Identification of proteasome related SNPs based candidate markers for multiple sclerosis in Latvian population

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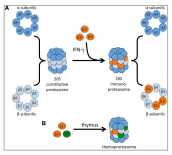
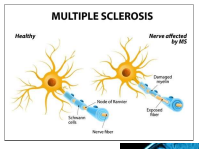
Background





Proteasomes, the multycatalytic protease complexes, play a critical role in the degradation of proteins via ATP/ubiquitin-dependent process or ubiquitin proteasome system, which plays a crucial role in immunity and its disregulation and/or modulation may influence the development and progression of different diseases.

20S proteasome induction with **interferon** causes replacement of PSMB5, PSMB6 and PSMB1 by PSMB8 (LMP7), 2 PSMB9 (LMP2) and PSMB10 (MECL-1), respectively, and forms **immunoproteasome**. Expression of PSMB8 (LMP7), and PSMB9 (LMP2) genes is decreased in patients with autoimmune diseases.

Multiple sclerosis (MS) is **autoimmune inflammatory disease, that** involves an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system (CNS: brain, spinal cord and optic nerves). Within the CNS, the immune system causes **inflammation that damages myelin** — the fatty substance that surrounds and insulates the nerve fibers — as well as the nerve fibers themselves, and the specialized cells that make myelin. When myelin or nerve fibers are damaged or destroyed in MS, **messages** within the CNS are **altered** or **stopped** completely.

The **proteolytic activities** of proteasomes are **reduced** in brain tissue of **MS** patients. The 20S proteasome had been identified as a target of the humoral autoreactive immune response and a major autoantigen in MS patients.

The **Aim** of study was to determine the **association of SNPs** of several proteasomal genes **with multiple sclerosis** in Latvia population

Materials and methods

289/200 samples of MS patients/control:

1. 70,71% women in MS and 58,60% - in control group
2. 187 with relapsing-remitting MS (RRMS) and 93 with secondary progressive MS (SPMS)

Three SNPs of proteasomal genes:

1. *PSMB8 (LMP7)* - proteasome subunit beta 8: rs2071543 > NM_004159.4:c.135+427C>A (Gln49Lys)
2. *PSMB9 (LMP2)* - proteasome subunit beta 9 rs17587 > NM_002800.4:c.179G>A
3. *PSMD9* - proteasome 26S subunit, non-ATPase 9 rs74421874 > NM_002813.6:c.454-460G>A

Genotyping was made using allele specific PCR and restriction enzyme site polymorphism method. **The difference** in the frequencies of the allele or genotype between the groups was determined by χ^2 criteria (Pirson χ^2 test) or Fisher exact test (with Monte Karlo permutation) and clinical significance of differences with Odds ratio (OR)

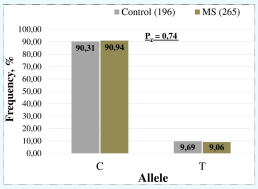
Results

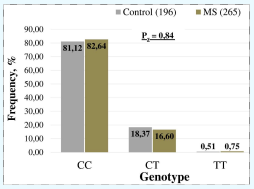
MAF – minor allele frequency; EUR – European population; Px – statistical significant of crosstab table; OR – odds ratio

PSMB8 (LMP7) rs2071543 - MAF in EUR: 0.15

No **statistically significant** difference of frequencies of alleles and genotypes of **rs2071543 of PSMB8** in control and case samples in all group together or in subgroups.

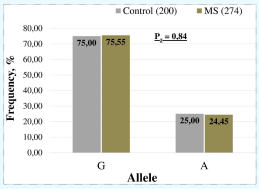
No TT or rear allele homozygote genotype for male samples of MS or control groups

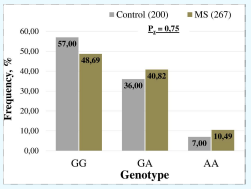




PSMB9 (LMP2) rs17587 - MAF in EUR: 0.27

No **statistically significant** difference of frequencies of alleles and genotypes of **rs17587 of PSMB9** in control and case samples in all group together or in subgroups.

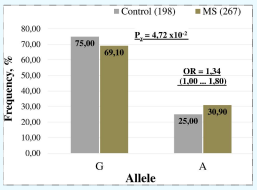


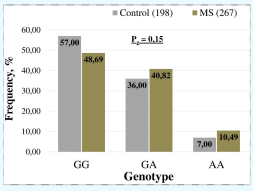


PSMD9 rs74421874 - MAF in EUR: 0.31

There are **statistically significant** difference of frequencies of **alleles** of **rs74421874 of PSMD9** in control/case samples with risk form G, but no significant different of frequencies of genotype.

No **statistically significant** difference of frequencies of alleles and genotypes in subgroups of gender of MS subtypes.





Conclusion

- **Common allele (G) of rs74421874 of *PSMD9* are risk form for MS patients in Latvian population.**
- **SNPs: rs2071543 of *PSMB8* and rs17587 of PSMB9, aren't individual associated with MS in Latvian population.**

Acknowledgements

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