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**Rare ceruloplasmin variants are associated with hyperferritinemia and increased hepatic iron in NAFLD patients: results from a NGS study**

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**Background and Aims:** Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease resulting from the interaction of genetic and environmental factors.

Hyperferritinemia has been associated with altered hepatic iron metabolism, increased hepatic iron stores and worse hepatic and cardiometabolic outcomes in patients with NAFLD and metabolic syndrome.

Our aim was to evaluate the prevalence of genetic variants of iron-related genes and their association with HyperFt and increased hepatic iron stores in NAFLD patients.

**Method:** From a published cohort of 347 subjects with histological NAFLD and available serum iron parameters, hepatic iron staining and genetic characterization, 23 cases with hyperferritinemia and positive iron staining (HyperFt) and 25 controls with lowest ferritin and negative iron staining (NormoFt) were selected.

Patients with beta-thalassemia trait, increased transferrin saturation, anemia, inflammation, and, within HyperFt group, carriers of HFE genotype at risk of iron overload or ferroportin mutations were excluded.

A custom AmpliSeq™ NGS panel of 33 genes associated with iron homeostasis was designed and tested. Literature and in silico predictions were used for prioritization of possibly pathogenic mutations.

**Results:** The two groups did not significantly differ in components of metabolic syndrome and severity of liver disease.

Potential pathogenic variants were found in 54% of HyperFT patients and in 4% of NormoFT patients ($p=0.0001$), and ceruloplasmin (CP) resulted to be the most mutated gene, with the identification of 4 different variants harbored in heterozygosis by 6 HyperFt patients ($p<0.01$) (Fig.1).

When polymorphisms possibly affecting iron metabolism such as TF c.829G>A or CP c.1652C>T were included in the analysis, 78% of HyperFt versus 38% of NormoFt patients resulted to have such variants ($p=0.0016$). TMPRSS6 A736V distribution was not significantly different between IperFt and NormoFt patients.

When patients were checked for polymorphisms previously associated to advanced liver fibrosis or severe iron overload in HFE-hemochromatosis, such as PCSK7 rs2369918G>C and GNPAT rs11558492 (D519G), no significant difference in the distribution was found between the two groups.

**Conclusion:** Variants in non-HFE iron genes, particularly ceruloplasmin, seem associated with hyperferritinemia and increased hepatic iron stores in Italian NAFLD patients. Future studies are necessary to confirm these findings in larger cohorts and to evaluate their clinical relevance.

**Figure:** Number of patients carrying iron-genes pathogenic mutations in HyperFt and NormoFt group.