

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. During the follow-up period, the rate of progression slowed down in all three groups of patients, depending on the progression, and at the end of the study was 0.25 +/- 0.1 points/year (Figure 1). 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) (Figure 2).

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 (Figure 3).

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 (Figure 4).

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.

Figure 1 - Dynamics of the rate of progression

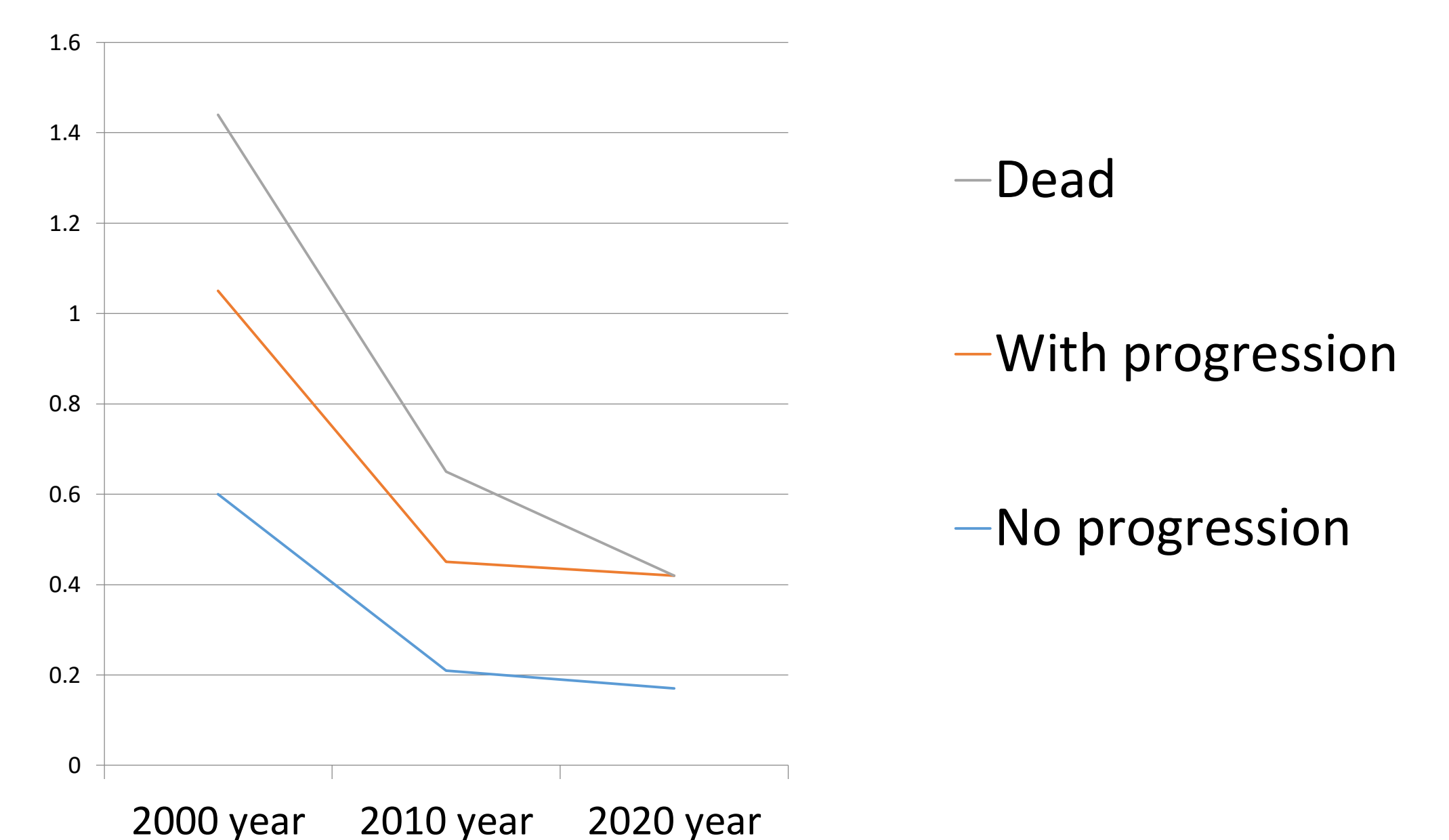


Figure 2 - Dynamics of the rate of progression depending on gender

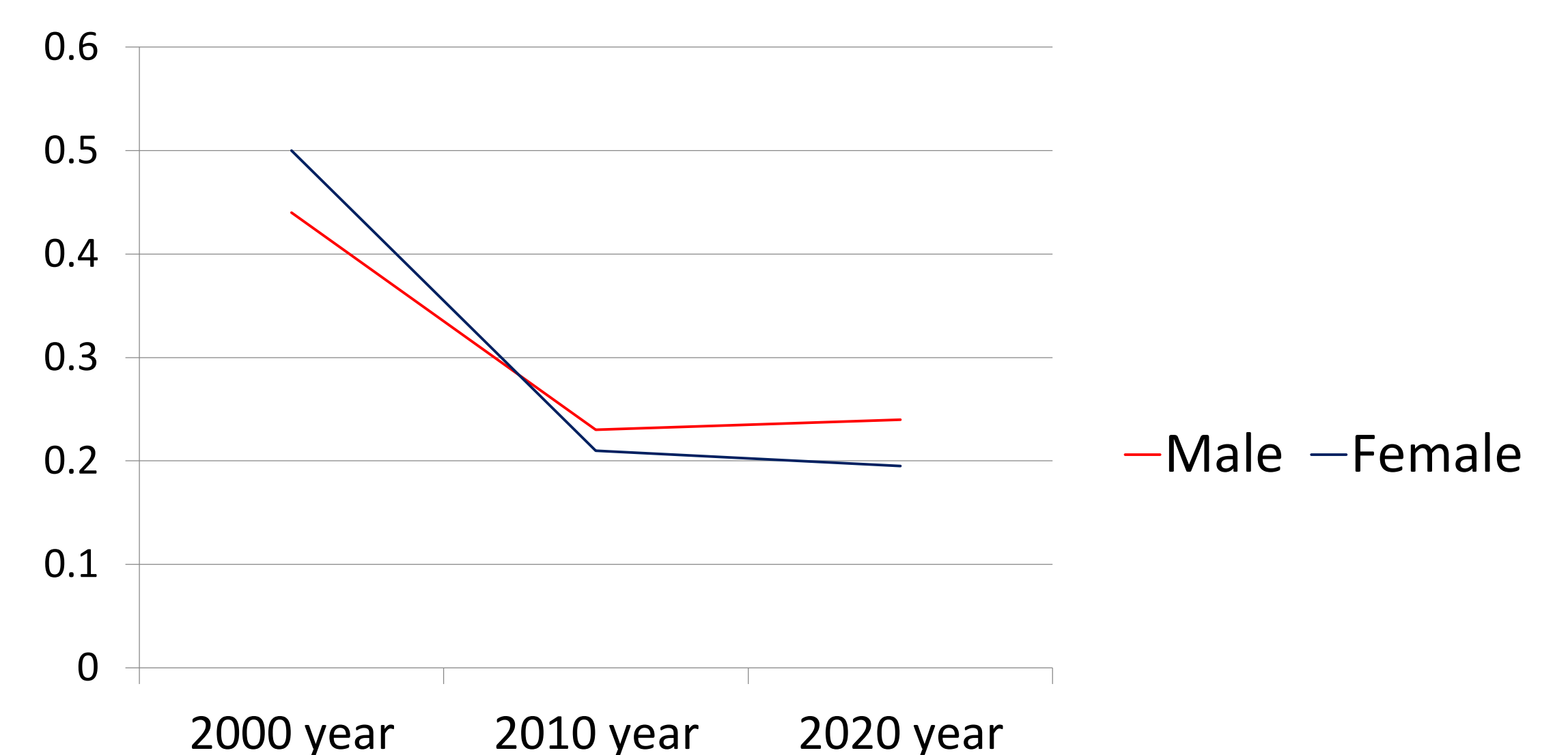


Figure 3- Symptoms of debut in three groups

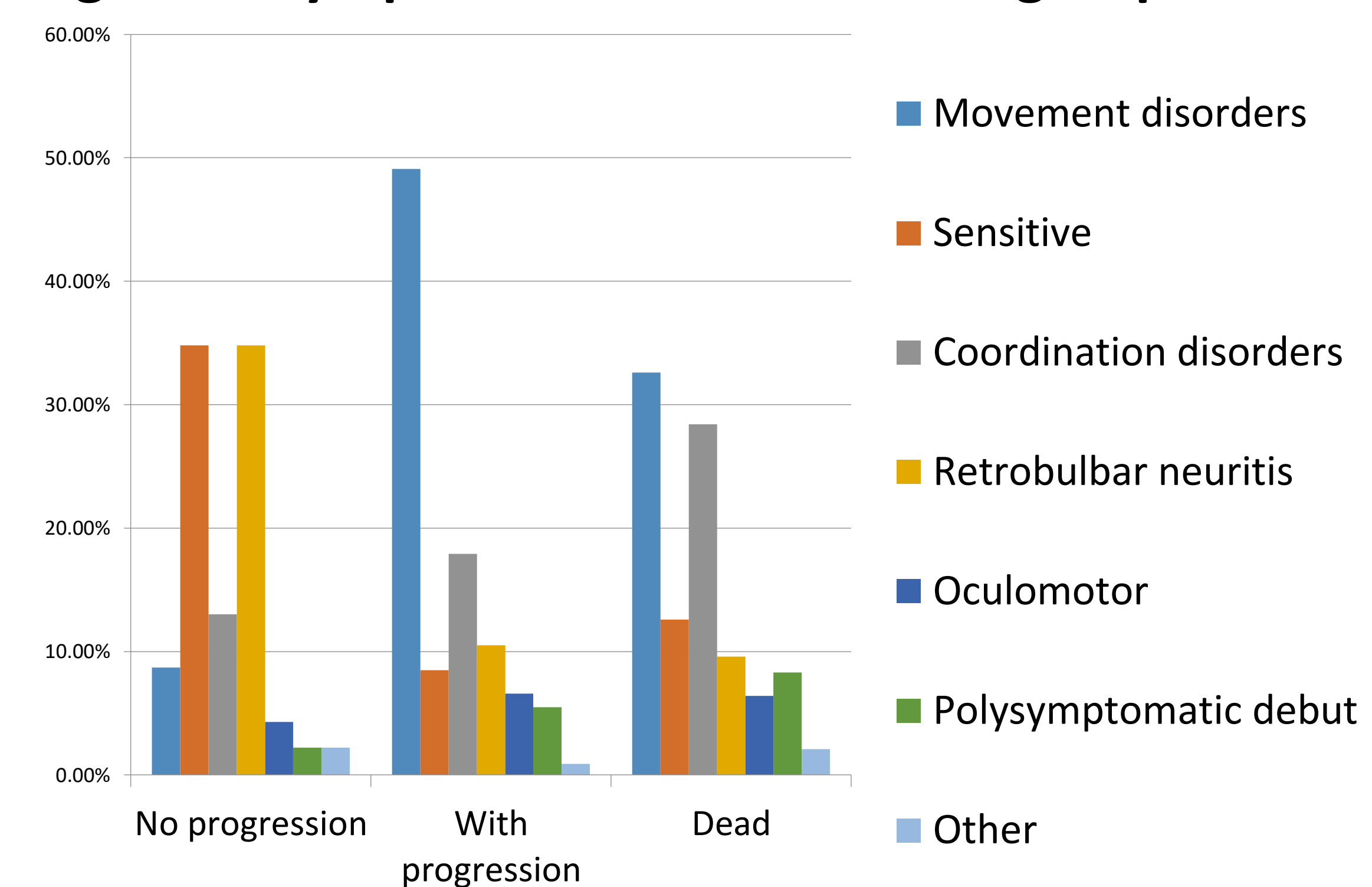


Figure 4 - Association of gene polymorphism with the progression of multiple sclerosis

