



Familial hypercholesterolemia: The Italian Atherosclerosis Society Network (LIPIGEN)

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Abstract

Background and aims: Primary dyslipidemias are a heterogeneous group of disorders characterized by abnormal levels of circulating lipoproteins. Among them, familial hypercholesterolemia is the most common lipid disorder that predisposes for premature cardiovascular disease. We set up an Italian nationwide network aimed at facilitating the clinical and genetic diagnosis of genetic dyslipidemias named LIPIGEN (LIpid TransPort Disorders Italian GENetic Network).

Methods: Observational, multicenter, retrospective and prospective study involving about 40 Italian clinical centers. Genetic testing of the appropriate candidate genes at one of six molecular diagnostic laboratories serving as nationwide DNA diagnostic centers.

Results and conclusions: From 2012 to October 2016, available biochemical and clinical information of 3480 subjects with familial hypercholesterolemia identified according to the Dutch Lipid Clinic Network (DLCN) score were included in the database and genetic analysis was performed in 97.8% of subjects, with a mutation detection rate of 92.0% in patients with DLCN score ≥ 6 . The establishment of the LIPIGEN network will have important effects on clinical management and it will improve the overall identification and treatment of primary dyslipidemias in Italy.

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Keywords: Dyslipidemias; Genetic testing; National network

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1. Introduction

Primary or monogenic dyslipidemias are a heterogeneous group of disorders characterized by abnormal levels of circulating cholesterol, triglycerides or a combination of the two due to single gene defects. Monogenic

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hypercholesterolemias are characterized by elevated low-density lipoprotein-cholesterol (LDL-C) levels and very high risk of premature atherosclerotic disease; they are caused by mutations in genes involved in the receptor-mediated uptake of LDL-C by the LDL receptor (LDLR) in hepatocytes [1]. Primary or genetic forms of hypertriglyceridemia (HTG) with a monogenic etiology include mostly severe forms characterized by the accumulation in plasma of TG-rich lipoproteins (chylomicrons, VLDL and remnant lipoproteins) [2] and an increased risk of developing recurrent episodes of pancreatitis [3].

Despite substantial progresses in genetic testing and counseling in addition to novel treatment opportunities, primary dyslipidemias remain largely underdiagnosed and undertreated in Western countries, including Italy [1]. The development of nationwide clinical and genetic screening programs may improve early identification and clinical management through lifestyle modification or evidence-based pharmacological intervention in order to reduce risk of clinical endpoints, as well as promote genetic counseling and guide efficacious health policy-making.

2. The model of the National FH screening program in the Netherlands

In 1994 the Dutch government recognized the burden of familial hypercholesterolemia (FH) on public health and this prompted the development of a national Program aimed at Identification of Persons with Inherited Hypercholesterolemia (in Dutch: StOEH). The first step was to inform all specialists in vascular medicine, cardiology and endocrinology in the Netherlands of the screening program in order to encourage the referral of patients with suspected FH. In a later stage, general practitioners were also involved in this process through direct mail, articles and specific campaigns. A questionnaire was used to collect information on medical history; blood samples were drawn to determine lipid profiles and a screening program based on a genetic cascade testing approach was developed and implemented. Patients with clinical suspicion of FH were referred to the StOEH and genetically tested for the presence of mutations in the candidate genes [1] at the molecular diagnostic laboratory of the Academic Medical Center (AMC) in Amsterdam, serving as a nationwide DNA diagnostic center. Furthermore, if an FH causing mutation was found in an index patient, the first-degree relatives were contacted to be tested for the mutation of the index patient as well. In turn, if the mutation was identified in one of the first-degree relatives, the first-degree relatives were then also offered to participate. This cascade process stops in that branch of the family when the index-mutation was not found in a tested subject. All participants were informed of the DNA test result by letter and carriers of an FH mutation were encouraged to contact a specialist or their general practitioner to discuss initiation of lipid lowering therapy.

By the beginning of 2014, more than 60,000 subjects had undergone genetic testing for FH in the Netherlands [4]. The performance of the screening program was initially evaluated after five years showing a participation rate over 90%. Only 39% of FH patients were treated with a statin at time of screening, but this proportion increased to 93% in the first year after the diagnosis of FH was made [5], underlining that cascade testing approach may effectively allow to identify those patients that require lipid-lowering treatment (LLT) to prevent coronary heart disease (CHD) as early as possible.

In fact, in line with coronary heart disease (CHD) mortality rates reported in heterozygous FH (HeFH) patients from the UK [6], the risk for CHD was increased by almost four-fold in HeFH patients in the Netherlands [7] compared to unaffected relatives.

Yet, of the expected 66,800 HeFH patients in the Netherlands based on the estimated prevalence of HeFH of 1:250 [6], only 38.6% were diagnosed after 20 years of screening, underlying that policy makers and health care professionals need to be made more strongly aware of the urgency of identification of FH patients.

Together with clinical improvements for individuals diagnosed with FH, the Dutch screening program has also improved scientific knowledge on this disorder. For example, it has been recently shown that the prevalence of type 2 diabetes mellitus (T2DM) is decreased in FH patients, linking the LDL-R mediated cholesterol uptake to pancreatic beta cell dysfunction in humans [8]. Moreover, the registry allowed to evaluate in a prospective way the proportion of FH patients reaching their treatment target [9], and the awareness of the presence of the disease may help in choosing better treatment options or in promoting motivation of FH patients to participate in clinical trials for innovative treatments.

3. The Italian national network

The Italian Atherosclerosis Society (SISA) proposed in 2009 the establishment through its scientific Foundation of a Network aimed at facilitating the clinical and genetic diagnosis of genetic dyslipidemias, named LIPIGEN (LIpid TransPort Disorders Italian GEnetic Network). The network consists of about forty clinical centers with a long lasting experience in identifying and managing patients with primary dyslipidemias including pediatric and LDL apheresis institutions located throughout the country (Fig. 1). The structure of LIPIGEN is based on a close interaction between clinical centers, general practitioners and associations of patients (Fig. 2).

This project represents the opportunity to build in Italy a nationwide network of clinical and laboratory centers sharing common diagnostic protocols in order to: i) improve diagnosis and clinical management of patients with genetic dyslipidemias; ii) promote the genetic diagnosis; iii) increase awareness among physicians and



Fig. 1. Map of the location of clinical centers of LIPIGEN Network in Italy.

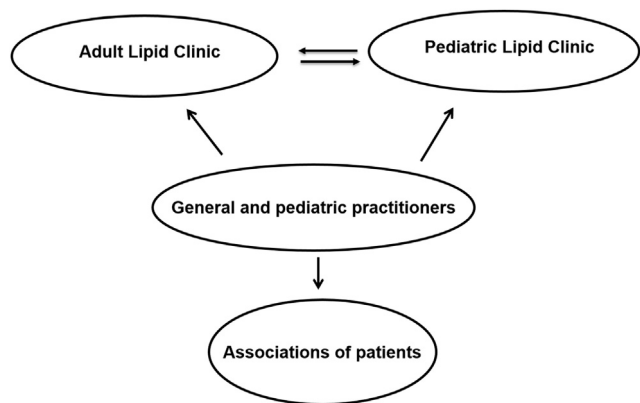


Fig. 2. Interaction between clinical centers, general practitioners and associations of patients in the LIPIGEN program.

patients; iv) create a national registry of FH, and v) promote research activities in the field. To achieve these objectives, the LIPIGEN steering committee started in 2012 a multicenter initiative, the LIPIGEN-FH study,

focused on the most common genetic dyslipidemia, familial hypercholesterolemia.

4. LIPIGEN-FH study

LIPIGEN-FH study is an observational, multicenter, retrospective and prospective study, aimed at identifying and registering patients with FH. LIPIGEN centers will also focus their attention to other familial dyslipidemias; Table 1 shows the forms of dyslipidemias and their estimated prevalence in Italy for which we are planning to build specific registries.

Patients participating in the study do not undergo any procedure other than normal clinical practice; clinical variables that are collected for the study are those commonly collected by physicians in daily clinical practice.

The program has been approved by the Institutional Review Board of the participating centers and conducted in accordance with the principles of the Helsinki Declaration (latest revision, October 2008), the standards of Good

Table 1
Estimated prevalence of primary dyslipidemias in Italy.

Dyslipidemia	Expected cases
Familial hypercholesterolemia	230,000
Type III hyperlipidemia	10,000 (?)
Severe hypertriglyceridemia	200 (?)
Familial hypertriglyceridemia	?
Familial hypobetalipoproteinemia	20,000
Familial combined hypolipidemia	?
Abetalipoproteinemia & chylomicron retention disease	50–100
Familial hypoalphalipoproteinemia	?
Familial hyperalphalipoproteinemia	?

Clinical Practice (ICH GCP), the data protection laws and other applicable regulations.

Patients with clinical suspicion of primary dyslipidemias are referred for genetic testing of the appropriate candidate genes at one of six molecular diagnostic laboratories serving as nationwide DNA diagnostic centers.

The clinical diagnosis of familial hypercholesterolemia is based on the Dutch Lipid Network score, which indicates the probability of FH [1]. The DLCN criteria allow to select out individuals/families with a definite or probable diagnosis of FH (DLCN ≥ 6) in whom molecular genetic testing is strongly recommended.

Clinical centers will base the suspicion of other genetic dyslipidemias (Table 1) on common and standardized clinical criteria both for pediatric and adult patients that have been set by a board of Italian lipidologists. The criteria are available in a dedicated web page managed by the SISA Foundation accessible by network members authentication.

Given the complexity of genetic testing, professionals at each clinical center manage genetic counseling. This includes an explanation of inheritance patterns, information about genetic testing, including potential benefits, risks, and potential for incidental or uncertain findings and once results are obtained, genetic counselors should discuss the results and interpretations of the genetic tests with patients and test family members in case of positive results.

Clinical centers also discuss with patients with definite clinical diagnosis who have no identifiable mutations (for example in FH about 20–30%) the need of adherence to treatments, follow-up visits and further genetic testing modalities if required.

5. Data collection

At first, the program has taken advantage of surveys conducted with the aim of assessing the molecular bases and the clinical features of familial dyslipidemias (ie, FH, severe HTG, familial hypocholesterolemias) in a cohort of patients attending Italian Lipid Clinics [10–13].

Patients of any age and sex with clinical suspicion of familial dyslipidemias who are able to understand the study procedures and who voluntarily agree to participate by providing written informed consent specifically intended

for adult and children, may be referred to LIPIGEN study through 40 Italian clinical centers included in the network. For each subject enrolled in the study, all available demographic and clinical data (for example age, details of past medical history, family history, smoking status, alcohol consumption) as well as information on medication both at baseline and during follow-up visits were recorded in an electronic Case Report Form (eCRF) platform.

From 2012 to October 2016, available biochemical and clinical data of 3480 subjects were included in the database; 56.1% of them had a DLCN score ≥ 6 , 23.6% had a score between 6 and 8 (probable FH) and 32.5% a score >8 (definite FH). Preliminary data analysis revealed that tendon xanthomas and corneal arc were observed in 21.8% and in 8.8% of cases respectively, family history of premature coronary events was reported in 38.8% and the personal history of premature coronary artery disease or of stroke and peripheral vascular disease had a prevalence of 11.3% and 9.6% respectively.

Genetic analysis has been performed in 97.8% of subjects with a mutation detection rate of 92.0% in patients with a DLCN score ≥ 6 ; more than 98% of patients with genetic diagnosis were carriers of mutations in the LDL receptor (LDLR) gene and 49 (1.7%) were true homozygous, 46 (1.6%) compound heterozygotes and 28 (1.0%) double heterozygous.

The inclusion of data of index cases and affected and unaffected relatives will contribute to build for the first time in Italy the register of familial hypercholesterolemia. Similar studies will follow for the other genetic dyslipidemias.

6. Conclusions

Identification and management of patients with familial dyslipidemias remain a challenge. The robust numbers coming from the experience of the Netherlands stress the value of registries for the early identification and clinical management of patients with familial hypercholesterolemia.

The LIPIGEN network is aimed at identifying and registering patients with FH and other familial dyslipidemias in Italy. The consortium of clinical centers should uniform definition of the clinical diagnosis and promote a nationwide systematic approach to identify patients with familial dyslipidemias and promote genetic cascade testing.

We are aware it will be a continuous task to organize a country-wide program for the screening and identification of patients with a wide range of familial disorders but we are convinced that the establishment of national diseases registers will have important effects on clinical management and will improve knowledge of the natural history of the diseases and the effect of treatments, including the evaluation of innovative therapies and their follow-up.

Conflict of interest

None declared.

Appendix

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