ELSEVIER

CrossMark

Atherosclerosis Supplements 29 (2017) 11–16

ATHEROSCLEROSIS SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Familial hypercholesterolemia: The Italian Atherosclerosis Society Network (LIPIGEN)

Maurizio Averna [a,*,1], Angelo B. Cefalù [a], Manuela Casula [b], Davide Noto [a], Marcello Arca [c,1], Stefano Bertolini [d,1], Sebastiano Calandra [e,1], Alberico L. Catapano [f,g,1], Patrizia Tarugi [h,1], on behalf of the LIPIGEN Group[2]

[a] *Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S.), University of Palermo, Palermo, Italy*
[b] *Epidemiology and Preventive Pharmacology Centre (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy*
[c] *Department of Internal Medicine and Medical Specialties, Sapienza University, Rome, Italy*
[d] *Department of Internal Medicine, University of Genoa, Genoa, Italy*
[e] *Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy*
[f] *Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy*
[g] *IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy*
[h] *Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy*

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 $\geq$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.

Keywords: Dyslipidemias; Genetic testing; National network

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

* Corresponding author. Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S), University of Palermo, Via del Vespro 141, I-90127 Palermo, Italy.
E-mail address: maurizio.averna@unipa.it (M. Averna).
[1] Members of the LIPIGEN Steering Committee.
[2] Please see Appendix section for Members of the LIPIGEN Steering Committee.

http://dx.doi.org/10.1016/j.atherosclerosissup.2017.07.001

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 (**LI**pid Trans**P**ort Disorders **I**talian **GE**netic **N**etwork). 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.

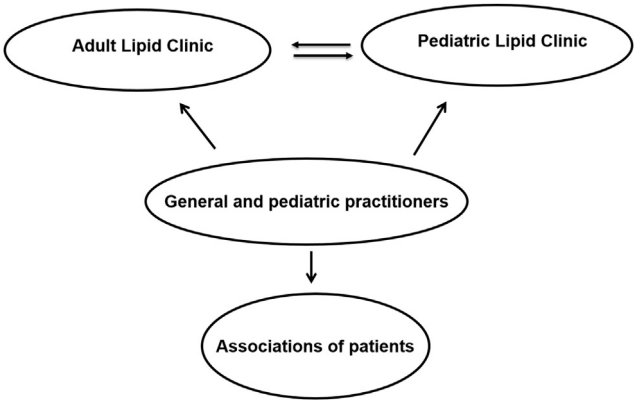

Fig. 2. Interaction between clinical centers, general practitioners and associations of patients in the LIPIGEN program.

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.

Dylipidemia	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 $\geq$ 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 $\geq$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 $\geq$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

[§]**MEMBERS OF THE LIPIGEN STEERING COMMITTEE:** Arca Marcello[1], Averna Maurizio[2], Bertolini Stefano[3], Calandra Sebastiano[4], Catapano Alberico Luigi[5], Tarugi Patrizia[4]; **PRINCIPAL INVESTIGATORS: Coordinator Center:** Pellegatta Fabio[6]; **Participant Centers:** Angelico Francesco[1], Arca Marcello[1], Averna Maurizio[2], Bartuli Andrea[7], Biasucci Giacomo[8], Biolo Gianni[9], Bonanni Luca[10], Bonomo Katia[11], Borghi Claudio[12], Bossi Antonio Carlo[13], Branchi Adriana[14], Carubbi Francesca[15], Cipollone Francesco[16], Citroni Nadia[17], Federici Massimo[18], Ferri Claudio[19], Fiorenza Anna Maria[20], Giaccari Andrea[21], Giorgino Francesco[22], Guardamagna Ornella[23], Iannuzzi Arcangelo[24], Iughetti Lorenzo[25], Lupattelli Graziana[26], Mandraffino Giuseppe[27], Marcucci Rossella[28], Mombelli Giuliana[29], Muntoni Sandro[30], Pecchioli Valerio[31], Pederiva Cristina[32], Pipolo Antonio[33], Pisciotta Livia[34], Pujia Arturo[35], Purrello Francesco[36], Repetti Elena[37], Rubba Paolo[38], Sabbà Carlo[39], Sampietro Tiziana[40], Sarzani Riccardo[41], Tagliabue Milena Paola[42], Trenti Chiara[43], Vigna Giovanni Battista[44], Werba Josè Pablo[45], Zambon Sabina[46], Zenti Maria Grazia[47]; **Participant Laboratories:** Montali Anna[48], Noto Davide[49], Bertolini Stefano[3], Calandra Sebastiano[4], Fortunato Giuliana[50]; **COLLABORATORS: Coordinator center:** Grigore Liliana[6]; **Participant Centers:** Del Ben Maria[1], Maranghi Marianna[1], Cefalù Angelo B.[2], Barbagallo Carlo M.[2], Buonuomo Paola Sabrina[7], Capra Maria Elena[8], Vinci Pierandrea[9], D'Addato Sergio[12], Galbiati Stella[13], Nascimbeni Fabio[15], Bucci Marco[16], Spagnoli Walter[17], Cardolini Iris[18], Cervelli Nazzareno[19], Emanuela Colombo[20], Vinsin A. Sun[21], Laviola Luigi[22], Bello Francesca[23], Chiariello Giuseppe[24], Predieri Barbara[25], Siepi Donatella[26], Saitta Antonino[27], Giusti Betti[28], Pavanello Chiara[29], Lussu Milena[30], Prati Lucia[31], Banderali Giuseppe[32], Balleari Giulia[34], Montalcini Tiziana[35], Scicali Roberto[36], Gentile Luigi[37], Gentile Marco[38], Suppressa Patrizia[39], Sbrana Francesco[40], Cocci Guido[41], Benso Andrea[42], Negri Emanuele Alberto[43], Ghirardello Omar[44], Vigo Lorenzo[45], Zambon Alberto[46], Bonora Enzo[47]; **Participant Laboratories:** Minicocci Ilenia[48], Spina Rossella[49], Orlando Camilla[3], Tarugi Patrizia[4], Di Taranto Maria Donata[50]; **STUDY CENTRAL LABORATORY AND ANALYSIS GROUP:** Catapano Alberico Luigi[5], Casula Manuela[51], Chiodo Lorenzo[51], Garlaschelli Katia[52], Manzato Enzo[53], Tragni Elena[51]

Affiliations: [1]Dipartimento di Medicina Interna e Specialità Mediche "La Sapienza", A.O. Policlinico Umberto I, Rome, Italy; [2]Centro di riferimento regionale per la prevenzione, diagnosi e cura delle malattie rare del metabolismo, A.O.U. Policlinico "P. Giaccone", Palermo, Italy; [3]Centro Ambulatorio Dislipidemie – U.O. Clinica di Medicina Interna 1, O. Universitaria San Martino, Genua, Italy; [4]Laboratorio Sequenziamento Genomico, Dipartimento di Scienze Biomediche, Università di Modena e Reggio Emilia, Modena, Italy; [5]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, and IRCCS Multimedica, Milan, Italy; [6]Centro per lo Studio dell'Aterosclerosi, IRCCS Multimedica, Sesto San Giovanni, Italy; [7]Ambulatorio Polispecialistico per le Malattie Rare, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; [8]Centro Dislipidemie in Età Evolutiva U.O. Pediatria e Neonatologia, Ospedale G. da Saliceto, Piacenza, Italy; [9]S.S. Diabetologia e Malattie Metaboliche, U.C.O. Clinica Medica Generale, Azienda Ospedaliera Universitaria OORR, Ospedale Maggiore, Trieste, Italy; [10]Ambulatorio Dislipidemie, UO Medicina Interna, Ospedale dell'Angelo di Mestre, Venice, Italy; [11]AOU San Luigi Gonzaga, Orbassano, Turin, Italy; [12]U.O. di Medicina Interna, Centro Aterosclerosi, Ambulatorio Dislipidemie, Ospedale Policlinico S. Orsola-Malpighi, Bologna, Italy; [13]U.O.C. Malattie Endocrine e Centro regionale per il Diabete (Diabetologia), Ospedale "Treviglio-Caravaggio" di Treviglio, Bergamo, Italy; [14]Ambulatorio Dislipidemie, Centro per lo Studio e la Prevenzione dell'Arteriosclerosi, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy; [15]U.O. Medicina ad indirizzo metabolico-nutrizionistico, Centro dislipidemie e centro di riferimento regionale per le malattie metaboliche rare, Nuovo Ospedale S. Agostino Estense (NOCSAE), Modena, Italy; [16]Centro di alta specializzazione per la prevenzione dell'arteriosclerosi, centro di eccellenza ESH per l'ipertensione arteriosa, centro di riferimento regionale per le Dislipidemie, Ospedale Policlino S.S. Annunziata, Chieti, Italy; [17]Centro Dislipidemia, UO Medicina Interna, Ospedale Santa Chiara, Trento, Italy; [18]Dipartimento Medicina Interna – Centro per l'Aterosclerosi, Policlinico Universtario "Tor Vergata", Rome, Italy; [19]Centro Ipertensione Arteriosa e Prevenzione Cardiovascolare UOC Medicina Interna e Nefrologia, l'Aquila, Italy; [20]Dip. Medicina Interna, Centro Prevenzione e Cura dell'aterosclerosi, A.O. "Guido Salvini", Garbagnate Milanese, Milan, Italy; [21]UOC Endocrinologia e Malattie del Metabolismo, Policlinico Gemelli, Rome, Italy; [22]U.O. Endocrinologia, Ambulatori di Diabetologia e Malattie Metaboliche, A.O. Universitaria Policlinico Consorziale, Università degli Studi di Bari "Aldo Moro", Bari, Italy; [23]U.O. Dislipidemie e Prevenzione Cardiovascolare, Ospedale Regina Margherita, Turin, Italy; [24]U.O. Medicina Interna 5, Centro per le malattie da arteriosclerosi, AORN Cardarelli, Naples, Italy; [25]U.O. Clinica Pediatrica, Policlinico di Modena, Modena, Italy; [26]U.O. Medicina Interna Angiologia, Malattie da Arteriosclerosi, Ambulatorio di malattie del ricambio lipidico, Ospedale Santa Maria della Misericordia, Perugia, Italy; [27]Dipartimento di Medicina Interna e Terapia Medica, Centro per la Diagnosi e Cura della Dislipidemia e Prevenzione dell'Aterosclerosi, A.O. Universitaria Policlinico "G.Martino", Messina, Italy; [28]Ambulatorio Malattie Aterotrombotiche, AOUC Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [29]Centro Universitario Dislipidemie "E. Grossi Paoletti", A.O.

Ospedale Niguarda Ca' Granda, Milan, Italy; [30]Centro per le Malattie Dismetaboliche e l'arteriosclerosi, Associazione ME.DI.CO Onlus, Cagliari, Italy; [31]UOSD 'Prevenzione cardiovascolare', Dipartimento di Scienze Mediche, Azienda Sanitaria Locale Frosinone, Frosinone, Italy; [32]U.O. Clinica Pediatrica, Servizio Clinico Dislipidemie per lo Studio e la Prevenzione dell'Aterosclerosi in età pediatrica, Ospedale San Paolo, Milan, Italy; [33]AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; [34]U.O. Clinica di Medicina Interna 1, Ambulatorio Dislipidemie, IRCCS – A.O.U. San Martino – IST, Genoa, Italy; [35]A.O.U. Mater Domini, Catanzaro, UOC di Nutrizione Clinica, Ambulatorio Dislipidemie, Catanzaro, Italy; [36]U.O. Medicina Interna, Ospedale "Garibaldi Nesima", Catania, Italy; [37]Società di Diabetologia e Malattie Metaboliche, Asti, Italy; [38]Centro Coordinamento regionale per le Iperlipidemie, AOU Policlinico Federico II, Naples, Italy; [39]U.O. di Medicina Interna "Frugoni" e Centro di Assistenza e Ricerca Malattie Rare, A.O. Universitaria Policlinico Consorziale, Università degli Studi di Bari "Aldo Moro", Bari, Italy; [40]U.O. Lipoaferesi, Centro Regionale di Riferimento per la diagnosi e cura delle Dislipidemie Ereditarie, Fondazione Toscana "G. Monasterio", Pisa, Italy; [41]Clinica di Medicina Interna e Geriatria, Centro di riferimento regionale ipertensione arteriosa e malattie cardiovascolari, INRCA Ospedale "Sestilli" e Azienda Ospedaliero-Universitaria Ospedali Riuniti di Torrette di Ancona, Ancona, Italy; [42]SCDU Endocrinologia, Diabetologia e Metabolismo, Dipartimento di Scienze Mediche, Università di Torino, Turin, Italy; [43]Arcispedale S. Maria Nuova – Azienda ospedaliera di Reggio Emilia, Reggio Emilia, Italy; [44]U. O Medicina Interna Universitaria, Centro per lo Studio delle Dislipidemie e dell'Aterosclerosi Azienda Ospedaliero-Universitaria di Ferrara, Polo di Cona, Ferrara, Italy; [45]U.O. Ambulatorio Prevenzione Aterosclerosi IRCCS Cardiologico Monzino, Milan, Italy; [46]U. O. Clinica Medica 1, Centro Dislipidemie e Aterosclerosi, A.O. di Padova, Padua, Italy; [47]U.O. Endocrinologia, Diabetologia e Malattie del Metabolismo, Centro regionale specializzato per la diagnosi e terapia delle dislipidemie e aferesi terapeutica, A.O. Universitaria Integrata di Verona, Verona, Italy; [48]Centro per l'Arteriosclerosi, Dipartimento di Medicina Interna e Specialità Mediche, Università di Roma "La Sapienza" – Azienda Policlinico Umberto I, Rome, Italy; [49]Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), Laboratory of Biochemistry, Molecular Biology and Genetics of Lipids "Laura Notarbartolo", University of Palermo, Palermo, Italy; [50]Laboratorio di screening di Malattie Metaboliche, CEINGE – Biotecnologie Avanzate, Dipartimento di Biochimica e Biotecnologie Mediche, Azienda Ospedaliera Universitaria "Federico II", Naples, Italy; [51]Centro Universitario di Epidemiologia e Farmacologia Preventiva (SEFAP), Dipartimento di Science Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy; [52]Centro per lo Studio dell'Aterosclerosi, Ospedale E. Bassini, Cinisello Balsamo, Milan, Italy; [53]Dipartimento di Medicina (DIMED), Sezione Geriatrica, Università di Padova, Padua, Italy.

References

[1] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34. 3478–3490a.

[2] Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2014;2:655–66.

[3] Brahm AJ, Hegele RA. Chylomicronaemia–current diagnosis and future therapies. Nat Rev Endocrinol 2015;11:352–62.

[4] Besseling J, Reitsma JB, Gaudet D, et al. Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia. Eur Heart J 2017; 38:565–73.

[5] Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in The Netherlands. Lancet 2001;357:165–8.

[6] Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008;29:2625–33.

[7] Huijgen R, Kindt I, Defesche JC, et al. Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variants. Eur Heart J 2012;33:2325–30.

[8] Besseling J, Kastelein JJ, Defesche JC, et al. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. JAMA 2015;313:1029–36.

[9] Huijgen R, Kindt I, Verhoeven SB, et al. Two years after molecular diagnosis of familial hypercholesterolemia: majority on cholesterol-lowering treatment but a minority reaches treatment goal. PLoS One 2010;5:e9220.

[10] Bertolini S, Pisciotta L, Rabacchi C, et al. Spectrum of mutations and phenotypic expression in patients with autosomal dominant hypercholesterolemia identified in Italy. Atherosclerosis 2013;227:342–8.

[11] Rabacchi C, Pisciotta L, Cefalu AB, et al. Spectrum of mutations of the LPL gene identified in Italy in patients with severe hypertriglyceridemia. Atherosclerosis 2015;241:79–86.

[12] Tarugi P, Averna M, Di Leo E, et al. Molecular diagnosis of hypobetalipoproteinemia: an ENID review. Atherosclerosis 2007;195: e19–27.

[13] Minicocci I, Santini S, Cantisani V, et al. Clinical characteristics and plasma lipids in subjects with familial combined hypolipidemia: a pooled analysis. J Lipid Res 2013;54:3481–90.