The Official Journal of the Italian Society for the Study of Hemostasis and Thrombosis
SISET
Società Italiana per lo Studio dell'Emostasi e della Trombosi
Corso Nazionale SISET
Bergamo | 23-25 ottobre 2025

29TH NATIONAL CONFERENCE OF THE ITALIAN SOCIETY FOR THE STUDY OF HEMOSTASIS AND THROMBOSIS, 2025

ABSTRACT N. CO13

TEV E PATOLOGIE CARDIOVASCOLARI

GENETIC BACKGROUND IN HYPERCHOLESTEROLEMIC PATIENTS FRAMING CARDIOVASCULAR RISK.

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Background and Aims: Familial hypercholesterolemia (FH) represents a condition affecting 1 out of 250 individuals. Many FH subjects (about 60%) did not demonstrate functional mutations in major candidate genes (LDLR, APOB, PCSK9, LDLRAP1).

Methods:FH patients genetic profile has been assessed by high-throughput sequencing (HTS). We analysed 167 FH patients [adults with possible/probable/definite FH according to Dutch Lipid Clinic Network Score (DLCN)]. Targeted HTS (57 genes involved in lipid metabolism, supposed to be involved in dyslipidaemia, pharmacogenetics of statins, related to FH polygenic forms, HDL and triglycerides related diseases) was assessed by Illumina technology.

Results: Among 167 patients [101 females/66 males, median age (IQR): 50 (26-61)] a total of 65 rare variants in LDLR gene in 61 patients were identified. Fifty-six patients showed LDLR variants classified as uncertain significance (VUS)/likely pathogenic (LP)/pathogenic (P) according to the American College of Medical Genetics guidelines for the interpretation of sequence variants (Richards et al., Genet Med.2015), while the other 111 patients did not carry any or only benign (B)/likely benign (LB) variants in LDLR gene.Among the LDLR negative, n=97 patients (87.4%) showed at least 1 rare variant in one of the other 56 genes of the panel, n=78 patients (70.3%) showed at least 2 variants, n=58 (52.3%) showed at least 3 variants in the other genes.In FH patients investigated, 436 rare variants were found in 53 genes (APOB, PCSK9, LDLRAP1, ABCA1, ABCB1, ABCG2, ABCG5, ABCG8, ANGPTL3, APOA1, APOA4, APOA5, APOC2, APOC3, APOE, BTN2A1, CELSR2, CETP, CH25H, CREB3L3, DAB2, DGAT1, EPHX2, GCKR, GHR, GPD1, GPIHBP1, HFE, HMGCR, INSIG2, ITIH4, LCAT, LIPC, LIPI, LMF1, LPA, LPL, LRP1, MTTP, NPC1, NPC1L1, NPC2, NYNRIN, OSBPL5, PON1, PPP1R17, SCARB1, SLC22A1, SLCO1B1, SREBF1, SREBF2, ST3GAL4, STAP1).We also evaluated the 12 SNPs Talmud genetic risk score (Talmud P et al., Lancet 2013), which takes into account polymorphic variants that have a cumulative effect on raising LDL-C levels to those achieved from patients with a LDLR mutation. Talmud score evaluation showed a significantly higher median value in patients LDLR-negative for the presence of a VUS or LP/P variant, with respect to LDLR-positive [median(IQR):1.02(0.90-1.11)vs0.94 (0.85-1.05), p=0.013].According to the abovementioned datum, we also stratified both groups according to a Talmud risk deciles cut off = 5 and we observed that 31/56 LDLR positive patients had a Talmud risk decile ≥5th decile (55.4%), while 89/111 LDLR negative patients had a Talmud risk decile ≥5th decile (80.2%), reaching statistical significance (p=0.0010).Among FH patients, 30 were younger than 18 yrs. Among adults, LDL-cholesterol levels were comparable between LDLR-positive and LDLR-negative group, whereas in younger subjects significantly higher LDL-cholesterol levels were observed among LDLR-positive.As concerns DLCN score, performed in adult population, significantly higher values in subjects carrying LDLR mutation were found. **Conclusion:**Present data suggest the involvement of multiple loci beyond LDLR gene in the modulation of lipid profile, as well as cardiovascular risk.Nevertheless, the expansion of genetic analysis to a largest cohort might allow a better comprehension of the role of further major/modifier genes, as well as of accumulation of common small- effect LDL-C raising alleles in determining LDL-C levels and cardiovascular events.

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