Three-month IAS grant provided me an opportunity to perform a research in the centre of excellence, Center for cardiovascular genetics at University College London, UK. Professor Steve Humphries is head of the laboratory, one of the leaders in research on the field of the cardiovascular genetics, more precise-familial hypercholesterolemia (FH) and was my mentor during research period. In this report I will provide the background of my research and the results.

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated Low Density Lipoprotein-cholesterol (LDL-C) and premature coronary heart disease (CHD). The main pathologic mechanism is an impaired removal of LDL-C particles from the plasma due to mutations in the gene coding for the LDL receptor (\textit{LDLR}). Less frequently mutations in the \textit{APOB} gene, coding for apolipoprotein B the major structural protein of LDL-C particles, or in the \textit{PCSK9} (proprotein convertase subtilisin/kexin type 9) gene can also cause FH. The high plasma LDL-C levels result in deposition of LDL cholesterol in tissues (xanthelasmas, tendinous xanthomas, arcus corneae), most importantly in arteries, forming atherosclerotic plaques what results in premature cardiovascular morbidity and mortality. Today more than 1100 mutations in \textit{LDLR} are described (http://www.ucl.ac.uk/fh). There are several different systems used worldwide for the clinical diagnosis of FH, but today genetic testing provides the possibility of making a definitive diagnosis based on pathogenic variations in the \textit{LDLR}, \textit{APOB} and \textit{PCSK9} genes. Several consensus guidelines for the diagnosis and management of FH have been published recently, and all recommend the use of “cascade testing” of relatives by testing for the mutation found in the proband.

The results from Croatia were sparse cause there is about 9000 patients in Croatia (the incidence of heterozgous form 1:500) that are mostly unrecognised and untreated. In the last decades there were only two studies published on this topic including genetic analysis, one reporting a novel missense \textit{LDLR} mutation, p.(C127R), and the second a novel nonsense mutation p.(Q92X) in a homozygous patient. Thanks to the IAS and generous 3-month period research grant we designed small pilot project on FH in Croatia. Firstly we performed genetic analysis on Croatian FH samples at the profesor Humphries laboratory and found interesting results. We took samples of unrelated individuals with clinically diagnosed FH and analyzed using a High-Resolution Melting method (HRM) on genes causing FH. We found three novel \textit{LDLR} variants p.(S470C),
p.(C698R) and c.2312-2A>C. All were predicted to be pathogenic using predictive algorithms. Three previously reported disease-causing mutations were identified (p.(G20R), p.(N272T) and p.(S286R); the latter was also carried by a hypercholesterolaemic relative. One patient carried the pathogenic \textit{APOB} variant \textit{p.}(R3527Q).

Parallel with pilot project at CVG-UCL we started back home in Croatia public campaign with the aim to increase the awareness of this insidious disease. Brochures and pamphlets were printed and distributed through the country to internists, endocrinologists, cardiologists and GPs with the short info about disease. When colleagues suspect that they have a patient with FH they send the patient to our department – Department of metabolic diseases at University hospital center Zagreb where the blood samples can be taken and DNA extraction performed. Further analysis is made at profesor Steve Humphries lab thanks to his enthusiasm and will to help. At the end all mentioned above was possible thanks to the generous grant from the International Atherosclerosis Society but also thanks to profesor Steve Humphries who invited me to perform a research in his laboratory-one of the most important steps in grant application proces.

Last lines of this report will use to invite you all to 9th Croatian congress on atherosclerosis that will take place in Rovinj, Croatia, from 09-11 May 2013.


See you in Rovinj!

Thank you!

Best regards,

Ivan Pecin, MD