

Genetica, emostasi e trombosi

THE ROLE OF SELECTED *LDLR* AND *LRP1* VARIANTS IN MODULATING LDL AND FVIII LEVELS IN METABOLIC SYNDROME

P. Agosti[1|2], A. Cairo[2], S. Spena[2], S. Pelusi[3], F. Malvestiti[1], D. Prati[3], M. Clerici[2], E. Scalambrino[2], A. Tripodi[1|2], V. La Mura[1|2], L. Valenti[1|3], F. Peyvandi[1|2]

[1]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milano, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, and Fondazione Luigi Villa, Milano, Italy; [3]Biological Resource Center and Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Background and Aims. Low-density lipoprotein receptor (LDLR) and LDLR-Related Protein 1 (LRP1) showed a synergistic activity in modulating the clearance of coagulation factor VIII (FVIII). As a result, high FVIII coagulant activity levels (FVIII:C>150 IU/dL) were observed in carriers of *LDLR* variants. The combination of high FVIII levels with high FVIII:C/Von Willebrand Factor antigen (VWF:Ag) ratio (>1.5) suggests a reduced FVIII clearance. To date, data on the effect of these variants in metabolic syndrome are scarce. This study aims to evaluate the impact of *LDLR* and *LRP1* variants on plasma levels of (1) low-density lipoprotein-cholesterol (LDL-c), (2) FVIII and FVIII:C/VWF:Ag in patients with metabolic syndrome.

Methods. Blood donors aged 40-65 with metabolic syndrome were consecutively enrolled from July 2019 to July 2021 in the frame of the Liver BIoBank Lombardia gEnomic (Liver-Bible) cohort. A list of 65 variants (61 in *LDLR* and 4 in *LRP1*) associated with cholesterol levels, coronary artery disease, or body mass index (BMI) were selected from the GWAS Catalog (https://www.ebi.ac.uk/gwas/). Among these, 54 variants were extracted from the Liver-Bible genome-wide association study. Linkage disequilibrium r2 was calculated using Plink and 28 tag variants were selected (r2>0.8). Association analyses were performed by linear regression models. Potential effect modifiers [e.g. age, sex, ABO blood group, C-reactive protein (CRP), BMI, glycated haemoglobin (HbA1c)] have been taken into account.

Results. A total of 1,190 subjects were eligible for aim (1), 574 for aim (2). After adjusting for age, sex and BMI, three variants (rs688, rs10422256 and rs6511721) were found associated with higher LDL-c levels. No association between analysed variants and FVIII levels was found. The variant rs74257940 was associated with higher FVIII:C/VWF:Ag ratio. A LDLR-LRP1 weighted polygenic score (PGS), calculated using the beta coefficients obtained from the association with LDL-c levels, correlated with higher FVIII:C/VWF:Ag ratio (Figure).

Conclusions. Among the 28 analysed *LDLR* and *LRP1* variants, three *LDLR* variants (rs688, rs10422256 and rs6511721) were associated with increased LDL-c levels in a cohort of subjects with metabolic syndrome. The developed polygenic score resulted to be associated with higher FVIII:C/VWF:Ag ratio, suggesting a potential role of the selected variants in reducing FVIII clearance.

