Familial Hypercholesterolemia in Asian Populations

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Familial hypercholesterolemia (FH) is the most common autosomal disorder characterized by an elevated low-density lipoprotein-cholesterol level and a high risk of premature cardiovascular disease. In this review, we summarize information on FH studies in Asian countries, focusing on mean cholesterol level, FH frequency, diagnostic criteria, genotypes, and clinical care of FH patients in Asian populations. Compared with Western countries, most Asian countries had lower mean cholesterol levels, with a significant variation between different countries. In the limited studies reported, a frequency of 1/900 was reported in Hokuriku district, Japan in 1977 and a frequency of 1/85 among Christian Lebanese in 1979. Recently, a population study in China reported frequencies of 0.47% and 0.28%. However, the different FH frequencies reported were based on different diagnostic criteria. Of 28 publications from 16 Asian countries or regions, 14 used self-defined FH criteria. Only one specific guideline for FH was available, which was developed by Japanese scientists. Six Asian countries joined the Make Early Diagnosis to Prevent Early Deaths program in the late 1990s, and the estimated diagnosis rates of FH ranged from 3% to 10% in these countries. A more recent study explored the awareness, knowledge, and perception of FH among practitioners in Japan, Korea, and Taiwan. The study found that the correct rates of these FH-related questions were low and concluded that lack of country-specific criteria and guidelines may contribute to the lack of FH knowledge in the present survey. More attention and resources should be focused on raising awareness, improving care, and increasing FH research in Asian populations.

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Key words: Familial hypercholesterolemia, Epidemiology, Asian population

Introduction

Familial hypercholesterolemia (FH) is the most common autosomal dominant disorder.1) Mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (ApoB), proprotein convertase subtilin/kexin9 (PCSK9), and low-density lipoprotein receptor adapter protein 1 (LDLRAP1) genes have been linked to FH.2-5) These mutations result in a disorder in low-density lipoprotein cholesterol (LDL-C) catabolism, and consequently, significantly elevating the levels of LDL-C in serum, eventually leading to specific clinical signs such as tendon xanthoma, corneal arcus, and premature cardiovascular disease (CVD).6)

FH should be considered as a more important risk factor for atherosclerotic CVD than an elevated LDL-C level, because FH is a hereditary disease and patients suffer from high LDL-C since they are born. And a longer exposure to elevated serum cholesterol levels is associated with a higher premature CVD risk. Additionally, an earlier detection of FH in patients can be an efficient method of identifying high-CVD-risk patients in their families, compared with the opportunistic screening of serum cholesterol levels in general population. Although FH indicates high CVD
risk and have several easily recognized phenotypes, including elevated LDL-C level, family history, tendon xanthoma, or corneal arcus, can be used to identify FH cases, few population surveys for CVD risk factors have reported FH frequencies. To date, the estimated frequencies of FH in some populations are largely based on the selected patients. A commonly cited estimation of the frequency of heterozygous FH (HeFH) is 1/500 individuals (0.2%)\(^7\). This estimation was calculated from the FH frequency in survivors of myocardial infarction, aged <60 years, in a single study with some assumptive frequencies, including the prevalence of coronary heart disease (CHD) in the population of the United States\(^7\). Based on the estimated HeFH frequency, the estimated homozygous FH (HoFH) frequency was approximately one per million \([1/500 \text{ (father)} \times 1/500 \text{ (mother)} \times 1/4 \text{ (child)}]\)\(^6\). This HeFH frequency estimation was supported by a study of myocardial infarction survivors in the United Kingdom (UK) and studies in other countries\(^8\)-\(^11\). In particular, the Copenhagen General Population Study in Denmark reported that the frequency of definite FH in a population of 69,016 was 1/504, close to the estimated frequency of the well-accepted figure of 1/500. The study also reported an FH frequency of 1/137, if FH patients were defined using a definite or probable definition of the Dutch Lipid Clinic Network (DLCN) criteria\(^11\). A nationwide FH screening program among patients who were referred to the molecular diagnostic laboratory of the Academic Medical Center in the Netherlands reported that the frequency of HoFH was 1/300,000 based on a genetic test, and the calculated frequency of HeFH was 1/244\(^12\). Higher heterozygous frequencies ranging from 1/400 to 1/67 were also found in the Finns, French Canadians, Indians in South Africa, Christian Lebanese, and Afrikaners in South Africa, which may result from the founder effect\(^13\)-\(^19\).

Increasing efforts have been focused on early detection and earlier treatment of FH patients worldwide. Six Asian countries or regions, including Japan, Hong Kong, Singapore, Malaysia, Lebanon, and Israel, took part in the Make Early Diagnosis to Prevent Early Deaths (MEDPED) program in the late 1990s, with the purpose of identifying and treating affected people, to prevent heart attacks at a young age\(^20\). Furthermore, there are an increasing number of FH studies in Asia; FH-related researches have been reported from 28 countries and regions in Asia. This review aims to provide summary information on FH studies in Asian populations, with a focus on mean cholesterol level, frequency, diagnostic criteria, identified genotypes, and clinical care of FH patients.

### Mean Cholesterol Level in Asian Populations

Data from the World Health Organization (WHO) identified the age-standardized estimate of the global mean total cholesterol (TC) level as 4.6 mmol/L for men and 4.8 mmol/L for women\(^21\). In general, the mean TC value in most Asian countries was lower, compared with Western countries. However, varied serum TC levels were observed among Asian populations (Fig. 1 and Fig. 2). The population of some Asian countries, such as Singapore, had higher mean TC level, and the age-standardized mean TC value in these countries was 5.2 mmol/L for men and 5.4 mmol/L for women. In other Asian countries, such as Afghanistan, a lower mean TC level has been reported, age-standardized mean TC values being 4.1 mmol/L for men and 4.2 mmol/L for women\(^21\).

### Frequency of FH in Asian Populations

Several valuable FH studies in Asian countries have reported the estimated FH frequency with different diagnostic criteria and estimation methods. The earliest report, published in 1977 by Mabuchi and colleagues, estimated that the HeFH frequency in Hokuriku district of Japan was 1/900\(^20\). Slack et al. reported an estimated HeFH frequency of 1/85 in Christian Lebanese, based on the number of HoFH cases in about one million people aged less than 30 years\(^23\). The HeFH frequency was estimated from the observed homozygous frequency, assuming 0.2 as the proportion of first-cousin marriages and using a modified Hardy–Weinberg equilibrium formula. This very high frequency of FH was considered because of the founder effect\(^24\). In 2011, Mabuchi et al. reported an updated estimation of FH frequency in Japan. Based on 18 HoFH cases identified in a population of 3,081,000 in Hokuriku district and calculated using the Hardy–Weinberg equilibrium, the authors estimated that the frequencies of HoFH and HeFH were 1/171,167 (5.8 per million) and 1/208 (0.48%), respectively\(^23\). The estimated frequencies of HoFH and HeFH, according to this study, were much higher than the well-known estimations in Western populations. Shi et al. reported the estimated FH frequency among Chinese adults in 2014\(^26\). This study proposed two definitions of FH for Chinese populations: the LDL-C-based FH definition and modified DLCN definition. For the LDL-C-based definition, an individual having LDL-C ≥ 6 mmol/L or LDL-C ≥ 3.5 mmol/L and <6 mmol/L plus a personal or family history of premature CHD was defined as having FH. For the modified DLCN definition, the lower LDL-C
level-based distribution of the LDL-C level in the
Chinese population replaced the LDL-C value
required by the original DLCN criteria, for a same
level score. For example, the score for the LDL-C level
3.5–4.9 mmol/L in the modified DLCN criteria
was equal to the score for that of 5–6.4 mmol/L in
the original DLCN criteria. Using the LDL-C-based
definition, 44 FH patients were identified in a sample
of 9,280 people, with an FH prevalence of 0.47%, or an
age-standardized rate of 0.31%. The prevalence and
age-standardized rate of probable FH were 0.28% and
0.18%, respectively, using the modified DLCN definition.
Based on the modified DLCN definition, 9.5% of
the population had possible FH.

Diagnostic Criteria for FH in Asian Countries

Internationally, the three most widely used diag-
nostic criteria were developed by the United States
MEDPED program\textsuperscript{27}, the UK Simon Broome Regis-
ter Group (SBRG)\textsuperscript{28}, and the DLCN\textsuperscript{29}. In Asia,
Japan and China have developed their own diagnostic
criteria\textsuperscript{26, 29, 30}. The FH diagnostic criteria issued by
Japanese scientists included three key diagnostic com-
ponents: LDL-C level, tendon xanthoma or xanthoma
tuberosum, and family history\textsuperscript{31}. The clinical criteria
developed by China can be found in the textbook
Clinical Coronary Heart Disease, which included two
key diagnostic components: TC/LDL-C level and
patients or family members with tendon xanthoma\textsuperscript{29}).

A recently published paper proposed new FH defini-
tions for Chinese populations; the new definitions
need to be accepted and recommended by the relevant
professorial societies before they can be used clini-
cally\textsuperscript{26}. Korean researchers compared the sensitivity
and specificity of several well-known diagnostic crite-
ria using pathogenic mutations identified in gene tests
as a gold standard of FH\textsuperscript{32}. This study, including 97
suspicious FH patients by phenotypes, highlighted
that Japan’s diagnostic criteria had higher sensitivity
Genotypes of FH Reported in Asian Populations

Currently, four genotypes, including LDLR, ApoB, PCSK9, and LDLRAP1, and about 1800 mutations in these genes have been reported for FH \cite{1,36}. Data from the UK LDLR mutation database (http://www.ucl.ac.uk/ldlr/LOVDv1.1.0/) for FH showed that there were 1,741 different types of mutations in the LDLR gene. Of all the mutations, about two-thirds were point mutations or small deletion and insertion mutations, and the remaining one-third were large fragment rearrangements. Additionally, 1,122 of these mutations were only reported once \cite{37}. However, the FH gene mutation studies were less reported in Asian countries, compared with Western countries. We selected eight studies from six countries or regions published in the last 10 years, with relatively large sample sizes (>20). Table 2 presents the proportion of different genotypes of FH patients in selected studies. In 2010, the genotypes of 102 unrelated FH

(74%), with a relatively acceptable level of specificity (45%). The combined criteria of definite and probable FH based on DLCN could have 65% sensitivity and 65% specificity. The SBRG criteria had a maximum sensitivity of 94% but only 21% specificity, and in contrast, MEDPED criteria had a sensitivity of 39% but a specificity of 94%. This study reported that the cutoff values for LDL-C 225 mg/dL or TC 310 mg/dL were of the best capacity to detect pathogenic mutations of FH in Korean patients.

Of 28 FH-relevant studies from 16 Asian countries and regions, 6 used DLCN criteria, 5 used SBRG criteria, 3 used MEDPED criteria, and 14 used their own criteria (Table 1). Even in the same country or region, different FH criteria were applied \cite{33-35}. The varied diagnostic criteria used in FH studies have resulted in poor comparability between these studies.
Table 1. The diagnostic criteria used in published FH studies from Asian countries

| Country | Reference | Diagnostic Criteria |
|---------|-----------|---------------------|
| China   | Shi et al., 2014<sup>30</sup> | LDL-C ≥ 6.0 (mmol/L) or LDL-C ≥ 3.5 (mmol/L) plus family (first-degree relative)/personal history of premature coronary heart disease  
Modified Dutch Lipid Clinic Network criteria:  
Family history of a first-degree relative with known premature coronary artery disease (CAD, including myocardial infarction or angina pectoris) or vascular disease (1 point);  
personal history of premature CAD (2 points), or premature cerebral vascular disease (1 point);  
LDL-C > 6.0 mmol/L (8 points), 5.0–5.9 mmol/L (5 points), 3.5–4.9 mmol/L (3 points), or 2.5–3.4 mmol/L (1 point).  
Based on the total score, FH status was classified as definite (> 8), probable (6–8), possible (3–5), and unlikely FH (< 3) |
| Hong Kong | Hu et al. 2013<sup>40</sup> | Criteria for index cases: TC ≥ 7.5 mmol/L or LDL-C ≥ 4.9 mmol/L  
Cascade screening: Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria |
| Taiwan | Chiou et al. 2012<sup>33</sup>, 2010<sup>34</sup>, 2005<sup>35</sup> | The Simon Broome Familial Hypercholesterolemia Register diagnostic criteria  
(1) TC > 7.77 mmol/L and LDL-C > 6.48 mmol/L, respectively  
(2) Positive family history of hypercholesterolemia or early coronary artery disease |
| Cyprus | Xenophontos et al. 2000<sup>49</sup> | TC > 290 mg/dL and LDL-C > 200 mg/dL with normal TG levels (< 175 mg/dL) |
| India | Setia et al. 2012<sup>50</sup> | Presumed homozygotes: LDL-C > 800 mg/dL  
Heterozygotes: LDL-C 200–800 mg/dL  
Unaffected individuals: < 100 mg/dL |
|       | Kondkar et al. 2007<sup>51</sup> | Presumed homozygotes: LDL-C > 800 mg/dL  
Heterozygotes: LDL-C 200–800 mg/dL  
Unaffected individuals: < 100 mg/dL |
| Iran  | Farrokhi et al. 2011<sup>43</sup> | The Dutch Lipid Clinic Network diagnostic criteria |
| Israel | Reshef et al. 1996<sup>52</sup> | Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria |
| Japan | Mabuchi et al. 2011<sup>25</sup> | HeFH:  
(1) Clinical diagnostic criteria: hypercholesterolemia with tendon xanthomas, or hypercholesterolemia in the first- or second-degree relative of FH patients  
(2) Genetic diagnostic criteria: mutations of FH genes  
HoFH:  
(1) Clinical diagnostic criteria: juvenile xanthomatosis with plasma cholesterol level about twice that of parents or other family members with hetero-FH  
(2) Genetic diagnostic criteria: true homozygotes, compound heterozygotes, and double heterozygotes for FH genes |
|       | Yasuko et al. 2009<sup>53</sup> | HeFH:  
(1) type II hyperlipoproteinemia > 260 mg/dL TC with tendon xanthomas;  
(2) type II hyperlipoproteinemia > 260 mg/dL TC and the presence of subjects with type II hyperlipoproteinemia > 260 mg/dL TC with tendon xanthomas in the proband’s first- or second-degree relatives;  
or (3) type II hyperlipoproteinemia > 260 mg/dL total cholesterol and LDL receptor activity of the proband’s fibroblasts lower than that of a normal control |
|       | Yamashita et al. 2008<sup>54</sup> | Definite HeFH: at least two of the major features: TC ≥ 260 mg/dL; tendon xanthoma or xanthoma tuberosum; reduced or abnormal receptor activity noted by LDL receptor analysis.  
Probable HeFH: at least one each of the major (as above) and minor features: palpebral xanthoma; arcus juvenilis (age < 50 years); juvenile (age < 50 years) ischemic heart disease |
|       | Yu et al. 2002<sup>55</sup> | Primary hypercholesterolemia (TC ≥ 5.9 mmol/L and < 12.9 mmol/L) with tendon xanthomas or primary hypercholesterolemia with/without tendon xanthomas in a family with FH patients among first-degree relatives |
patients in Taiwan were analyzed. Genetic mutations were found in 60 patients, of which 52 had \(LDLR\) gene mutations and eight had \(ApoB\) gene \(R3500W\) mutations. In 2012, the gene mutations for FH were identified in 130/208 patients clinically diagnosed by the SBRG criteria in Taiwan, and no patients with \(LDLR\) gene mutations were found. In all, 30 unrelated possible FH subjects with mutations in the \(LDLR\) gene were found in 36 clinically diagnosed patients in Turkey, and no patients with the \(R3500Q\) mutation in the \(ApoB\) gene were found. In 2014, a cohort of 1,055 HeFH patients and 41 HoFH patients was enrolled in a study in Japan. Of all the HeFH patients, 993 carried the \(LDLR\) gene mutation and 62 had the \(PCSK9\ E32K\) mutation. All 41 HoFH patients had \(LDLR\) mutations and 13/41 also had \(PCSK9\ E32K\) mutations. In a Korean study, 31 patients with pathogenic mutations in the \(LDLR\), \(APOB\), and \(PCSK9\) genes were found in 97 patients identified with \(LDL-C > 190\) mg/dL, combining with xanthoma or an FH-compatible family history. Of the 31 patients, 27 had mutations in the \(LDLR\) gene, two had mutations in the \(ApoB\) gene, and two had mutations in the \(PCSK9\) gene. A group of 164 FH patients were recruited to analyze the relationship between the phenotype and genotype in Malaysian FH patients. All of them were screened for mutations in the \(LDLR\) and \(ApoB\) genes, and 123 and 30 FH patients were found to have a mutation in the \(LDLR\) and \(ApoB\) genes, respectively. A total of 29 pediatric FH patients with mutations in the \(LDLR\) gene were found in 36 clinically diagnosed patients in Turkey, and no patients with the \(R3500Q\) mutation in the \(ApoB\) gene were found. In 2015, 30 unrelated possible FH subjects diagnosed by the DLCN criteria were tested for mutations in the \(LDLR\) and \(ApoB\) genes in Iran. LDLR mutations were found in 17% (5/30) of the study population, and no variation was found in the \(ApoB\) gene. Livy et al. summarized the mutations reported in Asia in 2011. Of the 66 mutations reported from different countries, 55 were in the \(LDLR\) gene and only five were in the \(ApoB\) gene. Therefore, the majority of mutations were in the \(LDLR\) gene, and few mutations in \(ApoB\) or \(PCSK9\) genes were reported in Asian populations. Bamimore et al. performed a
systematic review to identify all FH-related mutations reported in Middle Eastern and Northern Africa (MENA) countries to compare these with mutations reported in Western populations. More than 500 FH-related mutations were reported from Australia, Netherlands, and New Zealand, but only 57 FH-related mutations were reported from 17 MENA countries\(^{43}\).

### Clinical Care of FH Patients in Asian Countries

Of the globally estimated 15.4 million people with FH with a frequency of 1/500, 8.25 million FH patients could live in Asia, accounting for more than 50% of all FH cases. As a clear risk indicator of premature CVD, FH should be detected and treated as early as possible.

On searching all guidelines for the management of dyslipidemia, issued by Asian countries in English and Chinese, we found three guidelines issued by China, Japan, and Korea\(^ {31, 44, 45}\). Japanese scientists issued a specific guideline for FH management, having clear recommendations for FH diagnosis and the treatment of dyslipidemia\(^ {31}\). China’s 2007 guidelines for dyslipidemia lacked a separate section for FH and systematic recommendations for the diagnosis, detection, and treatment of FH\(^ {40}\). There is no description of FH in the lipid management guidelines issued by the Korean Society of Lipidology and Atherosclerosis\(^ {45}\).

Jing Pang \textit{et al.} reported the results of a survey to assess awareness, knowledge, and perception of FH among practicing physicians in Japan, Korea, and Taiwan. Of the 230 physicians surveyed, 47% were aware of the heritability, 27% of the prevalence, and 13% of the risk of CVD relating to FH\(^ {40}\). Lack of specific criteria and guidelines in specific populations may account for the lack of knowledge of FH in this survey. Professional intervention to improve physicians’ awareness and knowledge of FH is the first step toward improving the detection, diagnosis, and treatment to prevent CHD.

The MEDPED program was the earliest global program focusing on FH. Six Asian countries or regions participated in this program and four of them.

### Table 2. The proportion of LDLR, ApoB and PCSK9 genotypes for FH in different studies

| Country/Region | Sample size of study | No. of FH subject with mutations | Proportion of three genotypes for FH | Reference |
|----------------|----------------------|----------------------------------|-------------------------------------|-----------|
| Taiwan         | 102                  | 60 patients                      | 86.7% (52/60) LDLR; 13.3% (8/60) ApoB; not mentioned PCSK9 | Chiou \textit{et al.}, 2010\(^ {34}\) |
| Taiwan         | 208                  | 130 patients                     | 90.7% (118/130) LDLR; 9.3% (12/130) ApoB; not mentioned PCSK9 | Chiou \textit{et al.}, 2012\(^ {30}\) |
| Japan          | 25                   | 15 homozygotes; 10 compound heterozygotes | 92.0% (23/25) LDLR; 0% ApoB; 20% (5/25) PCSK9 | Mabuchi \textit{et al.}, 2011\(^ {25}\) |
| Japan          | 1096                 | 28 homozygotes; 13 compound heterozygotes; 1055 heterozygotes | 94.3% (1034/1096) LDLR; 0% ApoB; 6.8% (75/1096) PCSK9 | Mabuchi \textit{et al.}, 2014\(^ {30}\) |
| South Korea    | 97                   | 31 patients                      | 87.1% (27/31) LDLR; 6.5% (2/31) ApoB; 6.5% (2/31) PCSK9 | Shin \textit{et al.}, 2015\(^ {32}\) |
| Malaysia       | 164                  | 153 patients                     | 80.4% (123/153) LDLR; 19.6% (30/153) ApoB; not mentioned PCSK9 | Al-Khatib \textit{et al.}, 2013\(^ {39}\) |
| Turkey         | 36                   | 16 homozygotes, 13 heterozygotes  | 100.0% (29/29) LDLR; 0% ApoB; not mentioned PCSK9 | Sozen \textit{et al.}, 2005\(^ {40}\) |
| Iran           | 30                   | 5 patients                       | 100.0% (5/5) LDLR; 0% ApoB; not mentioned PCSK9 | Farrokhi \textit{et al.}, 2011\(^ {41}\) |

Abbreviations: FH = Familial hypercholesterolemia; LDLR = low-density lipoprotein receptor; ApoB = apolipoprotein B; PCSK9 = the proprotein convertase subtilisin/kexin9
including Hong Kong, Israel, Japan, and Singapore, reported the estimated number of FH patients, based on the estimated frequency of 1/500 and the total population of these countries or regions (Table 3)\textsuperscript{20}. The percentage of patients being diagnosed ranged from 3% to 10%, which only accounted for a small proportion of all patients. The percentage of the diagnosed patients on statins ranged from 3% to 100%, but well-controlled patients defined as having TC $\leq$ 6.2 mmol/L or LDL-C $\leq$ 3.4 mmol/L only accounted for a small proportion, from 1% to 46%. A computer registry was used in Hong Kong, Israel, and Japan. The MENA regions, including some Asian countries, proposed to build a MENA FH registry in 2015, which will help in identifying and reporting novel FH mutations and will have clinical and research benefits in MENA countries\textsuperscript{43}). Concurrently, the European Atherosclerosis Society FH Studies Collaboration has been launched as an ambitious global initiative, and through a consortium of major FH registries worldwide, aims to generate large-scale data on how FH is detected and managed and explore the clinical implications. The ultimate aims of this proposal are to disseminate FH information and facilitate all countries to improve the care of patients and families with FH\textsuperscript{47}).

In summary, there are relatively limited epidemiological data on FH in Asia, and the frequency of FH is unclear in many Asian countries. There are huge gaps among Asian countries about the knowledge and care of FH. Evidence-based, country-specific criteria and guidelines should be developed based on population-specific cholesterol levels and specific mutations of relevant genes. More attention and resources should be focused to raise awareness, improve care, and increase FH researches in Asian populations.

**Table 3**. The care situation of FH in four Asian countries participated in MEDPED program\textsuperscript{20}

| Country/Region | Total population (million) | Estimated patients with FH | %FH patients diagnosed | %FH patients on statins | %Well controlled patients |
|----------------|---------------------------|---------------------------|------------------------|-------------------------|-------------------------|
| Hong Kong      | 6.5                       | 13,000                    | 4                      | 3                       | 1                       |
| Israel         | 6.0                       | 12,000                    | <10                    | <10                     | <10                     |
| Japan          | 120.0                     | 240,000                   | 10                     | 100                     | 46                      |
| Singapore      | 3.4                       | 6,800                     | 3                      | 90                      | <10                     |

Abbreviations: FH = Familial hypercholesterolemia; MEDPED = Make Early Diagnosis to Prevent Early Deaths

Well-controlled patients were defined as: TC $\leq$ 6.2 mmol/L; LDL-C $\leq$ 3.4 mmol/L.

In 2015, Pfizer sponsored Dong Zhao a trip to attend AHA annual meeting in 2015.

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