AUCTORES
Globalize your Research

Journal of Clinical Research and Reports

Tania Leme da Rocha Martinez *

Open Access

Mini Review

Major Aspects of Genetic Dyslipidemias

Eneida Marcílio Cerqueira [1], Anita L R Saldanha [1], André Luis Valera Gasparoto [2], Ana Paula Pantoja Margeotto [1], Bruno de Carvalho Abdala [1], Giulia Mistsuko Schimidt Hatae [1], Gustavo Costa Pontes [1], Luiza Ferrari de Castro Melo [1], Tania Leme da Rocha Martinez [1]*

[1] Nephrology Department, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil

[2] Intensive Care Unit, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil.

***Corresponding Author:** Tania Leme da Rocha Martinez, Rua Comandante Ismael Guilherme, 358 - Jardim Lusitânia 04031-120 - São Paulo – SP, Brazil.

Received date: November 06, 2023; **Accepted date:** November 15, 2023; **Published date:** November 22, 2023

Citation: E.M. Cerqueira, A. L. R Saldanha, Gasparoto A LV, Margeotto A P P, Abdala B C, et al (2023), Major Aspects of Genetic Dyslipidemias, *J Clinical Research and Reports*, 14(2); **DOI:10.31579/2690-1919/340**

Abstract

This work addresses some dyslipidemias with known genetic conditioning and presents aspects related to genetic markers that have been pointed out as risk indicators of development of obstructive arterial coronary disease. Among all the anomalies related to lipid metabolism, with well-defined genetic conditioning, familial hypercholesterolemia is the one that has been most studied. The gene that informs the LDL-c receptor is located on the short arm of chromosome 19 and houses 18 exons. About 150 mutations in the LDL-c receptor gene, resulting from the replacement, addition or loss of a base (point mutation) or consequent to the loss or addition of more than one nucleotide (insertions and deletions), have already been identified. It results from mutations involving the gene that conditions the formation of Apo E. Apo E has several allelic forms, of which E3 is the most common and it is believed that the other forms (E2 and E4) have originated by mutations occurring in E3: a substitution of arginine for cysteine at position 112 of the amino acid sequence differentiates E4 from E3, and the same substitution at position 158 gives rise to E2. The identification of the type of mutation is therefore important for the genetic counseling of individuals.

Keywords: genetic; hyperlipidemia; familial hypercholesterolemia; apoprotein b; dysbetalipoproteinemia

Abbreviations

Apo: Apoprotein

IDL-c: Intermediate Density Lipoprotein Cholesterol

LDL-c: Low Density Lipoprotein Cholesterol

Lp(a): Lipoprotein (a)

VLDL-c: Very Low Density Lipoprotein Cholesterol

Introduction

The contribution of genetics in determining the variability of serum lipid levels is estimated at more than 60% [1]. Most of this variation is due to the joint and interactive action between polygenes and environmental factors. In this type of inheritance, several pairs of genes with more or less pronounced effects, still poorly defined, interact with each other and with the environment that, in this type of inheritance, has a notably marked participation in the determination of the phenotype. The interaction of these factors characteristically results in a continuous distribution of phenotypes at the population level. Thus, the serum lipid levels of a population, plotted on a graph, give rise to a normal curve, in which extreme phenotypes are rare and most individuals have intermediate levels. The identification of the genes involved in the determination of the different intermediate phenotypes and the metabolic steps with which these genes are involved is particularly important, since it would allow a better understanding of the means by which genetic variations determine clinical objectives, and would also allow the identification in a given individual, or in their relatives, of a genetic combination related to a higher or lower risk [2].

A well-defined genetic mechanism is present in a smaller proportion of cases of dyslipidemias, producing pictures with typical family distribution of monogenic inheritance. At the current stage of knowledge, there are at least 18 proteins with direct involvement in lipoprotein metabolism in which cloning, sequencing and chromosomal localization of the genes encoding them have already been performed and whose mutations result in greater or lesser changes in the levels of lipoproteins and/or free cholesterol and triglycerides.

The possession of this knowledge was fundamental for the identification of mutations responsible for the various dyslipidemic conditions of familial occurrence[3-6].

Some of the disorders identified are very rare, such as familial liver lipase deficiency. Others produce intense changes in lipoprotein levels leading to acute coronary heart disease at an early age, as is seen in

hypoalphalipoproteinemia, which results from mutations involving the apoprotein (Apo) A-I gene. Others are of more common occurrence and condition by themselves less drastic phenotypes, requiring the concomitance of other factors, as observed in dysbetalipoproteinemia. In this work will be addressed some dyslipidemias with known genetic conditioning and presented aspects related to genetic markers that have been pointed out as risk indicators of development of obstructive arterial coronary disease.

Familial hypercholesterolemia

Among all the anomalies related to lipid metabolism, with well-defined genetic conditioning, familial hypercholesterolemia is the one that has been most studied. It is a disease characterized by increased plasma concentration of low-density lipoprotein cholesterol (LDL-c) and, to a lesser extent, all the other lipoproteins associated with the appearance of xanthomas in tendons and skin, corneal arch and coronary obstruction at a young age, leading to ischemic disease, which usually leads to death[1,7]. The population frequency of heterozygotes is 1/500 and that of homozygotes is 1/1,000,000.

It results from different mutations involving the LDL-c receptor gene, most of which have phenotypic repercussions in homo and heterozygosity, although less markedly in the latter condition, thus characterizing a co-dominant expression pattern. The mean levels of LDL-c in heterozygotes are on average 250 mg/dl, with homozygotes presenting values two to four times higher [7].

LDL-c has a mass of approximately three million daltons. It has a central part with about 1,500 molecules of esterified cholesterol, mainly by linoleate. This highly hydrophobic core is surrounded by a layer of phospholipids and non-esterified cholesterol. The cover also contains a single copy of Apo B-100, a very large protein with 514 Kd. This protein, like all those involved in the transport of lipids, has basically two functions: it solubilizes the highly hydrophobic lipids and contains signals that regulate the movement of certain lipids in their entry and exit of specific target cells.

The uptake of LDL-c is done by a series of steps that were elucidated by Drs. Michael Brown and Joseph Goldstein, called in the set of receptor-mediated endocytosis. These steps include: a) binding of Apo B-100 to the receptor molecule, which is located in specialized regions of the cell membrane, called coated fossas that, in turn, house molecules of clathrin, a protein capable of forming a network around the LDL-c/receptor complex internalizing it and giving rise to the formation of the endosome, b) fusion of endocytic vesicles with lysosomes with release of Apo B-100 from the receptor, which returns unharmed to the cell membrane and is later hydrolyzed to free amino acids. Cholesterol esters are hydrolyzed by a lysosomal acid lipase and non-esterified cholesterol can be used for membrane biosynthesis, or, through activation of Acyl-Co-A, be re-esterified for storage inside the cell.

An absorption pathway of this type, performed in multiple steps, requires the LDL-c receptor protein to have multiple functions. The analysis of the effects of several mutations, whether spontaneous or induced in cells in culture, involving the gene that conditions it, revealed the existence of five domains in this protein, which has a weight of 115 Kd and approximately 839 amino acids, each with a specific function.

The aminoterminal domain with LDL-c binding function has 292 amino acids, and a cysteine-rich sequence of approximately 40 amino acids, which is repeated, with some variations, seven times. There are in this domain side chains of negatively charged amino acids, which interact with a positively charged domain of the B-100 aprotein. The release of the receptor protein of its ligand (Apo B-100) is done, in the endosome, by protanation of the glutamate and aspartate side chains present in it. Following this domain is a region consisting of 350 amino acids, homologous to a part of the epidermal growth factor precursor. In this domain, there are two N-bound oligolosidic chains, which are inserted at the level of the endoplasmic reticulum and then modified upon passage through the Golgi apparatus. A third domain rich in serine and threonine, made up of 58 amino acids, contains several O-bound oses. It is possible that they serve as props to maintain the binding domain with Apo B-100 properly positioned for access to this protein. The fourth domain corresponds to the transmembrane region and is formed by 22 hydrophobic amino acids that cross the plasma membrane. The last domain, the carboxyterminal domain, consists of 50 amino acids and- is located on the cytosolic side of the membrane, participating in the interaction between receptor and the coated fossa for the endocytosis process.

The gene that informs the LDL-c receptor is located on the short arm of chromosome 19 and houses 18 exons. About 150 mutations in the LDL-c receptor gene, resulting from the replacement, addition or loss of a base (point mutation) or consequent to the loss or addition of more than one nucleotide (insertions and deletions), have already been identified. These mutations can be grouped into five different classes, based on the normal cellular itinerary of the protein[8]:

In class 1, which is the most frequent type of mutation, there is no protein synthesis (null allele), which is probably a consequence of large deletions in the gene or the entry of a meaningless codon at the beginning of the message. Class 2 mutations are related to receptor transport (defective transport allele), that is, it is formed but is trapped in the endoplasmic reticulum, possibly by inappropriate folding of the protein or by defective glycosylation. The third class of mutations gives rise to alleles called deficient binding. The receptor is formed, reaches the plasma membrane, but is ineffective in establishing bonds with Apo B-100 (or with Apo E). In the fourth class of mutations, the cytoplasmic domain of the protein is compromised (defective internalization allele), resulting in the non-internalization of LDL-c, and the fifth class of mutants involves the return of the receptor to the plasma membrane (defective recycling allele) due to the latter's inability, at the endosome level, to release its binding with Apo B-100.

An aspect that has been much discussed, in relation to the phenotypic variations presented by individuals affected by familial hypercholesterolemia, concerns the type of mutation that determines the clinical severity of the disease, which is not an easy answer, since it requires analysis of a variety of mutations and a sufficiently large number of those affected with such mutations so that their clinical characteristics can be compared.

There is ample evidence that other genetic and/or environmental factors influence the phenotype of familial hypercholesterolemia. In most populations in which the disease has been investigated, there is expression of the gene in homozygosis and heterozygosity, although, as already said, heterozygotes are less affected. Studies conducted in China and Tunisia show that only homozygotes present the characteristic changes of the disease, having heterozygous cholesterol values that are considered normal. Interestingly, this difference does not result from the type of mutation, since the same spectrum of mutations observed in individuals from other countries is also present in those populations. What's more, homozygotes are just as severely affected as those in other populations. The lack of expression in the heterozygote could be associated with nutritional differences, but the fact that in individuals from other populations hypercholesterolemia does not respond to the low-lipid diet suggests that the non-manifestation in those individuals is due more to the presence of differences in other genes, which would be of specific occurrence in those racial groups [9,10].

Familial defect of apoprotein B-100

Another disorder of cholesterol metabolism, discovered with the use of molecular probes, involves a mutation in the gene that informs Apo B-100, and results from a replacement of an arginine by glutamine in the codon 3,500 gene, which houses 29 exons and 28 introns. As a result of this substitution, Apo B-100 binding to the LDL-c receptor is not

performed, resulting in hypercholesterolemia of moderate severity (200 to 300 mg/dl) at the expense of an exclusive increase in LDL-c. The development of coronary heart disease occurs at the same rate as that observed in familial hypercholesterolemia and its occurrence is estimated at 1/500. Although Thompson [1] refers only to the moderate increase in cholesterol, Tybjaerg-Hansen [11] described, in a large study that included 135 individuals from 56 families from eight different countries, the occurrence of xanthomas in tendons, the presence of corneal arch and xanthelasmas.

Dysbetalipoproteinemia

This dyslipidemia, also called type III hyperlipoproteinemia, is clinically characterized by the presence of corneal arch, xanthelasma, tuberoeruptive xanthoma and palmar xanthomas[1]. Serum cholesterol and triglycerides are elevated. Atherosclerosis is frequent with about 50% of those affected developing coronary heart disease. LDL-c is normal or reduced because there is a lower conversion of IDL-c to LDL-c [12]. Dysbetalipoproteinemia results from mutations involving the gene that conditions the formation of Apo E. Apo E has several allelic forms, of which E3 is the most common and it is believed that the other forms (E2 and E4) originated from mutations that occurred in E3: a substitution of arginine for cysteine at position 112 of the amino acid sequence differentiates E4 from E3, and the same substitution at position 158 gives rise to E2. In adult white populations, the estimated frequencies of occurrence of E2, E3 and E4 are, respectively, 8%, 78% and 14%[13]. In vitro studies have shown that the receptor binds with high affinity to lipoproteins containing both Apo E3 and Apo E4, but particles containing Apo E2 show practically no binding with the receptor [12]. Individuals with dysbetalipoproteinemia type III are mostly homozygous for the arg 158cis mutation, which is therefore of autosomal recessive inheritance.

The need for cofactors for the development of hyperlipidemia is evident when comparing the frequency of the E2E2 genotype, which is 1/100 in most populations, and the frequency of hyperlipidemia, which is 1 in 5,000 [1,14-16]. Several other variants of Apo E, with different ability to bind to the receptor, have been discovered, some of them presenting a dominant inheritance pattern. The identification of the type of mutation is therefore important for the genetic counseling of individuals.

Acknowledgments

None

Conflict of interest

None

References

1. Thompson GR. Primary hyperlipidaemia. Br Med Bull. 1990;46(4):986-1004.
2. Humphries SE, Peacock RE, Talmud PJ. The genetic determinants of plasma cholesterol and response to diet. Baillieres Clin Endocrinol Metab. 1995;9(4): 797-823.
3. Berberich AJ, Hegele RA. A modern approach to dyslipidemia. Endocr Rev. 2022;43(4): 611-653.
4. Zuurbier LC, Defesche JC, Wiegman A. Successful genetic screening and creating awareness of familial hypercholesterolemia and other heritable dyslipidemias in the Netherlands. Genes (Basel). 2021;12(8): 1168.
5. Tada H, Kawashiri MA, Yamagishi M. Clinical perspectives of genetic analyses on dyslipidemia and coronary artery disease. J Atheroscler Thromb. 2017;24(5): 452-461.
6. Tada H, Kawashiri MA, Yamagishi M. Comprehensive genotyping in dyslipidemia: mendelian dyslipidemias caused by rare variants and Mendelian randomization studies using common variants. J Hum Genet. 2017;62(4): 453-458.
7. Schaefer EJ. Familial lipoprotein disorders and premature coronary disease. Med Clin North Am. 1994;78(1): 21-39.
8. Kesäniemi YA, Lilja M, Kerviren K, Rantala A. Multiple metabolic syndrome: aspects of genetic epidemiology and molecular genetics. Ann Med. 1992;24(6): 461-464.
9. Sun XM, Webb JC, Gudnason V, Humphries S, Seed M, Thompson GR, et al. Characterization of deletions in the LDL receptor gene in patients with familial hypercholesterolemia in the United Kingdom. Arterioscler Thromb. 1992;12(7): 762-770.
10. Slimane MN, Pousse H, Maatoug F, Hammami M, Ben Farhat MH, et aI. Phenotypic expression of familial hypercholesterolaemia in Central and Southern Tunisia. Atherosclerosis. 1993;104(1-2): 153-158.
11. Tybjaerg-Hansen A. rare and common mutations in hyperlipidemia and atherosclerosis. With special reference to familial defective apolipoprotein B-100. Scand J Clin Lab Invest Suppl. 1995;220:57-76.
12. Mahley RW, Innerarity TL, Rall SC Jr, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1984;25(12): 1277-1294.
13. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis. 1988;8(1): 1-21.
14. Brown MS, Goldstein JL, Fredrickson DS (1983) Familial type 3 hyperlipoproteinemia (dysbetalipoproteinemia). In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS (eds) The metabolic basis of inherited disease, 5th edn. McGraw-Hill, New York, pp 655–671.
15. Innerarity TL, Weisgraber KH, Arnold KS, Rall SC Jr. Mahley RW. Normalization of receptor binding of apolipoprotein E2. Evidence for modulation of the binding site conformation. J Biol Chem. 1984;259(11): 7261-7267.
16. Innerarity TL, Hui DY, Bersot TP, Mahley RW. Type III hyperlipoproteinemia: a focus on lipoprotein receptor-apolipoprotein E2 interactions. Adv Exp Med Biol. 1986;201: 273-288.

DOI:10.31579/2690-1919/340