Journal of Clinical Lipidology (2016) 10, 490–496

Journal of Clinical Lipidology

Genetic diagnosis of familial hypercholesterolemia in Han Chinese

Kuan-Rau Chiou, MD, Min-Ji Charng, MD, PhD***

Faculty of Medicine, School of Medicine, National Yang–Ming University, Taipei, Taiwan, R.O.C (Drs Chiou and Charng); Division of Cardiology, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, R.O.C (Dr Chiou); and Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C (Dr Charng)

KEYWORDS:
Chinese;
Familial hypercholesterolemia;
Genetics;
Low-density lipoprotein receptor;
Mutation

Abstract: Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism resulting in elevated serum levels of low-density lipoprotein cholesterol (LDL-C), which lead to increased risk for premature cardiovascular disease. The recognized cause is mutations of the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin type 9 genes. This study reviewed the literature in Han Chinese to investigate the frequency and spectrum of mutations that are recognized by molecular genetics as causes of FH, the clinical characteristics, and mutation detection rates of FH. MEDLINE, EMBASE, BIOSIS, Wanfang, CNKI, and FH websites, were reviewed through December 2014. Sixty-six studies met inclusion criteria. Totally, 143 different *LDLR* mutations were identified, including 134 point mutations and 9 large rearrangements; functional characteristics of 46 point mutations were studied. The 5 most frequent mutations included *APOB* 10579C>T, *LDLR* 986G>A, 1747C>T, 1879G>A, and 268G>A. Most of these mutations were reported in Southeast China, Hong Kong, and Taiwan. DNA detection rates of heterozygous FH were 6.5% to 77.5%, depending on the inclusion criteria and chosen screening method. With the economic growth and Western-like diet patterns being adopted over the past decade in municipalities in mainland China and Taiwan, the mean pretreatment concentration of LDL-C is higher among heterozygous FH patients reported since 2005 than in patients reported before 2005 (231 vs 196 mg/dL, $P < .001$). This review of DNA data for Han Chinese patients with FH updates the frequency and spectrum of FH scenarios. Large-scale investigations are needed to determine the interactions between mutations and LDL-C level in relation to cardiovascular risk assessment and management.

Introduction

Familial hypercholesterolemia (FH, OMIM #143890) is an autosomal dominant disorder, characterized by an increased level of circulating low-density lipoprotein cholesterol (LDL-C) that leads to lipid accumulation in skin, tendons and arteries, premature atherosclerosis, and increased risk of cardiovascular disease (CVD). Gene

* Corresponding author. Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.

** Corresponding author. Division of Cardiology, Department of Medicine, Kaohsiung Veterans General Hospital, No.386, Dar-Chung First Road, Kaohsiung 813, Taiwan, R.O.C.

E-mail address: krchiou@hotmail.com; mjcharng@vghtpe.gov.tw

Submitted August 23, 2015. Accepted for publication January 26, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.01.009

mutations affecting 3 genes have been accepted as its causative mutations, mutations in the low-density lipoprotein receptor gene (*LDLR*, Mendelian Inheritance in Man (MIM) # 606945), which lead to lack or defect of functional hepatic receptors for uptake of circulating low-density lipoprotein; mutations in the apolipoprotein B gene (*APOB*, MIM # 107730), which is the ligand for interaction with the LDLR; and mutations in the proprotein convertase subtilisin kexin type 9 gene (*PCSK9*, MIM # 607786), which is involved in the degradation of LDLR protein.[1–3] FH frequency in the Caucasian population ranges from 1/200 to 1/500 individuals.[4,5] Genetic DNA testing can be used to diagnose hypercholesterolemia-associated mutations at any age, which allows for early intervention to prevent or delay the development of CVD.[6]

The percentage of Han Chinese, an ethnic group native to East Asia, in the total national population is approximately 92% in mainland China, 95% in Hong Kong, 98% in Taiwan, 74% in Singapore, and 25% in Malaysia. At an estimated FH prevalence of 1/500, more than 2.6 million Han Chinese have FH. However, almost all cases of FH are undetected in clinical practice.[7] Newly developed molecular diagnostic capabilities are expected to provide the impetus for correcting this situation. The focus of this review is 3 fold: the frequency and spectrum of mutations recognized by molecular genetics to cause FH, the phenotypic expressions, and the lipid changes over time in Han Chinese with FH.

Materials and methods

Patient search strategy and eligibility criteria

Genetically diagnosed Han Chinese FH patients from publications in English or Chinese between 1986 and December 2014 were enrolled. The electronic databases in English included MEDLINE, EMBASE, BIOSIS, and 2 online FH data banks: the British Heart Foundation and the JoJo Genetics DNA Diagnostiek,[8–10] and those in Chinese included Wanfang and CNKI data. The search terms were "familial hypercholesterolemia," "LDL receptor," "APOB-100," "PCSK 9," "genetics," "Han Chinese," or "Chinese," and these terms' variants and combinations. For a study to be considered eligible, it had to have reported genetic data related to FH in sample populations of Chinese subjects that fit the clinical criteria for diagnosis of FH. In addition, the probands of these studies would have undergone DNA testing for either *LDLR*, *APOB*, or/and *PCSK9*. The following literature bodies were excluded: studies that did not apply the FH diagnosis criteria, non-research–based publications (such as press releases, newsletters, forum discussions, and so forth), redundant Chinese editions that had been published in English (Medline), or studies that did not disclose when the data were collected.

Study data extraction and nomenclature of sequence variations

General information, including authors, year, title, and type of publication, was extracted for each study. Once a mutation had been identified in a patient with clinically diagnosed FH, the patient was referred to as a proband. Clinical characteristics (including age at genetic diagnosis, gender, and pretreatment lipid levels) of probands and their family members were recorded if available. Functional characterization of *LDLR* mutations, discovered in *ex vivo* or *in vitro* studies, were collected if available. Nomenclature of sequence variations at DNA level and its predicted effect at the protein level were described as recommended by the Ad-Hoc Nomenclature Committee of the Human Genome Variation Society.[11] Mutations were considered in accordance with the following criteria: (1) confirmed presence in affected probands and cosegregation with hypercholesterolemia in affected family members; (2) absence from a public database of polymorphisms (http://www.ncbi.nlm.nih.gov/projects/SNP/); (3) absence of a previous report of the gene as an FH-causing mutation. Private mutations referred to those mutations found in only 1 to 3 single probands.[10]

To predict possible impact of an amino acid substitution on the structure and function of protein products, newly discovered missense variants were subjected to online computer prediction programs: PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.bii.a-star.edu.sg/).

Statistical analysis

Categorical variables were presented as numbers and percentages and compared using the chi-square test. Continuous variables were presented as mean ± standard deviation and compared using the Student's *t* test or 1-way analysis of variance. Ages were expressed as medians with range and compared using nonparametric Kruskal-Wallis H test. Data were collected and analyzed using SPSS version 18.0 (SPSS Inc, Chicago, IL). A *P* value less than .05 was considered statistically significant.

Results

Molecular genetic diagnosis of the LDLR and APOB genes

Sixty-six studies met inclusion criteria (Supplementary Table 1 and References). A total of 339 probands carrying FH gene mutations were obtained. Supplementary Table 2 summarizes the *LDLR* gene substitutions and small deletions/insertions, and Table 1 summarizes the large DNA rearrangements. Among these results, there were 46 point mutations whose functional characterization had been