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DIAgnosis and Management Of familial hypercholesterolemia in a Nationwide Design (DIAMOND-FH): Prevalence in Switzerland, clinical characteristics and the diagnostic value of clinical scores

A.R. Miserez[a,b,*,1], F.J. Martin[a,b,1], D. Spirk[c]

[a] diagene Research Institute, Swiss FH-Center, Kaegenstrasse 17, CH-4153, Reinach, Switzerland
[b] Faculty of Medicine, University of Basel, Petersplatz 1, CH-4001, Basel, Switzerland
[c] Institute of Pharmacology, University of Bern, CH-3010, Bern, Switzerland

HIGHLIGHTS

- Prevalence estimation of familial hypercholesterolemia (FH) due to pathogenic LDLR and APOB variants in Switzerland.
- Comparison of phenotypic characteristics of FH due to pathogenic LDLR and APOB variants in Switzerland.
- Comparison of the diagnostic value of clinical scores in FH due to pathogenic LDLR and APOB variants.
- Comparison of premature atherosclerosis and the onset of cardiovascular complications in FH due to LDLR versus APOB variants.

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ABSTRACT

Background and aims: In Switzerland, the prevalence of familial hypercholesterolemia (FH) due to pathogenic apolipoprotein B-100 gene (*APOB*) variants was known, but not the prevalence of FH due to pathogenic low-density lipoprotein-receptor gene (*LDLR*) variants. Phenotypic differences (*LDLR* versus *APOB*) might affect the diagnostic value of the Dutch Lipid Clinic Network (DLCN) score and Simon Broome Diagnostic Criteria (SBDC).
Methods: A total of 2734 Swiss subjects were investigated, 2221 unselected subjects from three representative population surveys for estimation of the prevalence (*LDLR* variants), and 513 subjects from the DIAgnosis and Management Of familial hypercholesterolemia in a Nationwide Design (DIAMOND-FH) study for comparisons of phenotypic characteristics (*LDLR versus APOB* variants), diagnostic values of clinical scores, and cardiovascular outcome.
Results: In 7 of 2221 individuals, FH (*LDLR*) was diagnosed (prevalence of FH due to *LDLR* variants: 1/317, prevalence of FH due to both *LDLR* and *APOB* variants: 1/125 to 1/135). In FH (*APOB*) patients under 35 years of age, mean total cholesterol (TC) was < 8.5 mmoL/L but increased above 35. In FH (*LDLR*), TC was > 8.5 mmoL/L in all age groups. This difference was crucial for the diagnosis of FH and resulted in a significantly lower sensitivity of clinical scores in FH (*APOB*) (DLCN: 13.8%, $p < 0.0001$; SBDC: 22.5%, $p = 0.005$). Thus, both scores were not useful for the definite diagnosis of FH due to *APOB* variants. Regarding the cardiovascular outcome, no differences (*LDLR* versus *APOB*) were found above 60 years. In countries with high percentages of FH due to *APOB* variants, cascade screening and molecular testing appear to be much more cost-effective.

1. Introduction

The classical definition of familial hypercholesterolemia (FH) (OMIM#143890) comprises a monogenic disorder based on pathogenic variants in the low-density lipopoprotein-receptor gene (*LDLR,* MIM*606945). The clinical phenotype of this form, characterized by xanthomas, xanthelasms, and arcus lipoides (under 45 years of age), clinical manifestations of cardiovascular disease due to premature atherosclerosis under 55 (men) or 60 years (women), inherited in an autosomal co-dominant fashion, was described more than 75 years ago [1]; the LDL-receptor and its causal role in FH has been elucidated more than 40 years ago [2,3].

* Corresponding author. diagene Research Institute, Swiss FH-Center, Kaegenstrasse 17, CH-4153, Reinach, Switzerland.
E-mail address: a.miserez@diagene.com (A.R. Miserez).
[1] These authors contributed equally to this work.

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However, the initial classical definition of FH was incomplete. As an expression of locus heterogeneity, further disorders cause phenotypes identical or slightly different from that of a classical FH as defined above. These include pathogenic variants in the apolipoprotein B-100 gene (*APOB,* MIM*107730), known as familial-defective apolipoprotein B-100 (FDB) (OMIM#144010) [4], and gain-of-function variants in the proprotein convertase subtilisin/kexin-type 9 gene (*PCSK9,* MIM*607786), known as autosomal dominant hypercholesterolemia, type 3 (HCHOLA3) (OMIM#603776) [5]. In Switzerland, the prevalence of the p.R3,527Q (c.10,580G > A) pathogenic variant, previously described in the literature as the p.R3,500Q-mutation, is extremely high [4]. In contrast, the prevalence of *PCSK9*-variants is estimated to be low; pathogenic variants have not yet been described in Switzerland. The three forms, due to pathogenic *LDLR*-, *APOB*-, and *PCSK9*-variants, have been denoted as autosomal dominant hypercholesterolemia (ADH).

1.1. The use of genetic principles in clinical medicine: cascade screening

In various aspects, FH can be considered as a model disease for a most efficient translation of molecular genetics into clinical medicine. First, FH, inherited in an autosomal (co)dominant fashion, leads to severe clinical consequences, such as myocardial infarction and stroke. Early detection and consequent treatment can prevent premature atherosclerosis resulting in a normal life expectancy in heterozygous FH (heFH) patients. Unfortunately, at least in Switzerland, FH often remains undetected before the first cardiovascular event [6]. It is believed that such an underdiagnosis of FH might be significantly improved by widespread pediatric cholesterol screening [7,8]. However, at least in Switzerland, where FH due to *APOB* variants, thus familial defective apolipoprotein B-100 (FDB), is considered as the most common form of FH and is, in contrast to FH due to *LDLR* variants, not typically characterized by a distinct hypercholesterolemia before the age of 25 to 40 years, FH due to *APOB* variants is difficult to diagnose by cholesterol measurements alone [4,9]. On the other hand, untreated FH due to *APOB* variants is considered to result in a comparable severity of cardiovascular complications as FH due to *LDLR* variants [4,9–12].

Much more cost-effective than cholesterol screening appears therefore the so-called cascade screening [7,12]. In specialized centers, such as at the Swiss FH-Center at the diagene Research Institute, starting from an index patient, the family members of the next generation are tested for FH, usually including molecular genetic analyses. This approach allows early diagnosis and treatment, in FH due to both *LDLR* and *APOB* variants. In Switzerland, we introduced cascade screening in 1988. Thus, we can look back on 30 years of experience [10,12].

1.2. Challenges of translation of the genetic insights into clinical medicine

Since more than two decades, an international consensus on the use of genetic principles in FH by cascade screening has been effective [13]. Nevertheless, the translation of these recommendations vary extremely in the European countries [7,13]. Furthermore, not only the implementation of recommendations itself but also differences in the genetic background and health policy priorities affect the success of such recommendations. Crucial information in this respect comprises the awareness of the prevalence of FH in the general population and the frequency distribution of FH subgroups in the respective country as well as the course of clinical manifestations of this debilitating disease. The value of clinical scores to identify affected individuals may vary depending on the distribution of FH subgroups.

Hence, (i) we investigated the prevalence of FH due to *LDLR* variants in Switzerland, (ii) the phenotypic characteristics of untreated Swiss FH patients in different age groups and differences between FH due to pathogenic *LDLR versus APOB* variants, and (iii) the diagnostic value of the two most commonly applied clinical scores, the Dutch Lipid Clinic Network (DLCN) score [13] and the Simon Broome Diagnostic Criteria (SBDC) [14] in FH due to *LDLR versus APOB* variants. As described previously, the phenotype of FH caused by molecularly confirmed pathogenic *LDLR* variants differs from the phenotype of FH caused by molecularly confirmed pathogenic *APOB* variants [4,9]. The latter is characterized by lower TC/LDLC concentrations, particularly at an early age. As a consequence, the value of clinical scores, when used in individuals with proven pathogenic *LDLR* variants *versus* those with proven pathogenic *APOB* variants might differ.

Finally, (iv) we investigated the onset of the first clinical manifestation of atherosclerotic complications in FH patients with *LDLR versus APOB* variants.

2. Patients and methods

2.1. Subjects

A total of 2734 Swiss subjects were studied, 2221 subjects for the estimation of the prevalence of FH in Switzerland. Cross-sectional data from unselected, representative samples covering the whole age spectrum of the general Swiss population was collected. Among the 2221 subjects, 717 were from the Swiss PREvalence of Apolipoprotein Defects (SPREAD) study, comprising randomly selected subjects from all parts of Switzerland [4], 1097 were from the Screening In NOrmocholesterolemic PErsons (SINOPE) study, an observational prospective cross-sectional survey, comprising randomly selected subjects from the northwestern part of Switzerland, and 407 were from the Inter-Disciplinary study on Aging (IDA) [15], comprising subjects from northwestern part of Switzerland, randomly selected from the BASEL Study, a longitudinal survey initiated in 1959, including 6329 healthy employees of the chemical industry.

For comparisons of the clinical characteristics, the diagnostic value of clinical scores, and the progression of atherosclerosis in patients with FH due to *LDLR versus APOB* variants, 513 subjects from the DIAgnosis and Management Of familial hypercholesterolemia in a Nationwide Design (DIAMOND-FH) study were included. In 1988, a nationwide FH register has been initiated to identify subjects at risk of early cardiovascular events using a cascade screening approach [12]. In 1994, the Swiss FH program joined the international Make Early Diagnosis – Prevent Early Death (MED PED) FH initiative, endorsed by the World Health Organization [12,13]. The nationwide FH registry activities during the last 30 years, now presented as part of the DIAMOND-FH study, are currently located at the diagene Research Institute, Reinach, Switzerland.

All studies described above (SPREAD, SINOPE, IDA, DIAMOND-FH) have been approved by the respective ethics committees and written informed consent was received from all subjects enrolled.

2.2. Materials and methods

For the estimation of the prevalence of FH due to *LDLR* variants, data was analyzed from previously published studies (SPREAD, IDA [4,15]) and from the hitherto unpublished prospective SINOPE survey. In SINOPE, numerous parameters were determined. Coronary heart disease (CHD) was defined as myocardial infarction (MI), coronary artery bypass grafts (CABG), percutaneous transluminal coronary angioplasty (PTCA) or confirmed relevant stenosis in coronarography. From 12-hrs fasting blood, the lipid profile, (total cholesterol (TC), HDL cholesterol (HDLC), LDL cholesterol (LDLC), very low density lipoprotein cholesterol (VLDLC), triglycerides (TG)), glucose, and high-sensitivity C-reactive protein (hsCRP) were determined by wet chemistry photometric assays using a microlab 300 analyzer (Vital Scientific, Spankeren, Netherland) at the diagene Research Institute Laboratories, Reinach, Switzerland. Individuals achieving a DLCN score of ≥ 5 points were considered as patients with FH due to *LDLR* variants.

For assessment of the clinical characteristics of FH patients,