Genetic study on iron metabolism genes implicates *HIF1A* in MS progression

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Background
Iron enrichment is a core feature of chronic active lesions, a key marker of progressive MS, and can be detected by magnetic resonance imaging. In parallel, the molecular profile of the lesion-associated microglia supports the relevance of genes involved in iron metabolism. However, it is still unclear their role in disease progression.

Aims
We investigated the impact of Single Nucleotide Polymorphisms (SNPs) in genes implicated in iron metabolism on the risk of developing progressive MS.

Methods
We performed an association analysis on 63,241 SNPs in 319 genes involved in iron metabolism, comparing benign relapsing-remitting (RR) versus secondary progressive (SP) patients in a discovery Italian cohort from San Raffaele Hospital (OSR). Significant results were investigated in a nationwide replication cohort from Sweden (SWE). Benign RR-MS was defined as a confirmed RR course of $\geq$20 years and EDSS$\leq$3.5 at the end of follow-up. In the SP group, patients with confirmed conversion to SP within 20 years from onset and EDSS$\geq$4.0 were included.

Results
After quality controls, a total of 2,687 patients were studied. We found a significant association involving SNPs in the Hypoxia-Inducible-Factor-1-alfa (*HIF1A*) gene in the discovery cohort (n=625; lead SNP=rs11621525; p=5.31E-06, OR_SP=0.55), that was replicated in the SWE cohort (n=2,062; lead SNP=rs1951795; p=0.0079, OR_SP=0.79). Previous evidence has shown that the rs11621525_A allele down-regulates *HIF1A* expression in whole blood in healthy subjects. We replicated this effect in peripheral blood mononuclear cells from 78 RR-MS patients (p=0.034). We also studied the neurofilament (NFL) levels, a recognized marker of ongoing axonal injury and chronic white matter inflammation. RR-MS patients who were carriers of the A allele showed lower NFL, both in plasma (n=117; p=0.0026) and in cerebrospinal fluid (n=77; p=0.051).

Conclusion

Genetic variants in *HIF1A* are associated with risk of a progressive MS course and impact NFL levels. HIF1A is a fundamental regulator of iron metabolism, response to hypoxia and immune processes, and therefore represents a promising candidate for further investigation.