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Review Article

Shortcomings on genetic testing of Familial hypercholesterolemia (FH) in India: Can we collaborate to establish Indian FH registry?

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ABSTRACT

Familial hypercholesterolemia (FH) is a common autosomal dominant disorder that affects ~1 in 250 −500 individuals globally. The only prevalence study in India shows FH in 15% of patients with premature CAD in North Indians. There are only 6 genetic studies in India of the total mutations, 32% are LDLR mutations, 4% are ApoB, 2% are PCSK9 mutations and the mutational spectrum for 37% is unknown. This calls for widespread genetic screening which could help identify definite FH patients.

European Atherosclerosis Society-Familial Hypercholesterolemia Studies Collaboration (EAS- FHSC) has taken an initiative to develop a worldwide registry of FH. India is also a part of the collaboration and 3 groups from Mumbai, Delhi and Chennai are actively contributing to this registry. We believe this review might help to understand the Indian scenario of FH and investigators across India can contribute in managing FH in India and further help in the detection, diagnosis and treatment.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal, dominant, multifactorial disease which follows mendelian inheritance. FH results in very high levels of Low Density lipoprotein- Cholesterol (LDL-C) in blood, cholesterol deposits in peripheral tissues, presence of tendon xanthomas and increases the risk of early and accelerated Coronary Artery Disease (CAD).[1] It is the first genetic disorder of lipid metabolism that was characterized both clinically and molecularly.[2] FH can result primarily from gene mutations in either Low Density Lipoprotein-Receptor gene (*LDLR*), Apolipoprotein B-100 gene (*ApoB*), or proproteinConvertaseSubtilisin/Kexin type 9 gene (*PCSK9*), singly or in combination.[3] FH exists in two clinical forms. Heterozygous (He) FH is the most common and less severe which affects 1 in 200−250 where LDL-C levels are approximately twice as those of the normal population ranging from 190 to 400 mg/dL (4.9−10.3 mmol/L). Homozygous (Ho) FH is rare and severe, clinically characterized by high LDL-C levels >500 mg/dL (13 mmol/dL), with a prevalence of 1 in 1×10^6.[4]

In routine practice for FH patients, early diagnosis and appropriate treatment is necessary along with family cascade screening to prevent premature death as hypercholesterolemia itself is asymptomatic. Although there has been no accurate study on FH diagnosis rates in India, and hence they are assumed to be low. Therefore, there is an urgent need to raise FH detection and further contribute to FH management in our public health. This can be achieved through a collaborative Indian FH study to understand incidence and prevalence of the disorder which will help in the survey of FH patients all over India who are generally underdiagnosed in routine practice which ultimately will improve management and treatment of FH patients.

2. Background and history

In 1938 Carl Müller, described FH as an “inborn error of metabolism” that produces high blood cholesterol and myocardial infarction in young people.[5] Müller concluded that FH is transmitted as an autosomal dominant trait. In 1964, Khachadurian, showed that clinical phenotype can be further characterized into the mild heterozygous (HeFH) and more severe homozygous (HoFH) forms with dominant inheritance.[6] In 1972, Nobel laureates Goldstein and Brown in an attempt to understand about FH, applied the techniques of cell culture to explain the postulated regulatory defect in FH. These studies led to the discovery of low density lipoprotein receptor (LDLR) which is a cell surface protein for a plasma cholesterol transport. FH was shown to be caused by inherited gene defects in the LDL-R, which disrupt the normal function of cholesterol metabolism.[7] By the mid-1970s, there were

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four families of peptides associated with the major lipoproteins.[8] Apolipoprotein B100 functions as a ligand that links the LDL particle to the LDLR. Of >200 Apolipoprotein B variants, only a few are known to impair function and are included in genetic testing panels for FH.[9]

In 2003, Seidah et al identified the ninth member of the proprotein convertase family, PCSK9.[10] In the same year, the involvement of PCSK9 in regulating cholesterol metabolism became evident, with the identification of two gain-of-function (GOF) mutations in *PCSK9* gene, in two French families with a clinical diagnosis of Autosomal Dominant Hypercholesterolemia (ADH) and no detectable mutations in *LDLR* or *ApoB100* genes.[11] The first Loss Of Function (LOF) mutations were described in 2005 and the effect of lifelong reductions in LDL-C induced by these LOF mutations was examined in the atherosclerosis risk in communities study.[12]

Currently 3 accepted criteria for FH diagnosis are; the US MEDPED criteria, Simon Broom criteria and Dutch lipid Network Criteria (DLNC) (Supplementary 1). The Dutch criteria for the diagnosis of FH are the modification of the Simon-Broome criteria. Advantage of DLNC is, this criterion is set out in point system classified as Definite FH, Probable FH and Possible FH and is effective and acceptable in a day-to-day lipid clinic.[13]

3. Prevalence of FH in India

A number of studies in India have been carried out to study the lipid profile in CAD, but there has been little mention of FH in these publications. One previous study, which described clinical profiles and treatment patterns of 997 patients with premature CAD, just briefly mentioned that there was 1.3% prevalence of possible FH in the study population.[14] Also, a previous study from Tamil Nadu showed that even the awareness and knowledge of FH among primary care physicians remains suboptimal.[15] Similarly our group in Mumbai conducted a survey on FH awareness among General Practitioners (GPs) using a multiple choice questionnaire devised by Prof. Gerald Watts, (University of Western Australia, Royal Perth Hospital, Australia). Of 79 GPs who participated in the survey, 67% (n = 53) were unaware of the clinical definition of FH and 72%(n = 57) did not know about its prevalence.[16]

There have been many international initiatives such as Amgen, The Familial Hypercholesterolemia Foundation And Stanford Medicine Launch FIND FH™ Initiative, The FH Foundation (thefh-foundation.org/registry), European Atherosclerosis Society - Familial Hypercholesterolemia Studies Collaboration (EAS-FHSC) (easfhsc.org), ScreePro-FH studies (screenprofh.com) etc to increase awareness and early screening but the move has not been so encouraging except for a few countries.

Thus, there are huge gaps about the knowledge, frequency of occurrence, diagnosis and care of FH in India. But recently, Sawhney et al, 2019 show a high prevalence of FH in premature Coronary Artery Disease (CAD) patients to be 15% who were diagnosed according to Dutch Lipid Network Criteria (DLNC). They showed that the prevalence of potential (definite + probable FH) FH in premature CAD patients is about 15%, which is comparable with an estimate of 14.3% (95% confidence interval, 9.0%–19.5%) prevalence in an Australian study of 175 patients admitted in coronary care unit with CAD at age <60 years.[17] Moreover, in U.S the prevalence of FH in young adults with Myocardial Infarction (MI) is nearly 10%, which is about 20 times higher than that observed in general population.[18]

4. Genetic analysis of FH patients in India

Genetic testing for FH is important in individuals with high LDL–C as this disorder is not affecting a single patient but a condition affecting 50% of first degree relative in the families of FH. Genetic testing is widespread in entire Europe and especially in Netherlands and Norway because of founder effect, which is the loss of genetic variability in a population that occurs when a new population is formed through the migration of a small number of individuals who carry a higher proportion of FH mutations by chance in their population.[19] Also, Japan, Australia, New Zealand and Canada are doing well in genetic testing and diagnosis of FH. However, genetic testing is not widely practiced in many countries across the globe.[20]

Indian genetic data on FH is very limited and unfortunately, there are only 6 genetic studies which have been published and are mentioned in Table 1. Ashavaid et al, 2000, reported mutations on Exon 3 and 4 in *LDLR* gene in 25 FH Indian patients. After almost a decade, few more genetic studies have been performed by Kulkarni et al,2011, Aruljothi et al,2016 and Setia et al,2016 & 2018 and most recent Reddy et al, 2021 have reported known and novel mutations in *LDLR and PCSK9* genes. Also, these studies demonstrate heterogeneity of mutations in *LDLR* gene and other genes involved in this disorder within Indian population,[21] ([22]),[23] ([24]),[25] ([26]),.[27]

In these studies, FH patients were classified according to Simon Broome criteria or Dutch lipid criteria and all patients had LDL-C levels >200 mg/dL. A total of 106 FH patients have been screened in these studies and of total number of mutations found in these studies, 39% are LDLR mutations, 5% are *ApoB* mutations, 3% are PCSK9 mutations, 3% *ABCA1* and 1% *LPL*, and 0.52% mutations in *ABCG5, ABCG8, LDLRAP1* each. And the mutational spectrum for 48% is still unknown (Fig. 1). Also, the spectrum of mutations in the Indian population is quite heterogeneous since none of the mutations overlapped in these above studies. Moreover, there are patients who are phenotypically and clinically considered FH patient but no mutations were detected in these classical genes (*LDLR, ApoB & PCSK9*) suggesting there might be other genes involved. FH is now considered to be polygenic disorder where multiple genes also termed as non-classical FH genes are associated with LDL-C metabolism. These genes includes lysosomal acid lipase gene (*LIPA*), ATP- binding cassette sub-family G member 5 and 8 (*ABCG5/8*) and cholesterol 7 alpha-hydroxylase (*CYP7A1*), Apolipoprotein (*APOE*), or Signal Transducing Adaptor Family Member 1 (*STAP1*), and other genes involved in cholesterol metabolic process.[28] There are huge gaps in India about the genetic knowledge and mutation frequency and overall prevalence of FH patients. Early detection followed by aggressive therapy [e.g., statin dosage, ezetimibe, PCSK9 inhibitors], and cascade screening of extended families has to be initiated to reduce the morbidity and mortality in these patients. Setia et al, performed cascade screening for 30 families which led to identification of 88 new cases, with a pathogenic mutation, who were at a very high risk of developing premature CAD. In cascade screening program there are high possibility of identifying more individuals in the family asymptomatic and at a high risk of developing CAD and hence cascade screening has been effectively adopted worldwide for clinical risk evaluation.[29] Thus, a widespread whole exome/genome genetic screening for FH from different parts of India, could help identify patients who would normally not be diagnosed with the disease through conventional methods.

5. The global FH registry initiative: EAS-FHSC

The European Atherosclerosis Society - FH Studies Collaboration (EAS - FHSC) is an international initiative led by Prof. Kausik Ray (Imperial College London, UK), which aims to develop a worldwide, cross-regional registry of FH patients and promote a network of investigators interested in FH (www.eas-society.org/fhsc). EAS-FHSC has since 2015 collected data from FH investigators from all

Table 1
Consolidated Indian FH genetic Studies with mutations in *LDLR, ApoB, PCSK9* and other non-classical FH genes.

REFERENCES	SAMPLE SIZE	GENES SCREENED	METHOD	*LDLR*	*ApoB*	*PCSK9*	Non-classical genes
ASHAVAID ET AL., 2000, MUMBAI [21, 22]	**25 Hypercholesterolemic patients**	LDLR Apo B (exon 26)	Single-stranded conformation polymorphism (SSCP) and Hetroduplex Analysis (HAD)	**EXON 3** ins397G **EXON 4** ins242G	No mutation Found	_	_
KULKARNI ET AL, 2011, KARNATAKA [23]	**24 FH patients and 10 normal controls**	LDLR	Sanger sequencing	**Exon 3** g.18298A>C, **Exon 10** g.29209A>G & g.29372_29373insC **in Exon 10 was present in all 24 patients**	_	_	
ARULJYOTHI ET AL., 2016 TAMILNADU [24]	**30 out of 300 CAD** patients UK-Simon Broome criteria **EXON 6** c.862G>A **EXON 7** c.966 C>T **EXON 10** c.1399_1400delins AC>TA **EXON 12** c.1845+2T>C	- exons and exon-intron boundaries of LDLR gene, - ApoB (only exon 26) - PCSK9 (only exon 7)	High Resolution Melt (HRM) curve analysis	**EXON 4** c.694 + 8_694 + 18del **INTRON7**,c.1180 + 17C>T	No mutation Found		
SETIA ET AL., 2016 DELHI [25]	**16 Homo FH from 11 families**	- entire LDLR gene - ApoB - two exons 26 & 29 - PCSK9 – Exon 7	Sanger Sequencing and Multiplex ligation-dependent probe amplification (MLPA)	**EXON 4** c.530 C>T, c. 590 G>A **EXON 8** c.1070_1070delA **EXON 10** c.1418T>A **EXON 15** c.2286_2286 delG **EXON 16** c. 2370_2389 + 20 del c.2389G > A **EXON 17** c.2416_2417insG c.2547 + 5 G>A **EXON 12** deletion	No mutation Found	**EXON 7** c.1075G>A	
SETIA ET AL., 2020 DELHI [26]	100 unrelated probands (63 males and 37 females)	LDLR, ApoB 100 (exons 26 and 29), PCSK9, and APOE genes.	Sanger sequencing and multiplex ligation-dependent probe amplification technique. Targeted next-generation sequencing (NGS) panel of 18 genes involved in lipid metabolism	**5′UTR** c.-139C>T **EXON 2** c.91G>A **EXON 4** c.325T>A, c.346T>C, c.413C>G, c.519C>G, c.530C>T, c.590G>A **EXON 5** c.757C>T **EXON 8**	**EXON 8** c.897T>G EXON 10 c.1777G>C **EXON 16** c.2335A>T EXON 26 c.7619G>T; c.8462C>T; c.10025C>T EXON 29 c.13538T>G; c.12382G>A; c.12940A>G [a]p.Phe299Leu,	**EXON 1** c.42_43insCTG, **EXON 7** c.1075G>A **EXON 9** c.1487G>A, c.1486C>T	ABCA1, Exon 4; c.254C>T, Exon 15; c.1913G>A, Exon 16; c.2328G>C, Exon 19; c.2726G>A, Exon 24; c.3515A>G ABCG5, Exon3; c.511G>A ABCG8, Exon 11; p.Gly574Arg

(*continued on next page*)

Table 1 (*continued*)

REFERENCES	SAMPLE SIZE	GENES SCREENED	METHOD	*LDLR*	*ApoB*	*PCSK9*	Non-classical genes
				c.1061A>G, c.1066G>T, c.1070_1070delA **EXON 9** c.1285G>A, c.1322T>C **EXON 10** c.1387_1387delT, c.1418_1419delinsAA, **INTRON 10** c.1587-1G>A **EXON 11** c.1618G>A, c.1634G>A **INTRON 11** c.1706-10G>A **EXON 12** c.1783C>T, Exon 12 Deletion **INTRON 12** c.1845+2delT **EXON 13** c.1961T>C, **EXON 14** c.1998G>A, c.2072C>A **EXON 15** c.2286_2286delG, c.2242G>A **EXON 16** c.2370_2389 + 20del, c.2389G>A **EXON 16–18** Large Deletion **EXON 17** c.2396T>G, c.2416_2417insG **INTRON 17** c.2547 + 5 G>A	[a]p.Phe4513Cys, [a]p. Ile779Phe,		LDLRAP1, Exon7; c.712C>T LPL Exon2; c.106G>A; *p.Ser373Arg
REDDY ET Al., 2021 [27]	50 FH cases and 50 Healthy Controls	- entire PCSK9 gene - Exon 3, 4 and 9 of LDLR gene	HRM	**EXON 3** c.301G>A, c.313+1G>C **EXON 4** c.530C>T c.447T>C		**EXON 1** c.-64C>T **EXON 5**c.720C>T c.658-36G>A c.799 + 64C>A; c.799+3A>G; c.1026A>G **EXON7**c.1380A>G **EXON9**c.1420G>A	

[a] Novel.

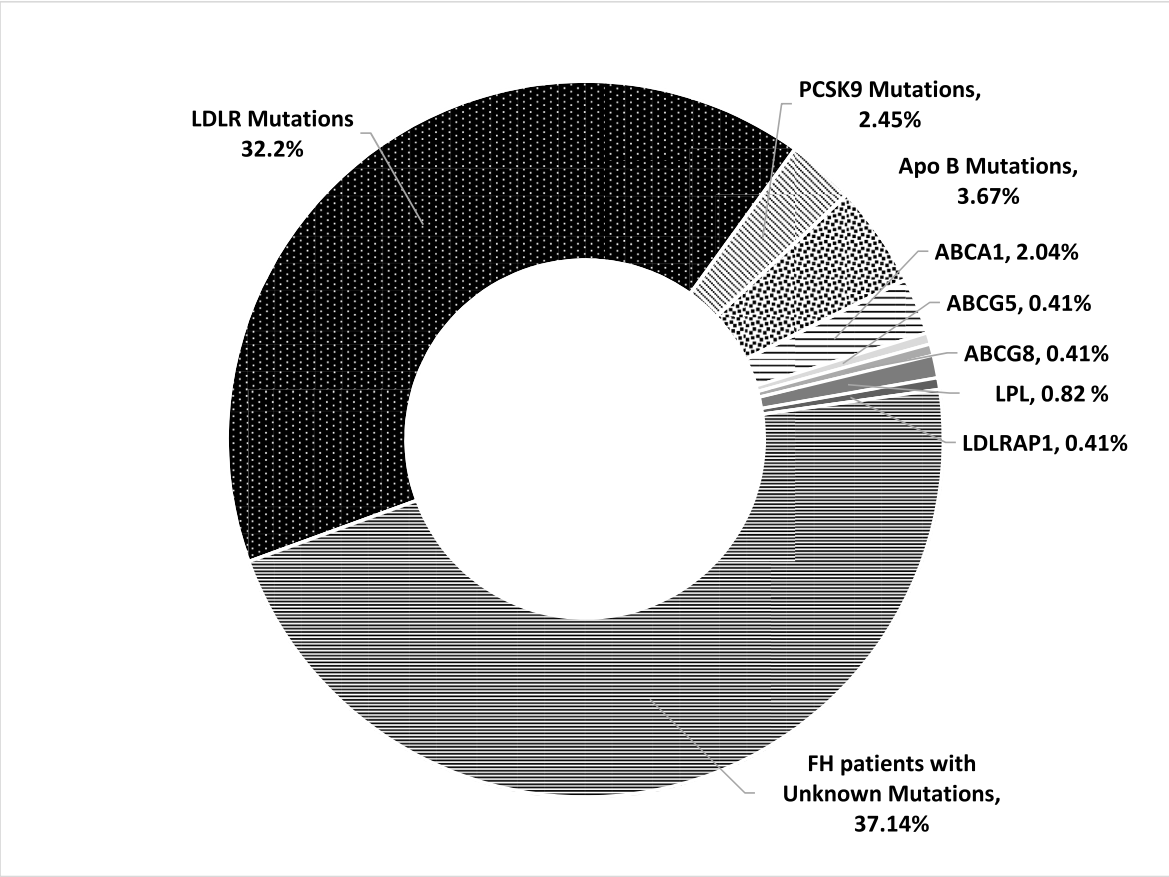

Fig. 1. Consolidation of all mutations found in 245 FH patients in all six genetic studies conducted in India.

over the world. Currently, investigators from ~70 countries are involved, with >50,000 cases already included in the registry [30].The registry is a comprehensive, robust database of compiled secondary, unidentifiable, anonymized data on the burden of FH worldwide. These secondary data are sourced from multiple active national/regional/local registries across countries, and submitted to the FHSC Registry where data is standardized, pooled, harmonized and integrated into a single global database.[30]

The EAS-FHSC represents an excellent opportunity to integrate individual efforts across the world to tackle the global burden of FH. The information garnered from the registry will help reduce gaps in knowledge, inform best practices, assist in clinical trials design, support clinical guidelines and policies development, and ultimately improve the care of FH patients,[31] ([32]).

Dr. Tester F. Ashavaid (P. D. Hinduja Hospital & Medical Research Centre, Mumbai) is the National Lead Investigator appointed by the EAS-FHSC to co-ordinate with the Indian collaborators. At present 2 centers; New Delhi (Sir Ganga Ram Hospital) and Chennai (SRM institute of Science and technology) have collaborated to contribute to the FH registry. A total of 215 FH patient details have been added to the registry where each patient has been assigned with unique FHSC-ID. Demographic details, Diagnostic criteria (Baseline characteristics, Baseline lipid lowering medication and other medications are recorded. Baseline Lipids and other laboratory parameters with follow-up tests with Angiography and Echocardiography are also included in the registry. Recently, the entire EAS-FHSC registry data from 70 countries of FH patients above 18 years has been published by The Lancet.[33]

India being an ethnically diverse country, a multicentric FH study can be conducted with doctors, consultants, researchers from different states/cities to develop a collaborative Indian FH registry which can raise awareness of the disease and encourage the development of programmes, initiatives and policies specifically focused on FH. This can be done by joining efforts from healthcare providers, patient organizations and the entire medical community. The Indian FH registry data will help to provide information about the real pathogenic mutational spectrum of FH across the states, and also, recognize the FH families through cascade screening to estimate the true FH prevalence. Hence, a nationwide consensus FH definition with criteria may lead to better identification, earlier treatment, and ultimately, prevention from premature CAD. This initiative of India can then be combined with the EAS-FHSC for further worldwide data analysis and management. **Conclusion:**

Burden of FH in India has to be tackled with efforts from all ethnic groups across the country which will result in collaborative and harmonized FH data from different cities or states. India is known for high degree of inbreeding. This makes it necessary to screen a large number of patients perhaps within each ethnic group along with cascade screening in order to get a true picture of all mutations. Once the spectrum of mutations is developed in Indian population, it will be little easy for the clinicians for early diagnosis of FH and make the treatment effective considering the cost, time and life of the patients.

There are important gaps to be addressed in detection, diagnosis and treatment for FH in India. Broader implementation of primary and pediatric care, general physicians, lipid clinics specialists,

dermatologist and education/training/research program workers are needed to improve the care of patients with FH in our country.

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Appendix A. Supplementary data

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