

Discriminative selection of alternative disease-modifying treatment in multiple sclerosis patients

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Background. Multiple sclerosis (MS) is a heterogeneous autoimmune disease of the central nervous system, which requires the long-term medication with specific disease modifying treatments (DMTs). The first-line immunomodulatory drugs interferon-beta (IFN β) and glatiramer acetate (GA) have been shown to reduce the disease activity. However the significant share of MS patients remains resistant to the therapy used. Diverse genetic background may define the variable therapy response. For discriminative selection of preferable first-line DMT we performed the comparative pharmacogenetic analysis in MS patients treated either with IFN β or GA. Unified set of immune-response genes, which are relevant for IFN β and/or GA modes of action, and identical clinical criteria of treatment

response were used.

Materials and Methods. 253 IFN β -treated unrelated MS patients and 285 GA-treated MS patients were studied (Moscow region residents of Russian ethnicity). The patients with event-free status during no less than 2 years of DMT course were classified as clinically optimal responders (Rs); other patients were classified as non-optimal responders (NRs). In this study we compared the distribution of alleles/genotypes/allelic combinations differing in carriage between IFN β responders and GA responders. A comparison between IFN β non-responders and GA non-responders was performed in order to confirm the found associations as well. The allelic sets, of which carriage was associated with discriminative DMT response, were identified using APSampler algorithm with subsequent validation by means of the exact Fisher's (p_f) and permutation (p_{perm}) tests. Functional polymorphisms in the following candidate genes were studied: *DRB1* HLA class II, *IFNB1* (rs1051922), *IFNARI* (rs1012335), *IFNG* (rs2430561), *TNF* (rs1800629), *TGFBI* (rs1800469), *IL7RA* (rs6897932), *CCR5* (rs333) and *CTLA4* (rs231775).

Results. We have found that discriminative polymorphic variants of *CCR5*, *IFNARI*, *TGFBI*, *DRB1* and *CTLA4* genes provide the preferable choice of IFN β or GA for MS patients. Some discriminative composite markers, of which carriage in Russians is beneficial for MS individuals on IFN β treatment whereas detrimental for those on GA treatment were identified. As compared to our previous conventional pharmacogenetics studies on IFN β and GA treatment response, it can be concluded that certain genes found upon conventional pharmacogenetic studies cannot be considered as discriminative genetic markers of IFN β versus GA treatment response.

Conclusions. Our study provides an option for identification of promising prognostic composite genetic markers for first-line immunomodulatory treatment selection for individual MS patients.