International Journal of Research and Review
Vol. 10; Issue: 6; June 2023
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Familial Hypercholesterolemia: How Far Should We Go?

Mutia Lailani[1], Desy Nofita Sari[2]

[1,2]Department of Physiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

Corresponding Author: Mutia Lailani

DOI: https://doi.org/10.52403/ijrr.20230628

ABSTRACT

Familial hypercholesterolemia (FH) is a common inherited disorder, yet the diagnosis methods and management are still challenging. The heterozygous FH (known as FH) is more common than the homozygous form, yet a mutation only found in only about 40% of patients with the phenotype of FH. In fact, most cases are most likely caused by polygenic aetiology with less severe clinical presentations than monogenic FH. Therefore, understanding FH is essential, so that the diagnosis methods and management, particularly the patients' preventive measures of the patients can be improved. This review aims to describe and discuss the type of FH, including the clinical and lipid presentation, molecular pathogenesis of monogenic FH, and further discussion on how polygenic FH should be diagnosed and managed.

Keywords: hypercholesterolemia, SNP, DNA testing

INTRODUCTION

Familial hypercholesterolemia (FH) is a common inherited disorder, yet the diagnosis methods and management are still challenging. The disorder is autosomal co-dominant and characterised by increased low-density lipoprotein (LDL) cholesterol levels and risk of premature atherosclerotic cardiovascular disease. It has been classified into heterozygous and homozygous forms, based on the alleles involved in a mutation in one of the three genes i.e., LDL receptor (*LDLR*), apolipoprotein B (*ApoB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*). The heterozygous FH (known as FH) is more common than the homozygous form, with a prevalence of 1/200 and 1/300.000 individuals in the world, respectively (1). However, a mutation is only found in only about 40% of patients with a phenotype of FH, while the others are most likely caused by a polygenic aetiology (2).

Furthermore, Sharifi *et al*. (2017) found that the patients with monogenic FH had more severe carotid and coronary preclinical atherosclerosis than those with polygenic FH. The study also reported younger age, longer statin treatment, and higher residual preclinical atherosclerosis in the monogenic FH patients than those with polygenic cause (3). Therefore, understanding FH is essential, so that the diagnosis methods and management, particularly the patients' preventive measures of the patients can be improved. This essay aims to describe and discuss both types of FH. Firstly, this essay will describe the clinical and lipid presentation of FH. Secondly, it will discuss the molecular pathogenesis of monogenic FH. At last, further discussion on how polygenic FH could be diagnosed and managed better will be offered.

THE CLINICAL AND LIPID PRESENTATION OF FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia can be clinically diagnosed by several available

criteria, including the Simon Broome criteria, the Dutch Lipid Clinic Network criteria, and the MedPed criteria. In the UK, the use of the Simon Broome and the Dutch Lipid Clinic Network criteria was recommended by the National Institute for Health and Care Excellence (NICE) (**Table 1**) (4). The criteria can be used in all ages, although the DNA diagnosis is extremely recommended to perform in children under 16 years because of the minimal presentation of clinical signs in affected children (5).

The Simon Broome criteria include family history, clinical findings, cholesterol concentration, and DNA testing, and allow a diagnosis of 'definite' or 'possible' FH. Meanwhile, the Dutch Lipid Clinic Network criteria use a point system and give a diagnosis of 'definite' (total score >8), 'probable' (total score 6-8), 'possible' (total score 3-5), or 'unlikely' (total score <3). Different to the two mentioned criteria, the MedPed criteria classified the FH patients into first-, second-and third-degree relatives with FH to provide cut-off points in cascade as well as general population screening using total cholesterol concentration (6).

Table 1. The Simon Broome and Dutch Lipid Network criteria for the diagnosis of FH. Both criteria are based on history, several phenotypes, and gene mutations in the patients (Adapted from McGowan *et al.*, 2019).

Simon Broome Criteria for the Diagnosis of FH	
Criteria	Possibility
In adults: TC >7.5 mmol/L (290.0 mg/dL) (or when available, LDL-C >4.9 mmol/L [189.5 mg.dL]) In pediatric patients: TC >6.7 mmol/L (259.1 mg/dL), or LDL-C >4 mmol/L (154.7 mg/dL), AND	Definite
Tendon xanthoma in the patient or first/second-degree relative, OR alternatively:	
Presence of *LDLR*, *ApoB*, or *PCSK9* mutation	
In adults: TC >7.5 mmol/L (290.0 mg/dL) (or when available, LDL-C >4.9 mmol/L [189.5 mg.dL]) In pediatric patients: TC >6.7 mmol/L (259.1 mg/dL), or LDL-C >4 mmol/L (154.7 mg/dL), AND	Possible
Family history of MI <50 y old in second-degree relative or <60 y old in first-degree relative OR alternatively	
Family history of TC >7.5 mmol/L (290.0 mg/dL) in a first- or second-degree relative.	
Dutch Lipid Network Criteria for Diagnosis of FH	
Criteria	Score
Family history	
Premature CVD (men <55 y old, women <60 y old) in first-degree relative, OR	1
LDL >95th percentile in first-degree relative AND/OR	B
Tendon xanthoma and/or arcus cornealis in first-degree relative, OR	2
LDL >95th percentile in children <18 y old	2
Personal history	
Premature CAD in patient (men <55 y old, women <60 y old)	2
Premature cerebral or peripheral vascular disease (men <55 y old, women <60 y old)	1
Clinical examination	
Tendon xanthomas, OR	6
Corneal arcus younger than 45 y old	4
LDL	
>330 mg/dL (8.5 mmol/L)	8
250–329 mg/dL (6.5–8.5 mmol/L)	5
190–249 mg/dL (4.9–6.4 mmol/L)	3
155–189 mg/dL (4.0–4.9 mmol/L)	1
Presence of functional *LDLR* mutation (in the *LDLR*, *ApoB*, or *PCSK9*	8

In addition, the American Heart Association also recommend FH diagnostic categories (heterozygous, homozygous, and family history of FH), with a guideline on when genetic testing should perform. The homozygous FH (HoFH) is rare, yet strongly related to more severe premature coronary artery disease than the heterozygous FH (HeFH) (7). The heterozygous FH is clinically diagnosed in this category if LDL cholesterol (LDL-C) 5 mmol/L (≥190 mg/dL) for adults or 4 mmol/L (≥160 mg/dL) for children and with one first-degree relative similarly affected or with premature CAD or with positive genetic testing for LDLR, apoB, or PCSK9. Meanwhile, the homozygous FH is clinically diagnosed if: (a) LDL-C 10 mmol/L (≥400 mg/dL) and one or both parents having clinically diagnosed FH, positive genetic testing for an LDLR, apoB, or PCSK9 gene defect, or autosomal-

recessive FH; or (b) If LDL-C 14 mmol/L (>560 mg/dL) or LDL-C 10 mmol/L (>400 mg/dL) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely (8). In this essay, we will further focus on the HeFH (referred to as FH).

However, the clinical diagnosis criteria can be used only after the clinical signs appear so primary prevention is not possible in this setting. There are no 100% specific or sensitive criteria, and all of those criteria have almost similar specificity and sensitivity compared to the molecular DNA diagnosis as the 'gold standard' (9). Therefore, an understanding of the molecular mechanism of FH as well as its molecular diagnosis is essential.

THE MOLECULAR PATHOGENESIS IN THE KEY GENES AND THE SPECTRUM OF THE MUTATION

Until today, the mutations in the LDLR, ApoB, or PCSK9 genes are known as the causes of FH. The mutations of the LDLR gene are the most common, with more than 1600 mutations of this gene having been identified as the causes of FH, which is responsible for 85-90% of the cases. The ApoB mutations are related to 5-10% of FH cases, while the PCSK9 mutations are the least common one, which is related to less than 5% of the cases (10).

Additionally, three new genes have been identified through next-generation sequencing (NGS), which are signal transducing adaptor protein family 1 (STAP1), lysosomal acid lipase (LIPA), and patatin-like phospholipase-domain-containing family (PNPLA5) (2). However, the studies of those potential causes of FH are still continuing. In this essay, we will focus on the three primary and key genes, *LDLR, ApoB,* and *PCSK9.*

Low-density lipoprotein receptor gene (LDLR)

The LDLR gene (*LDLR*) is located in chromosome 19, at position 13.2 of its short (p) arm (19p13.2). The function of this gene is to regulate the production of a protein called the low-density lipoprotein receptor (LDLR). LDLRs have a critical role in regulating the amount of cholesterol in the blood by binding to low-density lipoprotein (LDLs) particles in the blood. The LDLRs are mostly found in the liver, which is responsible for removing most excess cholesterol from the human body (11).

The mutations of *LDLR* results in the impairment of LDLRs related to their capacity to clear LDL from circulation. There are six classes of *LDLR* mutations, including (8):

- Class I: Whole LDLR is not synthesised.
- Class II: The expression on the cell surface of LDLRs is impaired due to the defect in the transportation of the receptors from the endoplasmic reticulum to the Golgi apparatus.
- Class III: LDLRs do not correctly bind LDL on the cell surface due to a defect either in the LDLR or in the apolipoprotein B (ApoB) -100 (R3500Q).
- Class IV: LDLRs bound to LDLs do not correctly cluster in clathrin-coated pits for endocytosis.
- Class V: LDLRs are not recycled back to the cell surface.
- Class VI: LDLRs fail to be targeted to the basolateral membrane, resulting in failed surface presentation.

Apolipoprotein (Apo) B gene (ApoB)

The ApoB gene (*ApoB*) is located in chromosome 2, at position 24.1 of its short (p) arm (2p24.1). The function of this gene is to regulate the production of two versions of the apolipoprotein B proteins, B-48 and B-100. The apolipoprotein B-100 allows LDLs to attach to specific receptors on the surface of the liver cells, which then use, store, or remove the cholesterol from the body (12). The mutations of *ApoB* result in elevated LDLs, although the increase is likely lower than in the setting of the *LDLR* mutations (8).

Proprotein convertase subtilisin/kexin type 9 gene (PCSK9)

The PCSK9 gene (*PCSK9*) is located in chromosome 1, at position 32.3 of its short (p) arm (1p32.3). The function of this gene is to control the number of LDLRs, which play an important role in regulating blood cholesterol levels. The number of LDLR on the surface of liver cells is correlated to the time needed to remove cholesterol from the bloodstream (13). The mutations of *PCSK9* increase the affinity of PCSK9 proteins to the LDLRs, resulting in a decrease in the number of functional LDLRs on the surface of liver cells (1). Additionally, the elevation of plasma total cholesterol caused by *PCSK9* is the most severe compared to the other mutations known (2).

The spectrum of the mutation in familial hypercholesterolemia

The molecular diagnosis of FH patients and their relatives have provided DNA-mutation information, which allowed the finding of the spectrum of the mutation related to the disease. In 2010, Taylor *et al.* conducted a study in familial hypercholesterolaemia patients in the UK pilot cascade project. This study included a comparison of the mutation spectrum in FH patients with clinical diagnosis (using Simon Broome criteria) of definite familial hypercholesterolemia (DFH), possible familial hypercholesterolemia (PFH), and unclassifiable familial hypercholesterolemia (UFH).

In this study, the results showed that more than 50% of the DFH patients had a mutation detected, while only about a quarter of the PFH and UFH had DNA mutations. Since there were no remarkable differences between the mutation detection rate of PFH and UFH patients, it has been suggested that although a patient who does not fulfil all the criteria of Simon Broome, there is still a possibility that the patient has monogenic familial hypercholesterolemia (14).

Furthermore, the comparison of the cholesterol levels of DFH, PFH and UFH patients with or without mutation detected also showed interesting results. The comparison in mutation-positive and mutation-negative subjects of DFH and PFH patients, with mutation-positive FH patients had a significantly higher cholesterol level. However, the cholesterol level of mutation-positive and mutation-negative UFH patients did not show significant differences. Based on these findings, this study strongly supported the clinical utility of molecular diagnosis, particularly DNA testing, in all of FH patients (14).

SINGLE NUCLEOTIDE POLYMORPHISMS (SNP) SCORE TO IDENTIFY A POLYGENIC CAUSE IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA PHENOTYPE

However, it is still questionable that only approximately 40% of FH patients that are with mutations, particularly mutations in one of the three key genes (*LDLR, ApoB, PCSK9)*. In a study of serum lipid with a genome-wide association screening (GWAS) in >100,000 people of European ancestry, it is found that a total of 95 loci are associated with serum lipid in multiracial population (15). However, it is important to note that one of the limitations of this study was that the study only included European ancestry, so the mutation spectrum in patients with other races is still questionable.

Despite its limitation, this study has successfully identified the loci correlated to serum lipid, and additionally, several loci were found to be correlated with coronary artery disease as well. Importantly, it is demonstrated that a combination of common variants in the loci resulted in extreme lipid phenotype as we found in clinically diagnosed FH patients (15). Therefore, this finding raised the hypothesis of polygenic causes in FH patients with the absence of mutation.

Furthermore, a study by Talmud, *et al.* (2013) was performed Global Lipid Genetic Consortium (GLGC) 12-SNP LDL-C gene

score calculation in UK patients (European ancestry) with familial hypercholesterolemia, which confirmed the polygenic hypothesis distinctly. The SNPs selected were the lead SNP of each locus and if the SNP was correlated with more than one lipid fraction, only the SNP with LDL-C as the lead trait was included. The samples consisted of patients with mutation-positive and mutation-negative, from three UK-based sources, which were compared with controls from the UK Whitehall II (WHII) study (16). In the previously mentioned study, the LDL-C-specific gene score calculation in every sample was performed by using the weighting sum of the risk allele based on the GLGC report. The result showed that in patients with LDL-C >4.9 mml/L without a known mutation had a significantly higher weighted LDL-C gene score distribution compared to the WHII controls. This study demonstrated that in clinically diagnosed FH patients without the genetic mutation, the hypercholesterolemia condition is likely caused by a polygenic cause, which is an accumulation of common small-effect LDL-C-raising alleles (16).

In a more recent study, Futema, *et al.* (2015) strived to develop the selection of the SNPs and successfully increased the number of SNPs to 33. However, compared to the 6 SNP and 12 SNP-score, the increase did not improve the score to distinguish the mutation-positive patient from the negative ones. Moreover, in this study, the weighted 6-SNP score showed a consistently higher score compare to controls, and indicated >95% possibility of a polygenic cause of the increased LDL-C as well as elevated plasma total cholesterol above cut-off (17).

THE CASCADE SCREENING IN POLYGENIC FAMILIAL HYPERCHOLESTEROLEMIA

Since FH is a common genetic disorder yet it has no early clinical signs, underdiagnosis and undertreatment of the patients still remain. The cascade screening in FH is a process of family tracing, at least first and second-degree biological relatives, to identify people at risk by using DNA testing or LDL-C measurement. This method offers the opportunity to identify people at risk of FH, thus enabling the effective prevention of cardiovascular disease (18). However, whether the cascade screening using the molecular diagnostic method should be offered to all FH patients or only to patients with monogenic causes, is still debatable.

The 2015 American Heart Association (AHA) scientific statement on familial hypercholesterolemia suggests that cascade screening be conducted only on the relatives of FH patients with the presence of mutation, considering the health and economic aspect. Particularly, further genetic testing to perform for those with clinical diagnosis, to identify the heterozygous or homozygous FH. The genetic test is not recommended to perform in those with a family history of FH whose LDL-C level is not a criterion, even though with a first-degree relative with confirmed FH. The molecular diagnosis in this group is a cost-effective effort since more than 50% of the first-degree relatives inherit the mutation (4,8). In contrast with the findings in relatives of monogenic FH patients, the study by Talmud, *et al* (2013) found that only less than 50% of relatives of polygenic FH patients are expected to have monogenic FH. Taking these findings into consideration the cascade screening by using DNA testing should be recommended only in the setting of monogenic FH, rather than both monogenic and polygenic FH (**Figure 1**).

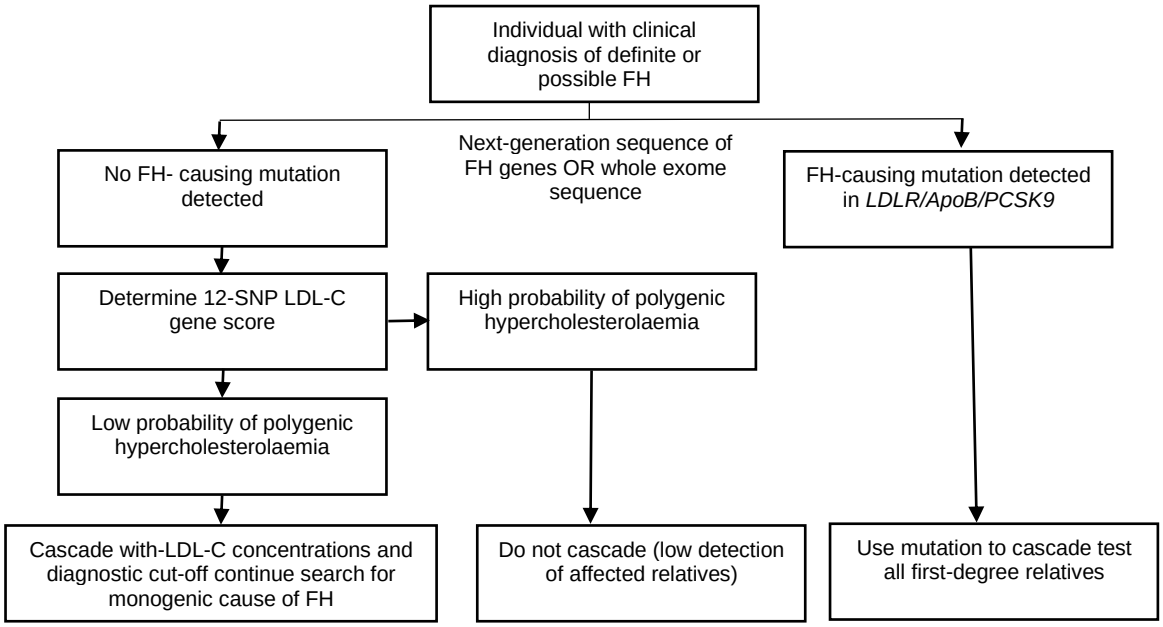

Figure 1. The recommendation of diagnosis workflow for cascade screening in FH patients. The figure shows that the cascade test only is recommended in FH patients with detected mutations (Adapted from Talmud *et al.*, 2013).

THE MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA

The management of familial hypercholesterolemia includes drug treatment as well as a lifestyle intervention to control the LDL-C concentration as well as the risk of future cardiovascular events, both in monogenic and polygenic FH. Despite the differences in the genetic background of FH patients, The 2018 AHA guidelines recommended lipid-lowering therapy for patients with LDL-C levels of 4.9 mmol/L (>190 mg/dL) or higher (6). Lipid-modifying drug therapy should be offered to adults with FH as well as children clinically or molecularly diagnosed with FH by the age of 10 years. Moreover, it is important to regard lifestyle interventions as a part of medical management, and not as a replacement for lipid-modifying therapy (4).

Drug treatments in adult patients

The life-long drug management of familial hypercholesterolemia includes (4,6):

a. High-intensity statin to decrease LDL-C by 50-60% as well as the risk of coronary artery disease (in cases with early diagnosis).
- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg

b. Ezetimibe targets Niemann-Pick C1-like protein 1 (NPC1L1) to inhibit cholesterol absorption in the intestine, 10 mg daily. Particularly, ezetimibe is recommended in adult FH patients with contraindications of initial statin therapy. Ezetimibe combination with a statin can be offered in the following conditions:
- LDL-C concentration is not controlled adequately after initial statin therapy, and
- When a change of statin therapy is in consideration.

c. Alirocumab and Evolocumab, the human monoclonal antibodies targeted against PCSK9 increase the availability of LDLR and secondary prevention from cardiovascular disease. It is recommended if LDL-C levels are not controlled appropriately despite the maximally tolerated dose of lipid-lowering therapy.

d. Colesevelam, a bile acid sequestrant or fibrate reduces LDL-C concentration for those who need modest additional LDL-C decrease after medication treatment with statins and ezetimibe.

Drug treatments in children and young patients

The cascade screening has enabled the diagnosis of FH in children and young people so that earlier therapy can be provided to prevent future cardiovascular events. The screening for FH should be conducted in relatives of mutation-positive FH patients (at least one parent) older than 2 years old, yet the therapy should not be started until the age of 10. The statin therapy available for children includes atorvastatin 10–80 mg/day and rosuvastatin 10–20 mg/day (19). Life-long statin therapy has been proven as a safe treatment dan is not associated with growth or maturation, myopathy, liver enzymes, and serum creatinine kinase (20).

Lifestyle intervention

Several lifestyle interventions have been recommended, including (4):

a. Dietary intervention, particularly by reducing fat intake. The total fat intake should be 30% or less of the total energy intake, and the saturated fats are 10% or less of the total energy intake.
b. Physical activity. Patients with FH should exercise for a minimum of 30 minutes daily (at least 5 days a week) of physical activity of at least moderate intensity.
c. Weight management
d. Limitation of alcohol consumption (3-4 units a day for men, 2-3 units a day for women)
e. Smoking cessation.

CONCLUSION

In conclusion, familial hypercholesterolemia is a common genetic disorder, which can be diagnosed by using available clinical criteria and DNA testing. Mutations of three key genes, LDLR, ApoB, and PCSK9, resulted in severely elevated LDL-C concentrations in FH patients. In clinically diagnosed FH patients without the known mutation, the SNP score calculation in the previous studies has shown the likelihood of a polygenic cause. Furthermore, early diagnosis and prevention can be performed by cascade screening in at least the first and second-degree relatives of monogenic FH patients. Both monogenic and polygenic FH patients should have drug treatments as well as lifestyle interventions to lower LDL-C concentration adequately, and subsequently, to prevent future cardiovascular disease.

Declaration by Authors

Ethical Approval: Not Required

Acknowledgement: We would like to extend our gratitude to Dr Mahtab Sharifi and Dr Marta Futema, as Mutia Lailani's lecturers on this topic during her study at the Institute of Cardiovascular Science, University College London.

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. 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(10):850–61.
2. Sharifi M, Futema M, Nair D, Humphries SE. Genetic Architecture of Familial Hypercholesterolaemia. Curr Cardiol Rep. 2017;19(5).
3. Sharifi M, Higginson E, Bos S, Gallivan A, Harvey D, Li KW, et al. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. Atherosclerosis. 2017;263:405–11.
4. NICE. Familial hypercholesterolaemia : identification and management (Last updated 4 October 2019). NICE Clin Guidel. 2008;(August).
5. DeMott K, Nherera L, Shaw E, Minhas R, Humphries S, Kathoria M, et al. Identification and management of familial hypercholesterolaemia (FH) Full guideline August 2008 National Collaborating Centre for Primary Care. London Natl Collab Cent Prim Care R Coll Gen Pract. 2008; (August):244.

6. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. J Am Heart Assoc. 2019;8(24):e013225.
7. Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72(6):662–80.
8. Gidding SS, Champagne MA, De Ferranti SD, Defesche J, Ito MK, Knowles JW, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement from the American Heart Association. Circulation. 2015;132(22): 2167–92.
9. Humphries SE. Guidelines for the identification and management of patients with familial hypercholesterolaemia (FH): Are we coming to a consensus? Atheroscler Suppl. 2011;12(2):217–20.
10. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 SUPPL.):S9.
11. GHR. LDLR gene. NIH Genetics Home Reference. 2020.
12. GHR. APOB gene. NIH Genetics Home Reference. 2020.
13. GHR. PCSK9 gene. NIH Genetics Home Reference. 2020.
14. Taylor A, Wang D, Patel K, Whittall R, Wood G, Farrer M, et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet. 2010;77(6):572–80.
15. Teslovich TM, Musunuru K, Smith A V., Edmondson AC, Stylianou IM, Koseki M, et al. Biological, Clinical, and Population Relevance of 95 Loci for Blood Lipids. Nature. 2010;466(7307):707–13.
16. 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(9874):1293–301.
17. Futema M, Shah S, Cooper JA, Li K, Whittall RA, Sharifi M, et al. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. Clin Chem. 2015;61(1):231–8.
18. Herman K, Van Heyningen C, Wile D. Cascade screening for familial hypercholesterolaemia and its effectiveness in the prevention of vascular disease. Br J Diabetes Vasc Dis. 2009;9(4):171–4.
19. Descamps OS, Tenoutasse S, Stephenne X, Gies I, Beauloye V, Lebrethon MC, et al. Management of familial hypercholesterolemia in children and young adults: Consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. Atherosclerosis. 2011;218(2):272–80.
20. Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia - Trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus? Atherosclerosis. 2013; 226(2):315–20.

How to cite this article: Mutia Lailani, Desy Nofita Sari. Familial hypercholesterolemia: how far should we go? *International Journal of Research and Review*. 2023; 10(6): 238-245. DOI: *https://doi.org/10.52403/ijrr.20230628*

******