THOUSAND WORDS ABOUT...

DOI: https://doi.org/10.20883/jms.245

Genetics in familial hypercholesterolaemia — from genetic research to new guidelines

Edyta Prokop[1, a], Paweł P. Jagodziński[2, b], Stefan Grajek[1, c]

[1] I Clinic of Cardiology, Poznan University of Medical Sciences, Poland
[2] Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poland

[a] https://orcid.org/0000-0002-5998-3633
[b] https://orcid.org/0000-0002-9046-6802
[c] https://orcid.org/0000-0001-8047-2881

ABSTRACT

Familial Hypercholesterolaemia (FH) is genetic disorder touching up to 1 to 250 people, increasing the risk of atherosclerotic cardiovascular disease risk and early death by 3–13 times. The majority of mutations are autosomal dominant among 3 genes related to cholesterole metabolism: LDL-receptor (LDLR), apolipoprotein B (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9). It comprises 60% of reported cases, which still is not at satisfactory level. This article summarizes new research in the field of FH and points out new therapeutic methods — PCSK9 inhibitors as advised in new European Society of Cardiology guidelines od dyslipidaemias.

Keywords: familial hypercholesterolaemia, PCSK9 inhibitors, evolocumab, alirocumab, dyslipidaemias.

Introduction

Familial hypercholesterolaemia (FH) is the genetic disorder touching 1 in 500 to, where the founder effect can be observed, even 1 in 250 people. Patients with this disorder have 3–13 times greater risk for developing premature atherosclerotic cardiovascular disease (ASVD) comparing to non-FH patients with normal blood lipid concentrations. It results in higher risk for sudden cardiac death, myocardial infarctions and ischemic heart disease events (i.e. frequent coronaroplasty), significantly reducing the life-expectancy of these patients [1].

Majority FH is linked to autosomal dominant inheritance of mutations in either LDL-receptor (LDLR), apolipoprotein B (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9) and other loci — 60% of FH patients is mutation-positive. Also single nucleotide polymorphism of LDL-cholesterole (LDL-C) was found in FH patients mutation-negative suggesting the 88% of them has polygenic basis [2]. LDLR is responsible for the LDL-C blood concentration by regulating LDL-C uptake by cells and until now has more than 1000 mutations reported among FH patients, being most described pathogenetic genetic cause of this disease. APOB enables binding between LDL-C molecules and LDLR. PCSK9 is an enzyme responsible for degradation in LDLR. FH is linked to cardiovascular events in earlier age, needs early diagnosis and treatment, if possible- in the childhood to extend life-expectancy to the FH patients of overall population [3]. To do so, Dutch Lipid Clinic Network (DLCN) criteria are used, which include: pedigree analysis for premature cardiovascular events in 1 degree relatives, cholesterol concentration, medical history of an individual and symptoms [4].

Although FH genetics and inheritance is well described there are some new data reported in recent years. Also it is worth pointing out that in already finished genetic studies only around 60% of patients have investigated mutations, which leaves a lot of space for future projects. Novel genetic variants were studied in Saudi Arabia in 12 FH-linked genes (LDLR, APOB, PCSK9, Abca1, Apoa2, Apoc3, Apon2, Arh, Ldlrap1, Apoc2, ApoE, and Lpl) that have been implicated in the homozygous phenotype of a proband pedigree to identify candidate variants by next generation sequencing. The investigators questioned classical genetic sequencing methods as ineffective due to multiplicity of loci in genome linked with lipid metabolism genes. This study confirmed only LDLR, APOB and PCSK9 genes were associated with FH, new location was found for heterozygous variant, the rest of 7 validated viariants was not linked with FH [5].

Next-generation targeting was used also in Swedish study of 77 FH patients investigating LDLR, APOB and PCSK9 genes. The result obtained remains satisfactory — 65% of probants had the studied variants, leading to the conclusion that next-generation sequencing together with DLCN criteria might be helpful tool in diagnosis for FH [6].

FH cohort studies are rare, because still FH is underdiagnosed. Spanish registry included 2938 patients belonging to 775 families with positive genetic testing for the FH. The multicenter research started in 2004 dividing genetic variants according to American College of Medical Genetics and genomics: total 194 variants, 65 were functionally linked with cause of FH, 111 — pathogenic and 59 likely pathogenic, giving 88% of studied variants. Interesting to note that 11% of the rest were of unknown significance leaving big space for further investigation. Patients were divided into groups of null alleles (911 pts), defective alleles (1259 pts) and non-determined alleles (NDA, 473 pts). Null alleles patients presented higher risk score according to their blood tests results, needing higher doses of statins or other treatment [7].

The genetic tests resulted in new treatment method. As recommended by European Society of Cardiology in 2016 in the Guidelines on Dyslipidaemias appeared not only statins, bile acid sequestrants, cholesterol absorption inhibitors and nicotinic acid, but also PCSK9 inhibitors — evolocumab and alirocumab [8]. Both are antibodies that combine with hepatocytes to increase the breakdown of LDL-C. They are injectable drugs taken twice a month together with cholesterol level lowering drugs when the patient's LDL--C levels are not satisfactory even though all the medications are at maximal dosage. FH patients are strong candidates for target group for PSK9 inhibitors. Evolocumab yields 60% lowering of LDL-C, giving the patients better chance to survive longer [9]. New drugs are still developed, so there is still a chance that genetics will not kill those patients anymore.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Haralambos K, Whatley SD, Edwards R, et al. Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales. Atherosclerosis. 2015;240(1):190–196. doi: http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.003.
2. Futema M, Shah S, Cooper JA, et al. Refinement of Variant Selection for the LDL Cholesterol Genetic Risk Score in the Diagnosis of the Polygenic Form of Clinical Familial Hypercholesterolemia and Replication in Samples from 6 Countries. Clin Chem. 2015;61(1):231–238, doi: 10.1373/clinchem.2014.231365.
3. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: A HuGE Prevalence Review. Am J Epidemiol. 2004;160(5):407–420, doi: 10.1093/aje/kwh236.
4. Umans-Eckenhausen MAW, Defesche JC, Sijbrands EJG, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. The Lancet. 2001;357(9251):165–168, doi: http://dx.doi.org/10.1016/S0140–6736(00)03587-X.
5. Al-Allaf FA, Athar M, Abduljaleel Z, et al. Next generation sequencing to identify novel genetic variants causative of autosomal dominant familial hypercholesterolemia associated with increased risk of coronary heart disease. Gene. 2015 July;565(1):76–84.
6. Maglio C, Mancina RM, Motta BM, et al. Genetic diagnosis of familial hypercholesterolaemia by targeted next-generation sequencing. J Intern Med. 2014;276:396–403.
7. Bourbon M, Alves AC, Alonso R, Nelva Mata, et al. Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART regis-

try. Atherosclerosis. 2017 July;262: 8–13, doi: https://doi.org/10.1016/j.atherosclerosis.2017.04.002.
8. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999–3058, doi: 10.1093/eurheartj/ehw272.
9. Ito MK, Santos RD. PCSK9 Inhibition With Monoclonal Antibodies: Modern Management of Hypercholesterolemia. The Journal of Clinical Pharmacology. 2017;57:7–32. doi:10.1002/jcph.766.

Acceptance for editing: 2019-08-10
Acceptance for publication: 2019-09-30

Correspondence address:
Edyta Kinga Prokop
I Clinic of Cardiology
Poznan University of Medical Sciences, Poland
e-mail: edyta.k.prokop@gmail.com