Endocrinología, Diabetes y Nutrición 70 (2023) 523–525

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

EDITORIAL

Familial dyslipidemias: Genotype-phenotype relationship

Dislipemias familiares: relación genotipo-fenotipo

Rosa M. Sánchez-Hernández[a,*], **Fernando Civeira**[b]

[a] *Sección de Endocrinología y Nutrición, Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria. Instituto Universitario de Investigaciones Biomédicas y Sanitarias de la Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain*

[b] *Hospital Universitario Miguel Servet, IIS Aragón, CIBERCV, Universidad de Zaragoza, Zaragoza, Spain*

Familial dyslipidaemias are lipid metabolism disorders which tend to cluster in certain families. Sometimes they have a genetic cause, but in most cases they are multifactorial, and the shared environment plays an important role. This is the case of the most common familial dyslipidaemia, multifactorial combined hyperlipidaemia, formerly called familial combined hyperlipidaemia, where the environmental component, especially diet and being overweight, influences the final patient phenotype.

Development of these dyslipidaemias follows different patterns in the family and they can be caused by monogenic, polygenic or multifactorial diseases. In general, the term familial should be reserved for dyslipidaemias caused by defects in a single gene, such as familial hypercholesterolaemia (FH).

The lipid phenotype can have a high degree of overlap between the different types of dyslipidaemia, depending on the severity of the genetic defect, the presence of other associated genetic variants and the interaction with the environment. Clinical diagnosis can be complex, as there are few pathognomonic phenotypic data, apart from tendinous xanthomas or corneal arcus in FH, palmar, flat or tuberous xanthomas in dysbetalipoproteinaemia and recurrent pancreatitis since childhood in familial chylomicronaemia due to lipoprotein lipase deficiency. However, the absence of these stigmata does not rule out the disease. Genetic testing is therefore of vital importance to ensure the most accurate possible approach to the diagnosis of these diseases.

The most common monogenic dyslipidaemia is FH, usually in heterozygosis (heterozygous FH or HeFH) and is caused by mutations in the gene encoding the LDL receptor *(LDLR)* (85%–90% of cases), apolipoprotein B *(APOB)* (5%), gain-of-function (GOF) mutations in the proprotein convertase subtilisin-kexin type 9 *(PCSK9)* gene (1%–3%), apolipoprotein E *(APOE)* (p.Leu167del variant) or LDL receptor adaptor protein type 1 *(LDLRAP1)*, the latter having an autosomal recessive inheritance pattern.[1] HeFH is characterised by very high levels of low-density lipoprotein cholesterol (LDL-C), generally above 250 mg/dl, vertical transmission of hypercholesterolaemia with approximately 50% of first-degree relatives affected, premature cardiovascular disease (CVD), corneal arcus before the age of 45 and in some cases tendinous xanthomas, mainly in the Achilles tendon.[1,2]

More than 4000 allelic variants have been described in the *LDLR* gene[3] which affect LDL receptor (LDLr) function differently, resulting in significant phenotypic variability[4] (Fig. 1). There are more severe mutations, in which LDLr is

* Corresponding author.
E-mail address: rsanherj@gobiernodecanarias.org (R.M. Sánchez-Hernández).

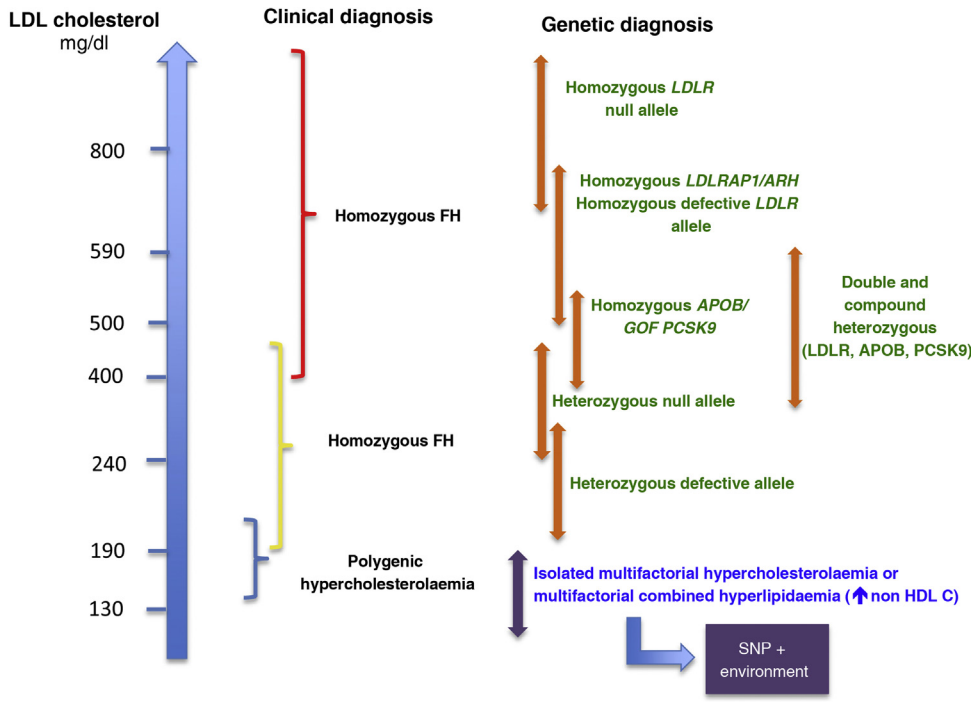

Figure 1 Genotype-phenotype relationship in hypercholesterolaemia.
APOB: apolipoprotein B gene; ARH: autosomal recessive hypercholesterolaemia; c: cholesterol; FH: familial hypercholesterolaemia; GOF: gain of function; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LDLR: LDL receptor gene; LDLRAP1: LDL receptor adaptor protein type 1 gene; PCSK9: proprotein convertase subtilixin-kexin type 9 gene; SNP: *single nucleotide polymorphism*.

not produced (null or class 1 alleles), associated with higher LDL-C levels, worse response to treatment and more CVD, and milder mutations (defective or non-class-1 allele), in which functional protein is present but altered.

The gene involved also has consequences on the phenotype. The severity usually follows the order *LDLR* > *APOB* > *PCSK9*. And within the GOF mutations of *PCSK9* there is also variability, depending on the presence of the p.(Asp374Tyr) variant, which generates a more severe phenotype, or others.[5]

Although there is a broad genotype-phenotype correlation, and the greater the severity of the genetic defect the worse the clinical phenotype, there are subjects with c-LDL levels which are not so high or are even normal despite having the mutation. There are also subjects with a clinical phenotype of FH who have a negative genetic diagnosis. This is partly due to the limited sensitivity and specificity of clinical diagnostic scores, such as the Dutch Lipid Clinic Network criteria,[2] which result in 20%–40% of cases with a clinical diagnosis of FH and a negative genetic study.[1] In general, the higher the LDL-C levels, the more likely it is to find a mutation in a causal gene for FH,[6] so the recommendation for genetic testing for suspected monogenic FH would be LDL-C levels >240 mg/dl.[7]

Within the spectrum of FH there are also less common homozygous forms or biallelic FH, comprising two mutations in the above-mentioned genes.[8] These forms are more severe, with LDL-C levels above 400 mg/dl, more premature CVD, early xanthomas, even from childhood, and both parents are usually affected by HeFH.[9] There is a marked genotype-phenotype correlation in HeFH, and if this condition is suspected, early genetic diagnosis is a priority, as the cardiovascular prognosis in these subjects is very poor if treatment is not started at an early stage.

Another form of primary hypercholesterolaemia is polygenic hypercholesterolaemia (PH), which comprises the sum of different point mutations or *single nucleotide polymorphisms* (SNP) in genes involved in lipid metabolism which, in isolation, have a small effect on LDL-C concentrations, but together generate primary hypercholesterolaemias with LDL-C values sometimes similar to those in monogenic forms. These SNP are grouped into scales called polygenic risk scores (PRS)[10] and are usually considered PH above the 75th or 90th percentile of the distribution of that PRS. PRS represent a major advance in the genetic characterisation of primary hypercholesterolaemia. Most cases of FH phenotypes with negative genetic testing are severe polygenic forms. Sometimes even the more severe phenotype observed in FH is due to the presence of polygenic or common variants which, in conjunction with the monogenic mutation, lead to a worsening lipid phenotype. In fact, these patients with monogenic mutation and elevated PRS have a worse cardiovascular prognosis.[11]

Last of all is isolated multifactorial hypercholesterolaemia or multifactorial combined hyperlipidaemia. It is often found with levels of LDL-C $\geq$ 130 mg/dl or non-HDL cholesterol $\geq$ 160 mg/dl as a result of the interaction of poorly understood polygenic and environmental factors, such as being overweight and obesity, which act as triggers for the lipid phenotype. In general, this sum of environment and genetics tends to be present in the same family, so the phenotype can appear in different generations, simulating a

monogenic form, but with variable phenotypes; sometimes it presents as isolated hypercholesterolaemia and sometimes as combined hyperlipidaemia. This disorder has been extensively studied and a monogenic origin has been ruled out.[1]

In conclusion, we can state that familial dyslipidaemias have a monogenic, polygenic or multifactorial genetic basis, and that the type of genetic defect will determine the severity of the phenotype in most cases. However, the addition of common variants in genes involved in lipid metabolism can often explain much of the variability in phenotypic expression in FH. For all these reasons, it is of vital importance to carry out a genetic study, including, if possible, PRS to assess the polygenic component. This will enable us to define dyslipidaemia more precisely, assess its prognosis, study family members and establish appropriate treatment.

Funding

This work was funded by a Health Research Project (PI20/00846) and a research intensification contract (INT21/00032) from the Instituto de Salud Carlos III (ISCIII) [Carlos III Health Institute].

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Bruikman CS, Hovingh GK, Kastelein JJP. Molecular basis of familial hypercholesterolemia. Curr Opin Cardiol. 2017;32:262–6, http://dx.doi.org/10.1097/HCO.0000000000000385.
2. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90, http://dx.doi.org/10.1093/eurheartj/eht273.
3. Fokkema IFAC, Taschner PEM, Schaafsma GCP, Celli J, Laros JFJ, den Dunnen JT. LOVD v.2.0: the next generation in gene variant databases. Hum Mutat. 2011;32:557–63, http://dx.doi.org/10.1002/humu.21438.
4. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol. 2016;4:850–61, http://dx.doi.org/10.1016/S2213-8587(16)30041-9.
5. Sánchez-Hernández RM, di Taranto MD, Benito-Vicente A, Uribe KB, Lamiquiz-Moneo I, Larrea-Sebal A, et al. The Arg499His gain-of-function mutation in the C-terminal domain of PCSK9. Atherosclerosis. 2019;289:162–72, http://dx.doi.org/10.1016/j.atherosclerosis.2019.08.020.
6. Lamiquiz-Moneo I, Civeira F, Mateo-Gallego R, Laclaustra M, Moreno-Franco B, Tejedor MT, et al. Rendimiento diagnóstico de la secuenciación de genes de hipercolesterolemia familiar en sujetos con hipercolesterolemia primaria. Rev Esp Cardiol. 2021;74:664–73, http://dx.doi.org/10.1016/j.recesp.2020.05.034.
7. Civeira F, Arca M, Cenarro A, Hegele RA. A mechanism-based operational definition and classification of hypercholesterolemia. J Clin Lipidol. 2022;16:813–21, http://dx.doi.org/10.1016/j.jacl.2022.09.006.
8. Cuchel M, Raal FJ, Hegele RA, al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J. 2023, http://dx.doi.org/10.1093/eurheartj/ehad197.
9. Sánchez-Hernández RM, Civeira F, Stef M, Perez-Calahorra S, Almagro F, Plana N, et al. Homozygous familial hypercholesterolemia in Spain: prevalence and phenotype-genotype relationship. Circ Cardiovasc Genet. 2016;9:504–10, http://dx.doi.org/10.1161/circgenetics.116.001545.
10. Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013;381:1293–301, http://dx.doi.org/10.1016/S0140-6736(12)62127-8.
11. Paquette M, Bernard S, Cariou B, Hegele RA, Genest J, Trinder M, et al. Familial Hypercholesterolemia-RiskScore: a new score predicting cardiovascular events and cardiovascular mortality in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2021;41:2632–40, http://dx.doi.org/10.1161/atvbaha.121.316106.