Biomedical Journal of Indonesia
Journal Homepage: https://bji-fk.ejournal.unsri.ac.id

Genetics of Familial Hypercholesterolemia

Ziske Maritska[1*], Aditya Rafrenda[2], Amirah Adillah[2], Balqis Wulandari[2], Endah Rahmadani[2], Ernes Putra Gunawan[2], Khumaisiyah[2], Nur Rakhman Pratama[2], Trizky Nataza Putra[2]

[1]Department of Biology Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Internal Medicine Residency Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Cholesterol
Familial hypercholesterolemia
Genetics

Corresponding author:
Ziske Maritska
E-mail address:
Ziske_maritska@unsri.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/BJI.v9i3.166

ABSTRACT

Cholesterol is a necessary component of numerous physiologic processes that must be strictly regulated. Multiple genetic disorders, such as Familial Hypercholesterolemia, frequently induce dysfunctional cholesterol metabolism. Familial hypercholesterolemia (FH) is a frequent hereditary autosomal co-dominant marked by disarray by increased plasma amounts of low-density lipoprotein (LDL) cholesterol and premature cardiovascular disease. Familial Hypercholesterolemia (FH) is increasing but often remains underdiagnosed. This review aims to outline existing information on Familial Hypercholesterolemia with a focus on genetics, diagnostic strategies, treatments, and guidelines for management.

1. Introduction

Familial hypercholesterolemia (FH) is a congenital condition defined by low-density lipoprotein cholesterol (LDL-C) levels that are elevated from birth.[1] The condition is passed down via families an autosomal dominant through the mutations in the encoding proteins of variants genes related to the LDL receptor (LDLR) metabolism and Apolipoprotein B (APOB), proprotein convertase subtilisin-Kexin type 9 (PCKS9) and other genes are occasionally affected.[2,3] Loss-of-function mutations in the LDLRAP1 gene produce an infrequent recessive type of hypercholesterolemia (autosomal recessive hypercholesterolemia).[1]

Because of submission to increased LDL-cholesterol (LDL-C) throughout the baby, familial hypercholesterolemia patients have a high risk of developing early cardiovascular disease. In Familial hypercholesterolemia patients, the chances of myocardial injury and mortality increase at an early age, especially inadequately treated. The practical result of FH's dominant genetic transmission is that a patient with FH also has at least one parent with the same ailment, and their siblings get a 50% risk of acquiring FH.[4]

Familial hypercholesterolemia is one of the most hereditary diseases, with heterozygote and homozygote rates estimated to be 1:500 and 1:1.000.000, respectively. The modified Dutch Lipid Clinics Network (DLCN) criteria were used to identify familial hypercholesterolemia. With an error range of 0.03%, the percentage of definite/probable familial hypercholesterolemia was 0.47% (about 1:250 persons).[5] Familial hypercholesterolemia was more prevalent in some races, such as African, Lebanese, Jewish, or French-Canadian descent. Because the FH gene is localized on chromosome 19, men and women inherit the same pattern. According to worldwide data, the population of the world in 2017 was 7.6 billion people, with Asia accounting for 4.5 billion people or 60% of the overall population. According to researchers from the "Ten Countries Study," over half of the people with familial hypercholesterolemia live in the Asia Pacific.[8]

The heterozygous variant of Familial hypercholesterolemia has a general population frequency of 1:500 to 1:200 and is defined by a 2-3-fold rise in LDL-C.[1] Cardiovascular disease is more frequent in males aged 30 to 50 and women aged 50 to 70. The risk of CAD in untreated heterozygous type is 13 times greater than in non-familial hypercholesterolemia.[6] The homozygous variant has

a frequency of 1:60.000 - 1:300.000 and is often associated with a higher significant LDL-C level profile.[7] This increased cholesterol load does result in the development of relatively early cardiovascular illness, with homozygous form patients experiencing a myocardial infarction before reaching the age of ten, especially in individuals who are homozygous for two receptor-negative mutations. Patients with APOB or PCSK9 gene mutations had a milder phenotype.[1]

The risk of coronary heart disease was quite high before statin administration for patients suffering from heterozygous familial hypercholesterolemia. Despite high-intensity statin treatment, the possibility of mortality in people with heterozygous FH following acute coronary syndrome is about double that of similar persons without familial hypercholesterolemia during the first year. In men and females, the risk of mortality or coronary artery disease in relatives of FH patients was 52% and 32%, respectively. Patients who suffer from homozygous FH have poor prognosis. They typically die from cardiovascular disease before reaching their third decade of life.[9] This literature reviews the information on Familial Hypercholesterolemia with a focus on genetics, diagnostic strategies, treatments, and guidelines for management.

2. The Pathogenesis of Familial Hypercholesterolemia

FH pathogenesis is a complicated system in the LDL receptor pathway that comprises pathogenic mutations in genes (LDLR, APOB, PCSK9, and LDLRAP1).[2,6,10,] The common cause of FH is LLDR.[6,4] A rare occurrence of FH induced by the APOE, signal transducing adaptor family member 1 (STAP1), lysosomal acid lipase (LIPA), ABCG5, or ABCG8 genes has also been documented.[11]

LDLR

The pathophysiology of FH involves the binding dysfunction of LDL-Receptors located on 19th chromosomes.[11] It inhibits the catabolism process of LDL, lowering LDL absorption in the liver and increasing LDL serum levels.[11] LDLR pathogenic variations include DNA copy amount variation, insertions and deletions, nonsense and missense mutations, and splicing mutations.[10] The effect of its mutation is classified depending on the phenotypic behavior, null protein synthesis, transport defective, binding defect, internalization defect, and recycling defect.[10,11]

Apo B-100

There are two ligands of LDLR, apolipoprotein B-100 (ApoB-100) and apolipoprotein E (ApoE).[2] Mutations in ApoB are highly related to receptor binding site in exons 26 and 29, and some new variants associated with the decreasing of LDL clearance which causes a high level of serum LDL.[10,11]

PCSK9

There are more than 30 PCSK9 pathogenic variants, most of which are associated with missense mutations.[10] Its pathophysiology either be loss of functions (LOF) or gain of functions (GOF) that produce more active protein.[10,11] GOF variants associated with increased degradation of LLDR cause elevation of plasma LDL.[10,11] Another mechanism described includes increased activity, increased transcription, and enhanced binding ability.[10] LOF mutations are less prevalent, resulting in lower plasma LDL levels and decreased coronary heart disease (CHD) risk.[10,11]

LDLRAP1

Another gene that is seldom the cause of FH is LDL receptor adaptor protein 1 (LDLRAP1). These mutations resulted in an autosomal recessive type of FH classified as a homozygous FH, defined by serious hypercholesterolemia.[12] The mutations disrupt clathrin-coated endosome development and limit LDL uptake, raising plasma LDL-C levels.[10]

3. Familial Hypercholesterolemia Variants

Familial hypercholesterolemia is divided into 2 categories; (1) Familial Hypercholesterolemia Homozygous (*FH Homozygous*), and (2) Familial Hypercholesterolemia Heterozygous (*FH Heterozygous*). There are differences about these two categories as discussed below.

FH Homozygous

Homozygous familial hypercholesterolemia occurs by mutations of the LDL-R gene inherited from both parents. Familial hypercholesterolemia consists of two: true homozygote, a disorder inherited from both parents with defects in the same gene. Compound heterozygous if the mutation of the LDL-R gene is different. Both disorders contain high levels of low-density lipoprotein cholesterol (LDL-C). Furthermore, cardiovascular abnormalities are at the same risk in children under ten.[13,14] Extremely high LDL-C readings are indicative of homozygous FH problems, about six times the normal value (650 – 1000 mg/dl). This abnormality can be identified at birth by examination of the blood of the umbilicus.[13,14,15]

FH Heterozygote

Familial hypercholesterolemia heterozygous occurs due to a defect of a gene inherited from one of the parents. The disorder is characterized by an increase in LDL-C levels that are twice the normal value (140 mg/dL). Heterozygous FH abnormalities also depend on other genetic disorders and environmental factors. Five percent of boys will have a myocardial infarction before 30. The prognosis of heterozygous FH is determined by high LDL-C levels in the blood and health risks for cardiovascular disease.[13,14,15]

4. Diagnostic of Familial Hypercholesterolemia

Clinical Diagnostic

Three clinical criteria for identifying people with heterozygous familial hypercholesterolemia (HeFH) have been developed as follows: 1) LDL-C greater

than 190 mg/dL, 2) Familial hypercholesterolemia or a family medical history of early cardiovascular disease, 3) Medical history, and 4) Physical manifestations include xanthelasma, xanthoma, and arcus cornealis, also known as corneal arcus.[16]

The occurrence of tendon xanthomas, a high plasma LDL-C level, a family history of hypercholesterolemia, a background of initial ASCVD, and an increased plasma LDL-C level all contribute to the clinical diagnosis of FH. As usual, adult patients have LDL-C values of more than 4.9 mmol/l; Lesser cholesterol levels, however, have been observed in certain FH patients and families, mostly in younger people, and overlaps in the spread of LDL-C values have been observed. Triglyceride levels are commonly expected, but high levels do not rule out FH if other indications indicate it. Tendon Xanthomas are a defining feature of the condition and are related to an increased risk of cardiovascular disease. Since xanthomas are found in 20% of FH patients with functional mutations, the lack of xanthomas does not rule out FH diagnosis.[17]

Three alternative clinical criteria for diagnosing FH have been enlarged during the last 30 years. DLCN criteria are the majority generally acknowledged and utilized diagnostic criteria for FH. This criterion determines a scoring depending on LDL-C levels, the existence of arcus cornealis and tendon xanthomas, familial hypercholesterolemia, and early CVD, and positive for genetic testing. An overall score of 8 or above implies that the diagnosis is valid.[17]

Familial hypercholesterolemia is defined in children and young adults as LDL-C greater than 4.9 mmol/l after excluding possible causes of hypercholesterolemia, or LDL-C greater than 3.9 mmol/l when one parent has established FH. Total cholesterol and LDL-C levels in children aged 1 to 9 years can discriminate between those who have and do not have FH. Affected parents should be genetically tested, and after the confirmation of the diagnosis, the impact of genetic testing on their children must be communicated to them.[17]

High LDL-C levels often define Homozygote Familial Hypercholesterolemia (HoFH) (LDL-C of more than 13 mmol/l in untreated patients or LDL-C of more than 7.8 mmol/l in treated patients on maximal lipid-lowering medication), and the occurrence of skin and tendon xanthomas within the first few decades of life. Both parents were heterozygous familial hypercholesterolemic and had high LDL-C levels.[17]

The Dutch Lipid Clinic Network Criteria (DLCN)

The most often used of the 3 types of criteria, DLCN creates a score based on LDL-C values, physical abnormalities, early cardiovascular illness in families, and positive genetic testing if available (Table 1). A score of eight or above indicates that the diagnosis is "certain," as 80% of those in that group have a genetic mutation.[16]

The Simon Broome Registrar criteria

Clinical, physical, and biochemical data are also used in the Simon Broome Registrar criteria, which were created in the United Kingdom (Table 2). Again, a definite diagnosis can be made if specific clinical findings are met.[16]

Table 1. Criteria of DLCN.[16]

Criteria	Points
Family history	
First-degree relative with known premature atherosclerotic cardiovascular disease (age<55 in men, age<60 in women) or first-degree relative with LDL-C >95th percentile	1
First-degree relative with tendon xanthomas or arcus cornealts, or child under age 18 with LDL-C >95th percentile	2
Clinical history	
Premature coronary artery disease	2
Premature cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthomas	6
Arcus cornealts before age 45	4
LDL-C levels, mg/dL	
≥330	8
2550-329	5
1903-249	3
155-1189	1
DNA analysis	8
Functional mutation in the LDLR, APOB, or PSCK9 gene	
Interpretation	**Total**
Definite familial hypercholesterolemia	>8
Probable familial hypercholesterolemia	6-8
Possible familial hypercholesterolemia	3-5
Unlikely familial hypercholesterolemia	<3

Table 2. The Simon Broome diagnostic criteria.[16]

Criteria	Description
A	Total cholesterol level > 290 mg/dL or LDL-C > 190 mg/dL in adults (age ≥ 16)
	Total cholesterol levek > 260 mg/dL or LDL-C > 155 mg/dL in children (age < 16)
B	Tendon xanthomas in the patient or in a first- or second-degree relative
C	DNA-based evidence of a mutation in LDLR, APOB, or PCSK9
D	Familial history of myocardial infarction before age 50 in a second-degree relative, or before age 60 in a first-degree relative
E	Total cholesterol > 290 mg/dL in a first- or second-degree relative

*'definite' familial hypercholesterolemia requires criteria C by itself, or children A plus B, 'probable' familial hypercholesterolemia requires either A plus B, or A plus E.

The MED-PED criteria

The MED-PED criteria prioritize lipid levels and family history over clinical symptomatic and genetic studies (Table 3). These Criteria have a 54% sensitivity and 98% specificity in detecting heterozygous familial hypercholesterolemia. When the criteria were applied to persons with a first-degree comparative who had heterozygous familial hypercholesterolemia, the sensitivity improved to 88%, 85% in those with a second-degree relative who had the disease, and 81% in those with a third-degree relative who had the disease. As a result, the authors proposed undertaking cascade screening on relatives of individuals identified to have heterozygous familial hypercholesterolemia mutations.[16]

Genetic Diagnostic

One of the most notable discoveries from FH NGS research is the DNA-based validation that the percentage of carriers of an FH-causing variation is 1/250 in numerous Caucasian populations worldwide.[18] In otherwise, many genetic tests for FH can help in other variants.

Restriction Fragment Length Polymorphisms

Before the extensive use of laboratory sequencing, it was possible to identify relatives who acquired a pathogenic variant from a sick cousin. This approach has already been used to treat some clinically significant genetic diseases.

Deletions, Direct Assays, and Rapid Screening of Exons

The southern blot technique detects the existence of large deletions/insertions in a gene. A 10 kb deletion of the 5′ sections of the LDLR gene, including part of exon 1, was determined to affect FH among persons of French-Canadian heritage, although the FH-Helsinki variation involves a loss of exons 16, 17, and a piece of exon 18. Due to the invention of the PCR, scientists used PCR-based techniques to swiftly and affordably discover these deletions, allowing the screening of numerous samples and comparing the characteristics of carriers of distinct variants. This genetic diagnostic explain 5% of molecularly complex FH index cases in the UK and many other populations globally, suggesting an essential component of a diagnostic strategy is a PCR.[18]

FH-Mutation Databases

More nations have constructed molecular diagnostic facilities for FH tests, and amount of reports of FH-causing mutations has enlarged as commercialized FH testing has grown. Finding consensus on the precise transcript and nomenclature to record a DNA or predicted protein mutation is one of the most challenging components of developing such a database because simply detecting a DNA alteration in a patient with FH does not mean the change is FH-causing. The newly updated LDLR variant database, which includes variations categorized based on these recommendations, found at http://databases.lovd.nl/shared/genes/LDLR.[19]

NGS Methods

DNA testing laboratories recently developed NGS procedures that we know autosomal dominant FH genes and LDLRAP1, an autosomal recessive gene, to be assembled and sequenced concurrently. It is also possible to group specimens from up to 96 individuals and examine them with high precision in a single run by including small "barcoding" sequence IDs into PCR primers. It has reduced costs to the point that a full FH diagnostic scan containing copy number analysis is now accessible (deletions and duplications are identified in 5% of patients).[18]

Variants of uncertain significance (VUS)

NGS-enabled whole-genome screening approaches have raised the frequency of diagnosis and the number of instances in which a VUS is detected, generating a diagnostic problem. It is important to determine if a variation discovered in a clinical situation or with an unintended discovery in genomics research is deleterious. For LDLR, convincing confirmation that a variant is harmful needs in vitro molecular experiments to assess the influence on transcription, correct splicing, or LDLR investigation to see whether further relatives who got this variant also have high LDL-C values, whereas relatives who do not have the inherited variant have

Table 3. MED.PED diagnostic criteria.[16]

	Closest relative with familial hypercholesterolemia							
	First-degree		Second-degree		Third-degree		None	
	Threshold cholesterol level (mg/dL) in the patient							
Age	Total	LDL-C	Total	LDL-C	Total	LCL-C	Total	LDL-C
<20	220	155	230	165	240	170	270	200
20-29	240	170	250	180	260	185	290	220
30-39	270	190	280	200	290	210	340	240
≥ 40	290	205	300	215	310	225	360	260

expression.[18] The highest standard for demonstrating a pathogenic mutation is a family normal LDL-C level. Such investigations take a long time and a lot of resources. Therefore, a technique for triaging VUS would be beneficial.[18]

LDL-C Polygenic Risk Score

A modification to the DLCN score has been proposed in which "negative" scores are allocated to the points based on fasting plasma triglyceride levels, with the assumption that these reduce a person's chance of developing FH. However, because the cost of NGS has reduced, it is less critical to choose persons who are most likely to have an FH-causing mutation because discovering the monogenic cause in a low-scoring individual is therapeutically helpful for controlling medication and testing family members.[18]

5. Treatments and Management

The main target therapy is to reduce the accumulation of massive Low-Density Lipoprotein-C (LDL-C) levels and prevent the progression of cardiovascular disease. In the absence of cardiovascular disease, the European Society of Cardiology (ESC) suggests lowering LDL-C to 70 mg/dl (1.8 mmol/L), or a 50% deduction from baseline. Meanwhile, in cases with ASCVD, the decrease in LDL-C is targeted at <55 mg/dl (1.4 mmol / L).20 The target of LDL-C reduction in homozygous and heterozygous type FH is the same as both primary prevention and secondary prevention.[6]

In achieving these LDL-C therapy targets, therapeutic management in familial hypercholesterolemia can be done with pharmacological and non-pharmacological approaches such as lifestyle modifications. Lifestyle modifications can be done by focusing on exercise and dietary changes, although they do not significantly improve lipid profile levels compared to pharmacological therapy.[21]

Statins are still the primary choice in the treatment of familial hypercholesterolemia. In addition, non-statins can also be considered for treatment in cases with a non-optimal therapeutic response to statins.[21,4] Non-statin use options can be PCSK9 inhibitors, lomitapide fibrates, mipomersen, and LDL apheresis.[20,21,4]

Statins

Using large dosages of statins is the primary option for lowering LDL-C levels and avoiding ASCVD consequences. All statins can decrease LDL-C, such as atorvastatin and rosuvastatin. The mechanism of action of statins by inhibiting the enzyme 3-hydroxyl-methyl-glutaryl-coenzyme A reductase which causes a reduces in cholesterol production and improves the expression of LDL receptors on the surface of hepatocytes which lowers plasma LDL-C levels.[21,4] The treatment response is affected by LDLR mutation, which causes defects in function until it loses function of LDL receptors (null LDLR). Null LDLR causes the mechanism of action of statins to be ineffective.[21]

PCSK 9 Inhibitor

Adequate preparation in diminishing plasma LDL-C levels both monotherapy and combination with statins is PCSK 9 inhibitor. The FDA has authorized the use of evolocumab and alirocumab as medicines that inhibit PCSK 9 in reducing plasma LDL-C levels. PCSK 9 inhibitors are recommended in cases of FH that lack a response to statins. The decrease in LDL-C levels can reach 50-60% with the combined use of PCSK 9 inhibitors and statin. In the case of null LDLR or no LDL receptor activity, the decrease in LDL-C levels can reach 20%.[21]

PCSK 9 inhibitor is a monoclonal antibody that binds to circulated LDLR in plasma to prevent interactions between PCSK 9 and the surface LDLR or siRNA (inclisiran) in hepatocytes.[5] This results in a reduction in plasma LDL-C levels and an improvement in the expression of LDL receptors.[2]

Fibrates

Fibrates do not show significant clinical results when used as monotherapy but can be used in combination with statins. The mechanism of action by lowering triglyceride levels and having side effects of myopathy.[21]

Lomitapide

Lomitapide is a microsomal triglyceride transfer protein inhibitor that inhibits triglyceride transport to develop Very Low-Density Lipoprotein (VLDL) in hepar and chylomicron in the gut. This decrease in the synthesis of VLDL and chylomicron causes LDL-C levels also to decrease.[20.4] Lomitapide can be used at the age of >18 years and lower 50% of LDL-C levels at week 26 and 40% at week 78. However, due to its mechanism that inhibits the transport of triglycerides, this causes the emergence of side effects in the form of accumulation of hepatic triglycerides, steatosis, and an increase in the level of hepar transaminases and diarrhea. So, strict monitoring and a low-fat diet are needed in combination with statins.[20,4,1]

Mipomersen

Mipomersen is an antisense oligonucleotide that binds APOB mRNA in hepar, thus inhibiting the synthesis of VLDL, LDL, and lipoprotein (a) through the LDLR-independent pathway. This causes plasma LDL-C levels to decrease. As a result of its mechanism, mipomersen is used only as an adjunct therapy in cases of familial hypercholesterolemia. In phase 3 clinical trials, mipomersen only lowered LDL-C levels by 21.3% (P=0.0003). Possible side effects are injection site reactions, flu-like syndrome, mild steatosis, and increased hepar transaminases.[20.1]

LDL Apheresis

LDL apheresis is an act of removing lipoproteins from plasma using an intravenous catheter that is carried out 1-2 times a week. After the release of lipoproteins from the plasma, it is necessary to add albumin to the plasma.[1,6] Due to its non-selective albumin plasma elimination, its use is only carried out on specific indications.[6] LDL apheresis is indicated in

severe cases of familial hypercholesterolemia, failing with the combined use of pharmacological therapy, non-response, or intolerance to the use of statins, and cases with a high risk of cardiovascular complications.[21] Side effects often occur as hypotension, nausea, and iron deficiency anemia. The combined use of LDL apheresis with lipid-lowering drugs showed improvements in the decrease of plasma LDL-C levels.[6, 21,1]

6. Conclusion

Familial hypercholesterolemia is a hereditary condition defined by low-density lipoprotein cholesterol (LDL-C) levels that are elevated from birth and transmitted on an autosomal dominant basis through mutations in genes encoding proteins required in LDL receptor (LDLR) metabolism. Furthermore, sometimes affects the gene for APOB, PCKS9, and others. Familial hypercholesterolemia is divided into 2 categories Familial Homozygous and Familial Heterozygous. A high plasma LDL-C level, a familial history of hypercholesterolemia, a history of early ASCVD, and the manifestation of tendon xanthomas contribute to the clinical diagnosis of FH. Otherwise, there are diagnostic criteria with The DLCN Criteria, The Simon Broome Registrar, and the MED-PED criteria. Next-generation sequencing (NGS) yielded the most significant results concerning FH, although restriction fragment length polymorphisms; deletions, direct tests, and quick screening of exons for any sequence variation; FH-mutation databases; vus; LDL-C polygenic risk score. The main target therapy is to reduce the accumulation of massive Low-Density Lipoprotein-C (LDL-C) levels and prevent the progression of cardiovascular disease.

7. Acknowledgements

None

8. References

1. Raal, Frederick J. Hovingh, G.Kees, Catapano, Alberico L. Familial hypercholesterolemia treatments: Guidelines and new therapies. Elsevier B.V. Atherosclerosis 277. 2018. 483-492.
2. Vrablik M, Tichý L, Freiberger T, Blaha V, Satny M and Hubacek JA. Genetics of Familial Hypercholesterolemia: New Insights. Front. Genet.2020. 11:574474. DOI: 10.3389/fgene.2020.574474.
3. Taranto, Maria Donata Di. Giacobbe, Carola. Fortunato, Giuliana. Familial hypercholesterolemia: A complex genetic disease with variable phenotypes. Elsevier. European Journal of Medical Genetics. 2019. https://doi.org/10.1016/j.ejmg.2019.103831.
4. Alonso, Rodrigo. Isla, Leopoldo Perez de. Et all. Familial hypercholesterolemia Diagnosis and Management. Dyslipidemia. Radcliffe Cardiology. 2018. 13(1); 14-20.
5. Santos, Raul D. Screening and management of familial hypercholesterolemia. Wolters Kluwer Health. 2019.
6. Shiba, Mariko Harada. Arai, Hidenori. Ishigaki, Yasushi. Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017. J Atherosclier Thromb. Japan Atherosclerosis Society. 2018. 25: 751-77-. HTTP // doi.org/10.5551/jat. CR003.
7. Hu, P., Dharmayat, K. I., Stevens, C. A. T., Sharabiani, M. T. A., Jones, R. S., Watts, G. F., et al. Prevalence of Familial Hypercholesterolemia Among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. 2020. Circulation 141, 1742–1759. DOI: 10.1161/ CIRCULATIONAHA.119.044795
8. Kalra S, Chen Z, Deerochanawong C, Shyu KG, Tan RS, Tomlinson B, Yeh HI. Familial Hypercholesterolemia in the Asia Pacific: A Review of Epidemiology, Diagnosis, and Management in the Region. J Atheroscler Thromb. 2021 May 1;28(5):417-434. DOI: 10.5551/jat.56762. Epub 2021 Mar 19. PMID: 33746137; PMCID: PMC8193778.
9. Vaezi, Zahra. Amini, Afshin. Familial Hypercholestrolemia. StatPearls Publishing LLC. 2021.
10. Vicente AB, Uribe KB, Jebari S, Garcia UG, Ostalaza H, Martin C. Familial Hypercholesterolemia: The Most Frequent Cholesterol Metabolism Disorder Caused Disease. Int. J. Mol. Sci. 2018, 19, 3426. Available from: http://doi.org/10.3390/ijms19113426.
11. Vaezi Z, Amini A. Familial Hypercholesterolemia.2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556009/.
12. Viviane Z, Rocha MD, Santos RD. Past, Present, and Future of Familial Hypercholesterolemia Management. e of Familial Hypercholesterolemia Management. Methodist DeBakey Cardiovasc J. 2021;17(4):28-35. DOI: 10.14797/mdcvj.887.
13. Atsusi, Nohara. Hayato, Tada. Masatsune, Ogura. Homozygous Familial Hypercholesterolemia. 2021. 2-4.
14. Brandon, K Bellows. PharmD, MS. Estimated Estimated Yield of Screening for Heterozygous Familial Hypercholesterolemia With and Without Genetic Testing in US Adults. J Am Heart Assoc. 2022. 1-3.
15. Castro-Oros, Isabel De. Pocovi, Miguel. The genetic basis of familial hypercholesterolemia: inheritance, linkage, and mutations. The Application of Clinical Genetics. 2018. 55-57.
16. Nishant P. Shah, MD; Haitham M. Ahmed, MD, MPH; W. H. Wilson Tang, MD. Familial hypercholesterolemia: Detect, treat, and ask about family. 2020. Cleveland Clinic Journal Of

Medicine Volume 87 Number 2. Available from: www.ccjm.org.
17. Rodrigo Alonso, Leopoldo Perez de Isla, Ovidio Muñiz-Grijalvo, Jose Luis Diaz-Diaz and Pedro Mata. Familial Hypercholesterolaemia Diagnosis and Management. 2018. Radcliffe cardiology. European Cardiology Review.
18. Futema1 Marta, Taylor-Beadling Alison, Williams Maggie and Humphries Steve E. Thematic Review Series: The Science of FH. Genetic testing for familial hypercholesterolemia—past, present, and future. J. Lipid Res. 2021. https://doi.org/10.1016/j.jlr.2021.100139.
19. Chora, J. R., Iacocca, M. A., Tichy, L., Wand, H., Kurtz, C. L., Zimmermann, H., Leon, A., Williams, M., Humphries, S. E., Hooper, A. J., Trinder, M., Brunham, L. R., Costa Pereira, A., Jannes, C. E., Chen, M., et al. 2021. The Clinical Genome Resource (ClinGen) Familial Hypercholesterolemia Variant Curation Expert Panel consensus guidelines for LDLR variant classification. medRxiv. https://doi.org/10.1101/2021.03.17.21252755.
20. Lui, DT., Lee, AC., Tan, KC. Management of Familial Hypercholesterolemia: Current Status and Future Perspectives. Journal of the Endocrine Society, 2021, Vol. 5, No. 1, 1–14. doi:10.1210/jendso/bvaa122.
21. Shah, NP., Ahmed, HM., Tang, WH. Familial hypercholesterolemia: Detect, treat, and ask about family. Cleveland Clinic Journal of Medicine Vol 87 2020. doi:10.3949/ccjm.87a.19021.