Int. j. adv. multidisc. res. stud. 2024; 4(6):564-567

Received: 09-10-2024
Accepted: 19-11-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Pathogenesis of the Hypercholesterolemia and the Role in Public Health

[1] Cesar Eslí Rabadán-Martínez, [2] Yracema Martínez-Hernández, [3] Isabel Cruz-Cortes, [4] Norma Elvira Rosas-Paz, [5] Elva Montero-Toledo, [6] Luis Alberto Hernández-Osorio, [7] Taurino Sosa Amilcar, [8] Sergio Alberto Ramirez-Garcia

[1, 2, 3, 4, 7] Facultad de Enfermería y Obstetricia, de la Universidad Autónoma Benito Juárez de Oaxaca, México
[5, 6, 8] Facultad de Ciencias Químicas de la Universidad Autónoma Benito Juárez de Oaxaca, México

Corresponding Author: **Sergio Alberto Ramirez-Garcia**

Abstract
In this work we propose a pathogenic classification of hypercholesterolemia based on the genes involved, these mainly for the health public. Are dividing into non-syndromic forms where we group the variants in seven genes LDLR, APOB, PCSK9, ABCG5, ABCG8, ARH, CYP7A1. And the syndromic forms are dysmorphological pathologies where hypercholesterolemia is secondary, due to variants in the genes that code for G6Pase, PBK, AGL, JAG1, NPHS1, MYH9, APTX, TDP1, TTPA, WRNQ, CSB, and the ABCG9 gene. In public health, the study of syndromic forms of hypercholesterolemia shows genes not directly related to cholesterol metabolism, which must be ruled out in the molecular profile of the patient and at the population level.

Keywords: LDL Receptor, ARH Adapter, Phytosterolaemia, Hypercholesterolemia, Nephrin

Introduction

Hypercholesterolemia is the second most common dyslipidemia in the Mexican population; it is heterogeneous in terms of its etiopathogenesis. The etiology can be monogenic or polygenic. Regarding the form of inheritance, they can be Mendelian or mitochondrial transmission. There are syndromic forms that generally present secondarily with hypercholesterolemia, but it can also present as a polygenic or multifactorial trait. There are syndromic forms in which a responsible or associated genetic locus has not been described. There is complex hypercholesterolemia such as dysbetalipoproteinemia, which presents several inheritance patterns, which are due to different low penetrance variants in the APOE gene as well as in APOA5, the phenotype of this is classified as type III hyperlipoproteinemia [1-3].

Familial hypercholesterolemia (FH) type I and the LDLR gene

The gene for the LDL receptor has its locus at 19p13.2, is made up of 18 exons and encodes a 120KD precursor glycoprotein (809 amino acids), which subsequently receives the covalent union of another 40KD fraction to form the mature fraction. of 160KD [7-9]. The clinical heterogeneity of patients with FH is related to the type of mutation. More than 800 genetic variants have been described in the LDLR gene, which are grouped into five classes; null alleles, alleles that produce transport defects, alleles that lead to defects in ligand binding, as well as alleles that lead to defects in protein internalization and recycling. The most frequent genetic variants are deletions and depending on the population studied, they are observed with frequencies ranging from 2.5 to 20%. Many of these deletions are located in mutation-prone regions rich in Alu sequences. The frequency of heterozygotes varies in the populations studied from 1/100 to 1/600, and for homozygotes 1/30,000. Homozygotes have cholesterol levels greater than 500 mg/dl, a concentration that remains constant throughout life [8-9]. On the other hand, heterozygotes have serum levels that range between 300 and 500 mg/dl. Premature coronary heart disease is the most important manifestation of FH before 30 years of age in homozygotes or compound heterozygotes. Homozygous status for the c2271delT mutation has recently been reported in a female proband from Oaxaca, Mexico [10].

Familial hypercholesterolemia type III and PCSK9 gene

The PCSK9 gene has its locus at 1p32.3, contains 41 exons, encodes a protein with 609 amino acids, has a serine protease activity of the subtilase family called NARC-1-Neural-Apoptosis-Regulatory-Convertase 1 that reduces the levels hepatic and extrahepatic LDL receptor as well as LDL lipoprotein. The variants in the PCSK9 gene are responsible for familial hypercholesterolemia type III, they occur with an autosomal dominant inheritance pattern, among the most common are the nt 625T>A transversion in exon 2, or the insertions or specific changes that lead to the amino acid substitution in the gene region that codes for the active site of the enzyme, such is the case of the p.S127G, or p.F216L variants. It should be noted that there are genetic variants of the PCSK9 gene with a frequency of 3.2% in the general population, which are associated with a reduction in LDL cholesterol levels from 15% to 47%. The detection of these variants is important, since which are reducing the risk of coronary heart disease. In this sense, it has been reported that SNV rs2479409 is directly related to cholesterol concentrations, as well as to the measurement of LDL particles [10-18].

Autosomal recessive hypercholesterolemia and LDLRAP1

The LDLRAP1 gene has its locus at 1p31. It is expressed mainly in the liver and encodes the adapter protein ARH, which participates in the cholesterol endocytosis system mediated by clathrins, megalin and dad2. Genetic variants in this gene are associated with a phenotype very similar to homozygotes for LDLR. Obligate heterozygotes have normal levels of LDL cholesterol, they also present tendon xanthomas and premature coronary heart disease. In the Mexican population, a new mutation in intron 4 that affects alternative splicing (IVS4+2T>G) was reported. This mutation affects the PTB binding domain, the parents of the proband were heterozygous for this mutation and were not consanguineous [19-21].

Phytosterolemia and the ABCG5/ABCG8 genes

The phytosterolemia is an autosomal recessive disorder, which is characterized by the absorption of plant sterols, including phytosterols. Patients with this condition have greater reabsorption of cholesterol from the diet and eliminate less cholesterol through the bile. Mediterranean stomatosis and macrothrombocytopenia have been described in association with sitosterolemia. The genetic variants responsible for this phenotype have been located in the ABCG5 and ABCG8 genes. These genes encode proteins of the ABC family: ABCG5 and ABCG8 of 651 and 673 amino acids respectively that form a complex for the absorption in the intestinal lumen of phytosterols, as well as carrying out the transport of sterols to the bile duct. Probands with genetic variants in these genes are hyperresponders to dietary cholesterol restriction and treatment with resins [22-24].

Hypercholesterolemia with gallstones and the CYP7A1 gene

The CYP7A1 gene encodes the enzyme 7-α-hydroxylase, critical in the metabolism of bile acids. Its deficiency decreases the production of bile acids and increases liver cholesterol. Heterozygotes for genetic variants in this gene have intermediate values between unaffected relatives and homozygotes [25].

Inherence Pattern Mitochondrial Hypercholesterolemia

It has been found that the T>C transition at locus 4291 of the gene for tRNA of DNAm is responsible for the phenotype with hypomagnesemia, hypertension and hypercholesterolemia. Other additional findings are migraine headache and hypertrophic cardiomyopathy. This mutation presents matrilineal transmission in a homoplasmic state [26].

Combined familial hypercholesterolemia

It has an autosomal dominant inheritance pattern, generally beginning at 20 years of age. Obesity is associated with hypertension, obesity and diabetes. The responsible HYPLIP1 gene has been mapped to the 1q21-q23 locus; linkage studies have also found the D1S104 marker proximal to the APOA2 and APOA3 genes to be involved. Furthermore, evidence of linkage has been found in the region where the genes SOD2, USF1, CETP/LCATy AI-CII-AIV, Thioredoxin have their locus [27-29].

Other Hypercholesterolemias and new findings

There are genetic variants in genes not directly related to the synthesis, transport or storage of cholesterol, responsible for hypercholesterolemia, among them we have the genetic variants in the genes that code for glucose-6-phosphatase, or for the subunits of phosphorylase-b-kinase and for the glycogen debranching enzyme [30-32]. Allagile syndrome, caused by genetic variants in the JAG1 gene (encoding a NOTCH1 ligand) occurs with hypercholesterolemia.33 Or congenital nephritic syndrome associated with genetic variants in the NPHS1 gene that codes for the nephrin produced [34]. A variant known as Neuhauser syndrome has been reported, this causes megalocornea, mental retardation, hypothyroidism, osteopenia and hypercholesterolemia35. POTOCKI-LUPSKI syndrome, due to a duplication of the 17p11.2 locus, is accompanied by isolated hypercholesterolemia [36-37]. FECHTNER syndrome is due to genetic variants in the MYH9 gene with a locus at 22q12.3, and is characterized by hypercholesterolemia, macrothrombocytopenia, nephritis, deafness, and leukocyte inclusions [38]. Recently was published a severe case of hipercolesterolemia asociado a la variante en el DNAmt nt14810 C>G [39]. Two pathogenic variants in the LDLR gene were detected in 149 individuals: c.-139_-130del (n = 1) and c.2271del (n = 148). All patients had a heterozygous genotype. With the cascade screening of their relatives (n = 177), 15 heterozygous individuals for the c.2271del variant were identified, presenting a mean LDLc of 133 ± 35 mg/dL [40].

The causal mutation of HoFH was found in 8 of 11 unrelated patients. Excepting 1, all were true homozygotes. Six different variants in LDLR were identified: c.-139delCTCCCCCTGC, p.Glu140Lys, p.Asp360His, p.Asn405Lys, p.Ala755Glyfs*7, and p.Leu759Serfs*6. Of these, p.Asp360His and p.Asn405Lys were detected for the first time in Mexico; p.Leu759Serfs*6 showed to be the most frequent (43.7% of the alleles 7/16), and c.-139delCTCCCCCTGC is a new variant located in the promoter region [41].

In normal weight Mestizo subjects, the *APOB* TT and *LDLR* GG genotypes were associated risk factors for hypercholesterolemia (OR = 5.33, 95%CI: 1.537-

18.502, *P* = 0.008 and OR = 3.90, 95%CI: 1.042-14.583, *P* = 0.043, respectively), and displayed an increase in low-density lipoprotein cholesterol levels (*APOB*: β = 40.39, 95%CI: 14.415-66.366, *P* = 0.004; *LDLR*: β = 20.77, 95%CI: 5.763-35.784, *P* = 0.007) [42].

In the pupulation the Triunfo (Quimixtlan, Puebla) in a study cross seccionatility sixteen of 308 individuals presented an LDLc level >170 mg/dL and all of them turned out to be heterozygous for the LDLR p.Asp360His variant. Subsequently, 34 of their first-degree relatives (mainly siblings and parents) were genotyped rendering six additional HeFH patients, which resulted in 22 carriers of the mutated allele [43].

A total of 860 Mexicans of Mexico Center (between 18 and 25 years of age were genotyped for the *ABCG2* (Q191K), *SLC22A12* (517G>A), and *XDH* (518T>C) polymorphisms, the *ABCG2* polymorphism was associated with hyperuricemia (OR=2.43, 95% CI: 1.41-4.17, *p* =0.001) and hypercholesterolemia (OR = 4.89, 95% CI: 1.54-15.48, *p* = 0.003), employing a dominant model, but only in male participants [45].

In western population 306 subjects aged 18-65 years, classified as normal weight or excess weight (EW) according to their BMI. EW included BMI from 25 to 39.9 kg/m2. Participants were classified into two metabolic phenotypes: Metabolically healthy/metabolically unhealthy (MH/MUH), the FTO rs9939609 variant may influence serum lipid concentrations, increasing the risk of hypercholesterolemia [46].

In conclusión Hypercholesterolemia is a disorder of the global public health problem and worldwide. The understanding of its pathogenesis does not allow a clinical approach in communities and at the first level of health care. Therefore, due to the risk that hypercholesterolemia represents and because it is present in most lipid disorders, we consider that the family doctor should recognize the main entities that present with dyslipidemia that must be ruled out.

References

1. Rincón-Sánchez AR, Pérez-García G, Ramirez-García SA, Davalos NO, Cabrera CE, De la Mora DA, *et al*. Enfermedades Crónicas no Transmisibles de Alta Prevalencia Y Problemas Globales de Salud. Ed. Cuellar Ayala, Guadalajara, Jalisco, México, 2023.
2. Barquera S, Flores M, Olaiz FG, Monterrubio E, Villalpando S, González C, *et al*. Dyslipidemias and obesity in Mexico. Salud Publica Mex. 2007; 49(S3):338-347.
3. Córdova VJ, Barriguete-Meléndez JA, Lara-Esqueda A, Barquera S, Rosas-Peralta M, Hernández-Avila M, *et al*. Chronic non-communicable diseases in Mexico: Epidemiologic synopsis and integral prevention. Salud Publica Mex. 2008; 50:419-447.
4. Goldstein JL, Brown MS. The colesterol quaret. Sciense. 2001; 292:1310-1312.
5. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. En Scriver CR, Beaudet AL, Sly WS, Valle D (Editores). The metabolic and molecular basis of inherited disease. New York. Mc Graw Hill, 2001, 2863-913.
6. Wilson F, Hariri A, Farhi A, Zhao H, Petersen K, Toka H, *et al*. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. Science. 2004; 306:1190-1194.
7. Johansson F, Kramer F, Barnhart S, Kanter J, Vaisar T, Merrill R, *et al*. Type 1 diabetes promotes disruption of advanced atherosclerotic lesions in LDL receptor-deficient mice. Proc Nat Acad Sci. 2008; 105:2082-2087.
8. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt N, Roos C, *et al*. Polymorphisms associated with cholesterol and risk of cardiovascular events. New Eng J Med. 2008; 358:1240-1249.
9. Simard L, Viel J, Lambert M, Paradis G, Levy E, Delvin E, *et al*. The delta > 15 kb deletion French Canadian founder mutation in familial hypercholesterolemia: Rapid polymerase chain reaction-based diagnostic assay and prevalence in Quebec. Clin Genet. 2004; 65:202-208.
10. Martínez L, Ordóñez SM, Letona R, Olvera Sumano V, Guerra MM, Tusié-Luna MT, *et al*. Familial homozygous hypercholesterolemia due to the c2271delT mutation in the LDL receptor gene, detected exclusively in Mexicans. Gac Med Mex. 2011; 147(5):394-398.
11. Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, *et al*. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genet. 2003; 34:154-156.
12. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. New Eng J Med. 2006; 354:1264-1272.
13. Zhao Z, Tuakli WY, Lagace TA, Kinch L, Grishin NV, Horton JD, *et al*. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet. 2006; 79:514-523.
14. Al-Kateb H, Bahring S, Hoffmann K, Strauch K, Busjahn A, Nurnberg G, *et al*. Mutation in the ARH gene and a chromosome 13q locus influence cholesterol levels in a new form of digenic-recessive familial hypercholesterolemia. Circ Res. 2002; 90:951-958.
15. Canizales QS, Aguilar SC, Huertas VA, Ordonez SM, Rodriguez TM, Venturas GJ, *et al*. A novel ARH splice site mutation in a Mexican kindred with autosomal recessive hypercholesterolemia. Hum Genet. 2005; 116:114-120.
16. Jones C, Garuti R, Michaely P, Li WP, Maeda N, Cohen JC, *et al*. Disruption of LDL but not VLDL clearance in autosomal recessive hypercholesterolemia. J Clin Invest. 2007; 117:165-174.
17. Rees DC, Lolascon A, Carella M, O'Marcaigh AS, Kendra JR, Jowitt SN, *et al*. Stomatocytic haemolysis and macrothrombocytopenia (Mediterranean stomatocytosis/macrothrombocytopenia) is the haematological presentation of phytosterolaemia. Brit J Haemat. 2005; 130:297-309.
18. Repa JJ, Berge KE, Pomajzl C, Richardson JA, Hobbs H, Mangelsdorf DJ. Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. J Biol Chem. 2002; 277:18793-18800.
19. Rios J, Stein E, Shendure J, Hobbs HH, Cohen JC. Identification by whole-genome resequencing of gene

defect responsible for severe hypercholesterolemia. Hum Molec Genet. 2010; 19:4313-4318.
20. Southar AK, Naomuva RP, Trabu LM. Genetics, clinical phenotype and molecular cell biology of autosomal recesive hipercolesterolemia. Arterioscler Thromb Vasc Biol. 2003; 23:1963-1970.
21. Bodnar JS, Chatterjee A, Castellan LW, Ross DA, Ohmen J, Cavalcoli J, *et al*. Positional cloning of the combined hyperlipidemia gene Hyplip1. Nature Genet. 2002; 30:110-116.
22. Pajukanta P, Allayee H, Krass KL, Kuraishy A, Soro A, Lilja HE, *et al*. Combined analysis of genome scans of Dutch and Finnish families reveals a susceptibility locus for high-density lipoprotein cholesterol on chromosome 16q. Am J Hum Genet. 2003; 72:903-917.
23. Pajukanta P, Lilja HE, Sinsheimer JS, Cantor RM, Lusis AJ, Gentile M, *et al*. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). Nature Genet. 2004; 36:371-376.
24. Van der-Vleuten GM, Hijmans A, Kluijtmans LAJ, Blom HJ, Stalenhoef AFH, de Graaf J. Thioredoxin interacting protein in Dutch families with familial combined hyperlipidemia. Am J Med Genet. 2004; 130A:73-75.
25. Azael MA, Ayub M, Cantu JM, Flores LJ. Diet therapy in severe clinical expresión of debrancher deficiency. Arch Invest Med. 1991; 22:285-288.
26. Alvarado LJ, Gasca CE, Grier RE. Hepatic phosphorylase b kinase deficiency with normal enzyme activity in leucocytes. J Pediatr. 1988; 113:865-867.
27. Ramirez-Garcia SA, Pérez-García G, Órnelas-Arana ML, Ruíz-Mejía R, Flores-Alvarado LJ. Detección de glucogenosis en población mexicana. Bioquimia. 2009; 34(1):113. (una sola pagina).
28. Boyer-Di PJ, Wright-Crosnier C, Groyer-Picard MT, Driancourt C, Beau I, Hadchouel M, *et al*. Biological function of mutant forms of JAGGED1 proteins in Alagille syndrome: Inhibitory effect on Notch signaling. Hum Molec Genet. 2007; 16:2683-2692.
29. Shono A, Tsukaguchi H, Kitamura A, Hiramoto R, Qin XS, Doi T, *et al*. Predisposition to relapsing nephrotic syndrome by a nephrin mutation that interferes with assembly of functioning microdomains. Hum Molec Genet. 2009; 18:2943-2956.
30. Derbent M, Oto S, Alehan F, Ozcay F, Kinik S, Cetin I, *et al*. Megalocornea-mental retardation (MMR or Neuhauser) syndrome: Another case associated with cerebral cortical atrophy and bifid uvula (Letter). Genet Counsel. 2004; 5:477-480.
31. Greco D, Romano C, Reitano S, Barone C, Benedetto DD, Castiglia L, *et al*. Three new patients with dup(17)(p11.2p11.2) without autism. Clin Genet. 2008; 73:294-296.
32. Zhang F, Potocki L, Sampson JB, Liu P, Sanchez-Valle A, Robbins-Furman P, *et al*. Identification of uncommon recurrent Potocki-Lupski syndrome-associated duplications and the distribution of rearrangement types and mechanisms in PTLS. Am J Hum Genet. 2010; 86:462-470.
33. Seri M, Pecci A, Di Bari F, Cusano R, Savino M, Panza E, *et al*. MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome are not distinct entities but represent a variable expression of a single illness. Medicine. 2003; 82:203-215.
34. Cabrera Pivaral CE, Rincón Sánchez AR, Ramírez-García SA. Familial hypercholesterolemia associated to variant nt14810 C>G in MT-CYTB. Med Clin (Barc). 2022; 159(8):401-402. Doi: 10.1016/j.medcli.2022.07.008.
35. Rodríguez-Gutiérrez PG, Hernández-Flores TJ, Zepeda-Olmos PM, Reyes-Rodríguez CD, Robles-Espinoza K, Solís-Gómez U, *et al*. High Prevalence of Familial Hypercholesterolemia Due to the Founder Effect of the LDLR c.2271del Variant in Communities of Oaxaca, Mexico. Arch Med Res. 2024; 55(3):102971. Doi: 10.1016/j.arcmed.2024.102971.
36. Hernández Flores TJ, González García JR, Colima Fausto AG, Vázquez Cárdenas NA, Sánchez López Y, Zarate Morales CA, *et al*. Screening of LDLR and APOB gene mutations in Mexican patients with homozygous familial hypercholesterolemia. J Clin Lipidol. 2018; 12(3):693-701. Doi: 10.1016/j.jacl.2018.02.015.
37. Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K, Panduro A. Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among Native American and Mestizo Mexicans. World J Hepatol. 2022; 14(7):1408-1420. Doi: 10.4254/wjh.v14.i7.1408.
38. Hernández Flores TJ, González García JR, Colima Fausto AG, Vázquez Cárdenas NA, Sánchez López Y, Zarate Morales CA, *et al*. Screening of LDLR and APOB gene mutations in Mexican patients with homozygous familial hypercholesterolemia. J Clin Lipidol. 2018; 12(3):693-701. Doi: 10.1016/j.jacl.2018.02.015. Eub 2018 Mar 1.
39. Rodríguez-Gutiérrez PG, Hernández-Flores TJ, Zepeda-Olmos PM, Reyes-Rodríguez CD, Robles-Espinoza K, Solís-Gómez U, *et al*. High Prevalence of Familial Hypercholesterolemia Due to the Founder Effect of the LDLR c.2271del Variant in Communities of Oaxaca, Mexico. Arch Med Res. 2024; 55(3):102971. Doi: 10.1016/j.arcmed.2024.102971.
40. Vargas-Morales JM, Guevara-Cruz M, Aradillas-García C, G Noriega L, Tovar A, Alegría-Torres JA. Polymorphisms of the genes ABCG2, SLC22A12 and XDH and their relation with hyperuricemia and hypercholesterolemia in Mexican young adults. F1000Res. 2021; 10:217. Doi: 10.12688/f1000research.46399.2.
41. Sierra-Ruelas E, Campos-Pérez W, Torres-Castillo N, García-Solís P, Vizmanos B, Martínez-López E. The rs9939609 Variant in FTO Increases the Risk of Hypercholesterolemia in Metabolically Healthy Subjects with Excess Weight. Lifestyle Genom. 2022; 15(4):131-138. Doi: 10.1159/000527097.