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Haplotype analysis of the HFE gene among patients with different forms of tick-borne encephalitis

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Motivation and Aim: Human *HFE* gene is located in short arm of human chromosome 6, 4 megabases from the major histocompatibility complex on the telomeric side. This human-genome locus encodes for human leukocyte antigens and is characterized by significant linkage disequilibrium and a high polymorphism level at the same time. It has been shown that some intragenic *HFE* haplotype frequencies are race specific. We suppose the sharp phylogenetic difference in this locus could be explained by natural selection under pathogen pressure. Tick-borne encephalitis (TBE) was probably one of such endemic infections in North Eurasia.

Methods and Algorithms: Haplotype analysis for the rs1799945, rs1800730, rs1800562, rs2071303, rs1800708, and rs1572982 was performed in 166 Russian patients with different clinical forms of TBE and in a control population group (356 individuals). The case sample consists of 128 non-immunized (44 with fever, 49 with meningitis, and 35 with severe central nervous system disease) and 38 immunized Russian patients with TBE.

Results: We did not reveal any genetic difference among immunized patients with different forms of TBE. Frequency of the TTA haplotype of the *HFE* gene – in the groups of non-immunized patients with severe central nervous system disease – are higher than such frequencies in TBE patients with fever, with meningitis, and in Russian population (0.2 vs. 0.1, 0.15, and 0.14, respectively). Previously, TTA haplotype frequency was shown to be 0.02-0.07 in East Siberian native populations. Significant differences in the TTG/TTG genotype frequency were found between the sample of TBE patients with fever and population cohort (0.38 vs. 0.22, respectively, $P = 0.022$), as well as in the TTG allele frequency between the sample of TBE patients with fever and with severe central nervous system disease (0.57 vs. 0.4, respectively, $P = 0.026$).

Conclusion: TTA haplotype of the *HFE* gene is possibly associated with severe form of TBE and could be under selection pressure in North Eurasia. Additional studies with TBE patients are required for further validation of the results.

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