POLYMORPHISMS IN DOPAMINERGIC RECEPTOR GENES AND MULTIPLE SCLEROSIS PROGRESSION

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Introduction: Multiple Sclerosis (MS) is a chronic autoimmune disease characterized by inflammation and axonal loss and neurodegeneration in the central nervous system. Dopamine (DA), a key brain neurotransmitter is also a crucial transmitter in the neuroimmune network (Sarkar et al., Brain Behav Immun 2010, 24: 525-528; Pinoli et al., J Neuroimmune Pharmacol 2017, 12: 602-623), and several lines of evidence suggest that dopaminergic modulations of peripheral immunity is widely involved in MS progression and therapeutic response (reviewed in Cosentino and Marino, J Neuroimmune Pharmacol 2013, 8: 163-179). DA acts on 5different receptors (DR) and several genetic variants, in particular single nucleotide polymorphisms (SNPs), have been described in DR genes So far, however, the influence of SNPs in DR genes has not been examined in terms of MS progression and drug response. In order to evaluate the role of DR genetic variants in MS, we selected a panel of SNPs in DR genes, giving priority to the most frequent and best functionally characterized ones. We then compared DR genetic profile in a cohort of MS patients with clinical outcome measures, including MS progression and response to drug therapy.

Methods: Consecutive enrolment of MS patients. Collection of clinical data (including response to treatment) and blood samples. SNPs will be analyzed by real time PCR using a GeneAmp 9700 PCR System (ABI, Foster City, CA) and pre-designed genotyping assays (ABI). Criteria for SNP selection were reported previously (Ferrari et al. Eur J Clin Pharmacol. 2016, 72: 1335-1341). The correlation of DR gene variants with MS clinical progression as well as with therapeutic response will be examined for individual SNPs using a dominant model, as well as by combining the genotypes of individual DR into functional categories based on published evidence regarding the effects of individual gene variants on DR function.

Results: So far, we have enrolled 60 bout-onset MS patients (38women, mean age at onset 32±9years) who were on regular follow-up for at least 5years after diagnosis. Collected Clinical data included age at onset, expanded disability status score, number of relapses updated at 5years, and any disease-modifying therapies (DMTs). We also calculated the Multiple Sclerosis Severity Score (MSSS) for each patient. DMTs included both first line (IFN-beta and glatiramer acetate) and second line treatments (azathioprine, natalizumab, and fingolimod). At the time of this submission, genotyping is still ongoing and correlations with MS progression and drug response will be performed in the near future.

Conclusion: Our study points at providing reliable markers of MS progression and treatment response. This approach will eventually result in a more precise tailoring of pharmacological regimen, with a view to personalized medicine.