

CLINICAL AND GENETIC FEATURES OF MULTIPLE SCLEROSIS IN THE REPUBLIC OF BASHKORTOSTAN: A 20-YEAR FOLLOW-UP STUDY

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Multiple sclerosis (MS) is a complex disease caused by interaction of genetic and non-genetic factors. Our aim was to study clinical features of MS and replicate previously observed genome-wide associations with MS in three ethnic groups from the Republic of Bashkortostan (Russian Federation).

The study group consisted of 644 patients with MS (97 Bashkirs, 283 Russians, 264 Tatars) and 1408 healthy controls (231 Bashkirs, 490 Russians, 687 Tatars). The subset of patients enrolled in 2000 included 247 people (123 Russians, 98 Tatars, 26 Bashkirs). We performed replication of GWAS associations with MS of genetic variants in *CD6*, *CD40*, *CD58*, *CD86*, *SOX8*, *ZBTB46*, *MANBA*, *CLEC16A*, *RPS6KB1*, *PVT1* genes.

Upon enrollment, average age of patients was 38.4 ± 9.9 years, average disease duration 10.5 ± 8.3 , and rate of progression 0.48 (0.27; 1) points/year. Primary progressive MS was detected in 25 patients (10.1%), secondary progressive – in 127 (51.4%), relapsing-remitting – in 95 (38.5%). Average EDSS score in 2000 was 4.08 ± 1.4 , after 20-years follow-up – 5.4 ± 2.24 . EDSS scores and progression rate in men and women were equal upon enrollment, but after 10 years, neurological disability and progression were more pronounced in men ($P=0.04$). After 20 years, 96 people (38.87%) of the initial sample died. The groups of patients with progression and the deceased were characterized by late disease onset and early manifestation of movement and coordination disorders.

In the group of Bashkirs increased MS risk was associated with *PVT1* rs759648*A/C, *CD6* rs17824933*G/G and *CD40* rs6074022*C/C genotypes. In Russians, *CD86* rs9282641*G allele conferred higher MS risk. In Tatars, *CD86* rs9282641*G, *PVT1* rs759648*C, and *ZBTB46* rs6062314*T were found predisposing to MS. *CD58* rs2300747*A/A and *CD40* rs6074022*T/T were associated with increased risk of MS progression.

Our results indicate that the factors increasing MS progression risk include male sex, late disease onset, movement disorders as early disease manifestation, and *CD58* rs2300747*A/A and *CD40* rs6074022*T/T genotypes.