

Artículo Original de Investigación

Criteria of the Dutch Clinical Network and genetic testing in familial hyperlipidemia in a group of Colombian patients

Criterios de la Red de Clínicas Holandesas y pruebas genéticas en hiperlipidemias familiares en un grupo de pacientes colombiano

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ARTICLE INFORMATION

Received on April 3, 2025.

Accepted after review on August 4, 2025.

www.revistafac.org.ar

There are no conflicts of interest to disclose.

Keywords:

Hyperlipidemia,
Familial hypercholesterolemia,
Genetics,
Lipoproteins..

Palabras clave:

Hiperlipidemia,
Hipercolesterolemia familiar,
Genética,
Lipoproteínas.

ABSTRACT

Introduction: hyperlipidemia is a group of diseases, both hereditary and acquired, characterized by elevated levels of lipids in the human body, especially prevalent in the western hemisphere.

Methods: this study seeks to identify patients with familial hyperlipidemia using the criteria of the Dutch Clinical Network applied to the subsidized population of Bucaramanga, Colombia, and evaluate their individual profiles.

Results: the prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated to be 1 in 200 to 500 people, while the prevalence of homozygous familial hypercholesterolemia (HoFH) is 1 in 300,000 to 600,000 people. In Bucaramanga, it is projected that 240,000 people could have HeFH and from 160 to 300 cases of HoFH.

Conclusions: despite the estimates, the real prevalence of the disease in Colombia is unknown, which justifies carrying out this study to obtain more precise data on familial hyperlipidemia in the region.

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RESUMEN

Introducción: la hiperlipidemia es un grupo de enfermedades, tanto hereditarias como adquiridas, caracterizadas por niveles elevados de lípidos en el cuerpo humano, especialmente prevalentes en el hemisferio occidental.

Métodos: este estudio busca identificar pacientes con hiperlipidemia familiar utilizando los criterios de la Red Clínica Holandesa aplicados a la población subsidiada de Bucaramanga, Colombia, y evaluar sus perfiles individuales.

Resultados: se estima que la prevalencia de la hipercolesterolemia familiar heterocigota (HeFH) es de 1 en 200 a 500 personas, mientras que la prevalencia de la hipercolesterolemia familiar homocigota (HoFH) es de 1 en 300,000 a 600,000 personas. En Bucaramanga, se proyecta que 240,000 personas podrían tener HeFH y entre 160 a 300 casos de HoFH.

Conclusiones: a pesar de las estimaciones, la prevalencia real de la enfermedad en Colombia es desconocida, lo que justifica la realización de este estudio para obtener datos más precisos sobre la hiperlipidemia familiar en la región.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder manifested by persistently elevated LDL cholesterol (LDL-C) levels from an early age, which significantly increases the risk of premature atherosclerotic cardiovascular disease^{1,2,3}. Its heterozygous form is estimated to affect approximately 1 in 200 to 500 individuals, and its homozygous form affects 1 in 300,000 to 600,000 individuals, although these data may vary by region and ethnic origin^{4,5}.

FH is primarily transmitted in an autosomal dominant manner and is associated with mutations in the LDLR, APOB, and PCSK9 genes, which alter LDL-C metabolism^{2,6}. These mutations lead to a reduction in hepatic cholesterol uptake, elevating its plasma levels and accelerating the process of atherosclerosis^{1,2,6}. The homozygous form of the disease, although less common, is associated with cardiovascular disease in children due to the almost complete absence of functional LDL receptors^{3,6}.

Most cases of FH remain undiagnosed, limiting the timely implementation of preventive measures^{3,4,7}. Studies conducted in European and North American populations have reported prevalences of 1 in 217 in Denmark, 1 in 150 in Quebec, and up to 1 in 70 in Afrikaners in South Africa^{5,6,7}. These differences highlight the importance of conducting local studies that consider the genetic and epidemiological characteristics of each region.

To improve identification, diagnostic tools such as the Dutch Clinical Network (DLCN) criteria have been proposed, which integrate personal and family history, LDL-C levels, physical signs, and genetic findings^{2,8}. These criteria have demonstrated adequate sensitivity and specificity compared to molecular diagnosis, considered the gold standard².

In Colombia, the true prevalence of FH is unknown, and the application of standardized clinical criteria has been limited, especially in vulnerable populations such as those receiving subsidized healthcare. Bucaramanga, a mid-sized city in northeastern Colombia, has a population base that allows for the implementation of active screening strategies for FH^{9,10}.

The **objective** of this study was to identify patients with suspected familial hypercholesterolemia in a population of the subsidized healthcare system in Bucaramanga by applying the Dutch Clinical Network criteria and to evaluate their clinical, epidemiological, and genetic characteristics.

METHODS

The present is an observational study that sought to identify the presence of FH based on the Dutch Clinical Network criteria. Patients aged 18-95 years who had a record of cardiometabolic risk variables including lipid profile and others were included in the study. Patients that did not have the variables as well as secondary causes of hyperlipidemia, such as hypothyroidism, nephrotic syndrome, cholestasis, and treatment with specific drugs (steroids, immunosuppressors, etc.) were excluded. The population that met the

inclusion and exclusion criteria consisted of all health centers in the city of Bucaramanga, Santander, Colombia.

Socioeconomic level was classified according to the official Colombian stratification system, which groups the population into six levels based on the characteristics of their housing and surroundings. For this study, the classification was obtained from administrative health records, and strata 1, 2, and 3 were included, representing low to middle-low socioeconomic status.

Familial Hyperlipidemia

To establish the clinical diagnosis of familial hyperlipidemia in the index case, the criteria of the Dutch Lipid Clinic Network (DLCN) are currently used in several countries. These criteria are based on a punctuation system according to personal and familial history of certain variables. Clinical diagnosis is certain when the score is ≥ 8 and likely when it is ≥ 6 . The accuracy of the clinical criteria has been compared with the genetic diagnosis, which is the gold standard, with the DLCN criteria having the best overall sensitivity and specificity¹⁰.

They should only be used for diagnosis of FH over the age of 18 years and never in their family members. To detect FH, an opportunistic search should be performed in patients with premature CVD and those with personal and/or family history of hypercholesterolemia and/or premature CVD¹¹.

Criteria for clinical suspicion of familial hypercholesterolemia¹².

1. Individual with LDL-c $> 250\text{mg/dl}$ and at least one of the following criteria
 - a. Family member < 18 years with LDL-c $> 150\text{mg/dl}$
 - b. Family member > 18 years with LDL-c $> 190\text{mg/dl}$
 - c. Presence of premature coronary heart disease in the index case and/or a first degree relative
 - d. Presence of xanthomas in the index case and/or a first degree relative
2. If there is no family data available, familial hypercholesterolemia should be suspected in people with LDL-c $> 300\text{mg/dl}$.

Genetic test

Genetic testing for familial hyperlipidemia was performed using a kit from the Longwood Company (Lipid in Code[®]) and processed by molecular engineering DNA analysis using an Ion GeneStudio S5 Series device. The 7 genes involved in the following were analyzed: Familial hypercholesterolemia: LDLR, APOB, PCSK9, APOE and STAP1 genes, Autosomal recessive hypercholesterolemia: LDLRAP1 gene, Lysosomal acid lipase deficiency: LIPA gene.

Statistical analysis

The quantitative variables are presented as a median $\pm$ standard deviation or median (interquartile range) according to their distribution, and qualitative variables as percentages with confidence intervals (CI) of 95%. Student's t

test was performed to evaluate the differences between two variables. All statistical analyses of the database results were performed using the Statistical Package for the Social Sciences (SPSS for Windows, v.20.1; Chicago, IL) and Microsoft Excel was used to tabulate the corresponding databases.

Ethical considerations

The ethical aspects of this research study were conducted based on the criteria of the Belmont Report, adjusted to its principles of respect to the person, benevolence, and justice and, the Helsinki declaration of the World Medical Association of 1964. Likewise, this work will be subjected to the national legislation and its code of medical ethics of 1985 (currently in force) in its title V, chapter 4, regarding research on human beings. The highest of standards were maintained that permitted the protection of the participant’s privacy and physical integrity.

By means of informed consent, the objectives of this investigation were explained, in the same manner, the procedures performed, and their inherent risks and complications were explained in detail using clear and understandable language. The study was evaluated and approved by the ethics committee with the highest of standards.

RESULTS

Initially, we present the results of the epidemiological characterization after reviewing the statistics of the population of the cardiovascular risk programme of the subsidized population in Bucaramanga, Santander. *Table 1* presents the sociodemographic characteristics of the included population.

TABLE 1.
Sociodemographic characteristics of the included population

Variable	Values
Gender	Female 7256 68,8%
	Male 3285 31,2%
Median age	65,67 years
Civic status	Married 435 4,1%
	Other 599 5,7%
	Separated 88 0,8%
	Single 9033 85,7%
	Civil partnership 147 1,4%
	Widowed 110 1,0%
	No information 125 1,2%
Socioeconomic stratus	Strata 1 (n: 5952) Strata 2 (n: 3845) Strata 3 (n: 744)
Psychological assessment	24 / 10541
Nutritional assessment	3841 / 10541
Dentistry assessment	2150 / 10541

Table 2 depicts the principal comorbidities found in the population included in this study.

Table 3 shows the data corresponding to adherence, degree of control and mean lipid profile, renal function and glucose values of the patients included in the study.

After characterization of all the patients, the criteria for suspected familial hyperlipidemia of the Dutch Lipid Clinic Network were applied.

Genetic testing revealed various mutations: duplication of exons 13–15 with p.Asp47Asn and p.Ser326Cys in the LDLR gene; mutations p.Glu204* and Ile268Met in the APOE gene; and multiple substitutions in the PCSK9 gene, including T>A at nucleotide 621 and T>C at nucleotide 780. Among the patients, 15 were heterozygous, 2 were homozygous, 2 were compound heterozygous, and 1 was double heterozygous. Some PCSK9 mutations were of uncertain significance, with limited prior documentation in the literature (*Table 4*).

These findings support the utility of systematic screening using DLCN criteria in high-risk populations, and reveal a significant genetic burden of familial hyperlipidemia that remains underdiagnosed. The integration of genetic testing allowed for the identification of clinically relevant mutations, reinforcing the importance of targeted strategies in primary care for early detection and risk reduction.

DISCUSSION

As seen in *Table 1*, the majority of the total population were female (68.8%), which is consistent with prior national reports of higher healthcare-seeking behavior among wo-

TABLE 2.
Principal comorbidities of the patients included in this study.

Variable	Values n (%)
Hypertension	8580 (81,4%)
Non-insulin dependent diabetes mellitus	2971 (28,2%)
Insulin dependent diabetes mellitus	833 (7,9%)
Chronic kidney disease	2560 (24,3%)
Hypercholesterolemia	2560 (24,3%)
Chronic obstructive pulmonary disease	833 (7,9%)
Cancer	21 (0,05%)

TABLE 3.
Adherence, degree of control and mean lipid profile, renal function, and glucose values of the patients included in the study.

Variable	Values n (%)
Adherence	9592 (91%)
Control	7380 (70,2%)
Median total cholesterol	168,353 mg/dL
HDL median	42,735 mg/dL
LDL median	111,919 mg/dL
Renal function median	194,906 mg/dL
Triglycerides median	194,906 mg/dL

men¹⁰. Additionally, most participants were single (85.7%), a finding previously associated with limited social support and potentially worse adherence to chronic disease management¹¹.

Regarding comorbidities in the overall sample (Table 2), hypertension (81.4%) and non-insulin dependent diabetes mellitus (28.2%) were the most common, followed by hypercholesterolemia and chronic kidney disease (both 24.3%). These findings are similar to those reported in studies from similar populations in Latin America and globally^{12,13,14}.

As shown in Table 3, adherence to treatment was high (91%) and overall control of metabolic indicators was achieved in 70.2% of cases, similar to previous reports^{15,16}. However, these figures must be interpreted with caution, as they reflect the entire cohort and not specifically the subset of patients with suspected familial hypercholesterolemia (FH).

TABLE 4.

Clinical and genetic characteristics of patients with suspected familial hyperlipidemia.

Category	Variables	Values
Demographics	Female sex	17 (85%)
	Male sex	3 (15%)
	Age range	46–88 years
Cardiovascular risk	Very high estimated risk	18 (90%)
	High estimated risk	2 (10%)
Comorbidities	Hypertension	17 (85%)
	Coronary heart disease	14 (70%)
	Diabetes mellitus	6 (30%)
	Cerebrovascular disease	4 (20%)
	Chronic kidney disease	4 (20%)
	Adherence to lipid-lowering therapy	18 (90%)
	LDL-C control achieved (<100 mg/dL)	6 (30%)
Genetic findings	LDLR mutations	Pathogenic variants (e.g., exon 13–15 duplication, p.Asp47Asn, p.Ser326Cys); frequently observed among genetically altered cases.
	APOE mutations	Mutations such as p.Glu204* and Ile268Met; detected in a minority of patients.
	PCSK9 variants	Substitutions including nt. 621 T>A and nt. 780 T>C; mostly classified as variants of uncertain significance.
	Genetic mutation types	Heterozygous 15 (75%) Homozygous 2 (10%) Compound heterozygous 2 (10%) Double heterozygous 1 (5%)

When focusing on the 20 patients who met the DLCN criteria for suspected FH (Table 4), the clinical profile was markedly different. This subgroup had a higher cardiovascular burden: 90% had very high cardiovascular risk and 70% had documented coronary artery disease, consistent with patterns described in other FH populations^{17,18}. Hypertension, diabetes, and chronic kidney disease were also frequent comorbidities.

Interestingly, while adherence to lipid-lowering therapy was high (90%), only 30% of these high-risk patients achieved adequate LDL-C control. This therapeutic gap is well-documented in FH cohorts and is often due to both genetic resistance to standard therapies and delayed diagnosis^{3,4,13}.

Genetic analysis revealed mutations primarily in LDLR, along with variants in APOE and PCSK9, the latter often of uncertain significance. These findings align with the global literature, where LDLR mutations account for more than 80% of genetically confirmed FH cases^{1,2}. The identification of compound and double heterozygous mutations also highlights the phenotypic and genetic complexity of FH.

Taken together, these results reinforce the clinical utility of DLCN criteria in identifying suspected FH cases within primary care, especially in underserved health systems. The integration of targeted genetic testing not only confirmed diagnoses but also uncovered clinically actionable mutations, contributing to the growing body of data on FH in Latin American populations. Furthermore, our findings support expanding systematic screening strategies and cascade testing to improve early detection and cardiovascular prevention.

Future research should evaluate the cost-effectiveness of implementing routine FH screening in primary care settings using clinical algorithms and genetic tools. Such studies are necessary to validate the approach at a larger scale and determine its long-term impact on morbidity and mortality.

CONCLUSIONS

Familial hyperlipidemia (FH) remains significantly underdiagnosed and undertreated in clinical practice, particularly in low- and middle-income countries. This study identified patients with clinical suspicion of FH in a subsidized health population in Bucaramanga using the Dutch Lipid Clinic Network (DLCN) criteria, revealing a high burden of cardiovascular disease and a low rate of LDL-C control despite adequate treatment adherence. Genetic testing confirmed pathogenic variants—especially in the LDLR gene—reinforcing the role of molecular analysis as a complement to clinical screening.

These findings support the integration of standardized diagnostic tools and genetic testing into primary care, especially in resource-limited settings where specialized lipid clinics are not widely available. Primary care physicians are fundamental in the early recognition of red flags such as persistent hypercholesterolemia or premature cardiovascular events. However, gaps in knowledge and diagnostic capacity remain a barrier to early detection.

To address this challenge, educational programs, improved biochemical screening protocols, and support from multidisciplinary teams—including clinical geneticists—are needed¹⁹. Public awareness campaigns are also essential, particularly for families with a history of early cardiovascular disease or elevated LDL-C.

Future research should explore the broader implementation of systematic FH screening and its effect on cardiovascular outcomes. Advances in genomic technologies and their accessibility may further improve detection, risk stratification, and eventually, the development of personalized therapeutic strategies²⁰. Characterizing the genetic and clinical profile of FH within the Colombian population remains a key priority for national health institutions.

Acknowledgement

The authors thank the Hospital Local del Norte and its committees, the Universidad Autonoma de Bucaramanga, the Universidad de Santander, and the team that made this study possible.

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