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Genetics in familial hypercholesterolaemia – from genetic research to new guidelines

Edyta Prokop¹, Paweł P. Jagodziński², Stefan Grajek^{1, a}

¹ | 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/0000-0001-8047-2881>

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 cholesterol 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 of 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 coronaryplasty), 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-cholesterol (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 variants 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 probands 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 PCSK9 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.

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Conflict of interest statement

The authors declare no conflict of interest.

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Correspondence address:

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

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