



LP(A) AND CARDIOVASCULAR RISK IN FAMILIAL HYPERCHOLESTEROLEMIA

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Background and aims. Familial hypercholesterolemia (FH) is a genetic disorder marked by high low-density lipoprotein cholesterol (LDL-C) levels, mainly caused by mutations in *LDLR*, *APOB*, *PCSK9* or *LDLRAP1* genes. FH patients show a higher risk of adverse cardiovascular events than the general population, due to the alteration of lipid profile that causes atherosclerosis. An independent and mostly genetically determined atherosclerotic risk factor is lipoprotein (a) [Lp(a)]. Elevated Lp(a) levels have been demonstrated as a causal risk factor for coronary heart disease (CHD), aortic stenosis and ischemic stroke. A recent (2025) meta-analysis of 27,658 participants enrolled in 6 placebo-controlled statin trials demonstrates the independent and additive nature of Lp(a) and LDL-C levels for atherosclerotic cardiovascular disease (ASCVD) risk, and that LDL-C lowering does not fully offset Lp(a)-mediated risk. The aim of this study was to evaluate the contribution of Lp(a) serum levels in cardiovascular manifestations in Italian FH patients of a referral Center.

Methods. We analyzed 121 patients with possible/probable/definite FH using Dutch Lipid Clinic Network score diagnostic criteria. A targeted 57 genes panel (including genes involved in lipid metabolism and dyslipidaemias), was evaluated through a high throughput sequencing (HTS) technology, using MiSeq Illumina platform. The pathogenicity of *LDLR* variants was evaluated according to the American College of Medical Genetics guidelines. Lp(a) levels were measured by an immunonephelometric method (LPAX IMAGE, Beckman Coulter). Continuous variables were expressed as median (interquartile range).

Results. Our cohort was characterized by 91 adults and 30 pediatrics with median Lp(a) levels of 271.0 (85.0-1050.0) and 172.0 (56.5-829.5) mg/L, respectively. In adult population, 21/91 (23.1%) patients showed CHD events and 26/91 (28.6%) manifested both CHD or peripheral vascular events, while no events were registered in the pediatric population. In adult patients presenting cardiovascular manifestation, both coronary and/or peripheral, we observed higher median levels of Lp(a) with respect to patients not affected by these clinical complications [717.0 (233.2-1232.5) vs 229.0 (78.0-949.0) mg/L, $p=0.02$]. Among adults, HTS analysis allowed to identify 29 patients with at least one likely pathogenic/ pathogenic variant in *LDLR* gene, group defined as *LDLR*-positive (*LDLR*+). The remaining 62 patients were mutation-negative (*LDLR*-) or carried only benign/likely benign/uncertain significance variants in this gene. Among *LDLR*+ group, in subjects with CHD and/or peripheral vascular events (10/29=34.4%) higher levels of Lp(a) with respect to subjects without events were reported [257.5 (56.2-787.0) vs 89.0 (28.0-235.0) mg/L, $p=0.09$]. Among *LDLR*-, patients exhibiting CHD and/or peripheral vascular events (16/62=25.8%) showed significantly higher Lp(a) levels than the event-negative group [981.0 (396.7-1795.0) vs 286.0 (89.5-1095.0) mg/L, $p=0.02$].

Conclusions. Our data support the contribution of Lp(a) to the higher prevalence of cardiovascular manifestations in FH clinical phenotype, in particular in patients not showing a monogenic causative mutations. This study strengthens the importance of including Lp(a) in the cardiovascular risk assessment of patients also in the FH clinical setting, to better stratify cardiovascular risk and to improve the therapeutic management.