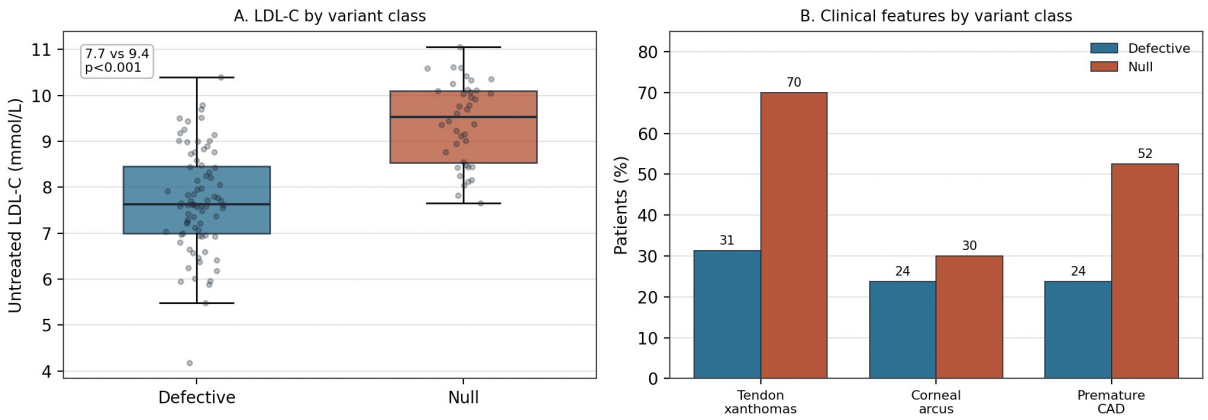


Figure 4: Untreated LDL cholesterol (A) and clinical features (B) by variant functional class

Three principal findings emerged. First, an LDLR variant was detected in 120 of 180 patients (66.7%), with the detection yield increasing substantially with greater clinical diagnostic certainty. Second, missense variants predominated, while the detected variants were distributed mainly across the ligand-binding and epidermal-growth-factor-precursor homology domains. Third, carriers of null variants had higher untreated LDL-C and greater frequencies of tendon xanthomas and premature coronary disease than carriers of defective variants.

The overall LDLR detection rate of 66.7% and its increase with clinical diagnostic certainty illustrate the complementary roles of clinical assessment and molecular testing. A negative LDLR result does not exclude familial hypercholesterolaemia because pathogenic variants may be located in other genes associated with FH, such as APOB and PCSK9, or may involve genetic mechanisms not captured by the assay used. Clinical criteria therefore remain important for diagnosis and for selecting patients for genetic testing, while molecular testing can strengthen diagnostic classification and facilitate cascade screening when a pathogenic variant is identified.

The molecular spectrum was dominated by missense variants (55.8%), while 33.3% of detected variants were classified as null and 66.7% as defective. The largest proportions occurred within the epidermal-growth-factor-precursor homology and ligand-binding domains, accounting for 45.0% and 38.3% of variants, respectively. Eighteen variants (15.0%) were reported as previously unreported. These findings illustrate the molecular heterogeneity of LDLR-related FH and emphasise the importance of systematic variant classification and curation according to established criteria.

The genotype–phenotype association was an important finding of the study. Carriers of variants classified as null had higher untreated LDL-C and greater frequencies of tendon xanthomas and premature coronary disease than carriers of defective variants, whereas corneal arcus did not differ significantly between groups. This pattern is consistent with the expected greater impairment of LDLR function associated with severe loss-of-function variants. However, because functional classification was based on variant characteristics and available evidence rather than direct functional testing of every variant, these findings should be interpreted as genotype–phenotype associations rather than direct demonstrations of receptor function.

These findings have potential clinical relevance because molecular characterisation can provide information beyond confirmation of the FH diagnosis. Identification of a pathogenic LDLR variant can facilitate cascade screening of relatives, while the observed association between functional class and phenotype may provide additional information about the expected severity of hypercholesterolaemia. Nevertheless, treatment decisions should remain based on the overall clinical phenotype, LDL-C burden, cardiovascular risk, and current guideline-based management rather than variant class alone. Prospective studies are needed to determine whether LDLR functional class provides incremental prognostic information beyond established clinical measures.

5. Strength and limitations

This study combined clinical characterisation with detailed LDLR variant analysis, including variant type,

functional class, receptor domain, and pathogenicity, allowing genotype–phenotype relationships to be evaluated. However, the cross-sectional design limits causal inference, the analysis was restricted to the LDLR gene, and functional classification was based on available evidence rather than direct functional testing for every variant. The single-centre design and moderate sample size may also limit generalisability and subgroup analyses. Further multicentre studies incorporating broader genetic testing and functional validation are warranted.

6. Conclusion

In this cross-sectional molecular study of clinically diagnosed familial hypercholesterolaemia, an LDLR variant was detected in 120 of 180 patients (66.7%), with the detection yield increasing with greater clinical diagnostic certainty. Among the detected variants, 69 (57.5%) were pathogenic, 29 (24.2%) were likely pathogenic, and 22 (18.3%) were variants of uncertain significance. Missense variants predominated, while the detected variants were distributed mainly across the ligand-binding and epidermal-growth-factor-precursor homology domains. Null variants were associated with higher untreated LDL-C and greater frequencies of tendon xanthomas and premature coronary disease than defective variants. These findings support the complementary role of molecular testing in the diagnosis and cascade screening of familial hypercholesterolaemia and suggest that LDLR functional class may provide additional information regarding phenotypic severity.

Ethical approval

The study was approved by the Institutional Ethics Committee (approval number IEC/MG/2023/109) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for genetic analysis was obtained from every participant after counselling.

Conflict of interest

The authors declare that no conflict of interest exists in relation to this work.

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Data availability

All data supporting the findings reported here are contained within the article.

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