SNPs of PSMA6 gene as potential biomarkers for multiple sclerosis in the Latvian population: case/control study and expression of gene

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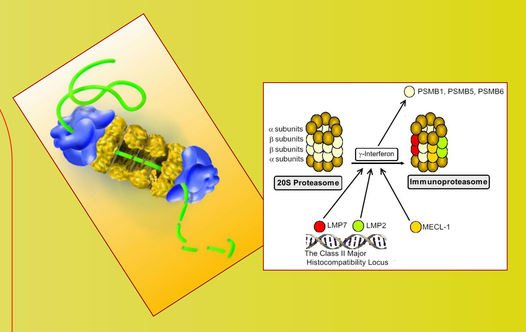
Background

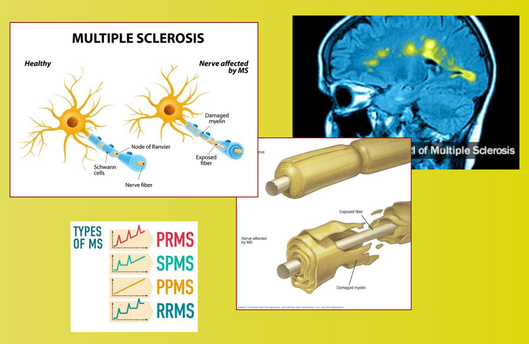
Proteasome system: Proteasomes, the multycatalytic protease complexes, play a critical role in the degradation of proteins via ATP/ubiquitin-dependent process or ubiquitin proteasome system, which plays a crucial role in immunity and its dysregulation and/or modulation may influence the development and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

20S proteasome induction with **interferon** causes replacement of three proteins of core and forms **immunoproteasome**. **Expression** of genes of proteins of immunoproteasome is decreased in patients with autoimmune diseases.

Multiple sclerosis (MS) is an **autoimmune inflammatory disease** of the central nervous system (brain, spinal cord and optic nerves). Inflammation damages myelin, which surrounds and insulates the nerve fibers, the nerve fibers themselves, and the specialized cells that make myelin, thus leading to neurodegeneration and disabilities. Damage to areas of the CNS may produce a variety of **neurological symptoms** that will vary among people with MS in **four** disease courses (**types**) and severity.

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.





Aim

to identify **SNPs of PSMA6** gene as potential **biomarkers** for **multiple sclerosis** in Latvian population

Materials and methods

Case/Control study with:

for genotyping 280 patients of MS (187 with relapsing-remitting MS and 93 with secondary progressive MS) and 305 controls

for gene expression 174 patients of multiple sclerosis.

SNPs of PSMA6 genes:

rs2277460 or c.-110C>A

rs1048990 or c.-8C>G

✓ **Laboratory analyze methods:**

- For genotyping was used allele specific PCR and restriction enzyme site polymorphism method.
- For gene expression was used qPCR

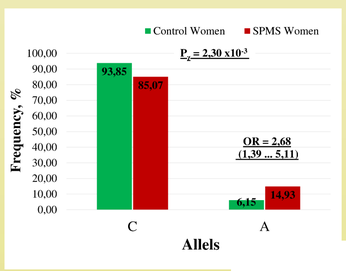
✓ **Statistical analyze:**

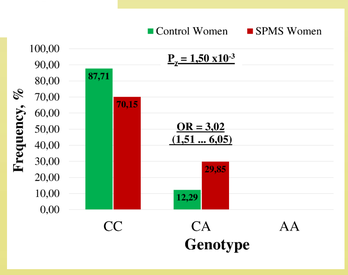
- for genotyping results difference between groups with χ^2 **criteria** (Pirson χ^2 test) or **Fisher exact test (with Monte Karlo permutation)** and clinical significance of differences with **Odds ratio (OR)**
- For gene expression, depending from **normal-distribution,** difference between groups by using **T-test** or **Mann Whitney U test** for two groups or **ANOVA** or **Kruskal-Walis** test for more than two groups; association with genotyping results with **eta (η)**.

Results

Case/control study of distribution of SNP

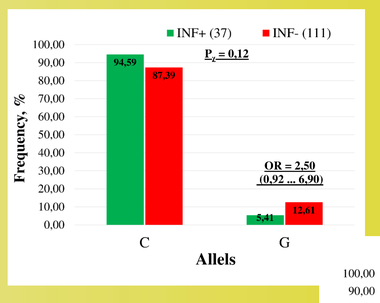
No statistically significant difference of frequencies of alleles and genotypes of rs1048990 (c.-8C>G) for MS or different subgroups, but in case of **rs2277460** (c-110C>A) **rear allele and heterozygote genotype** are **risk** form for **MS women patients**, especially, for SPMS type.

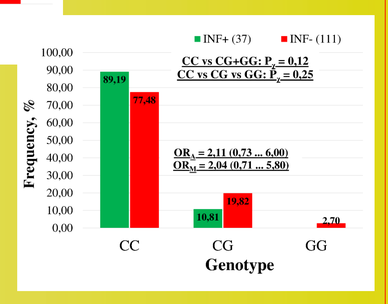




Cohort study of response to INF therapy

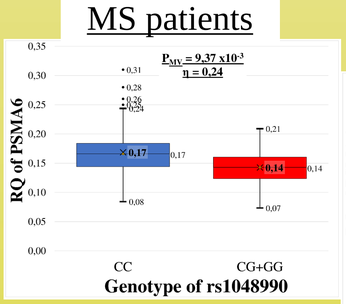
Rear allele and heterozygote genotype of rs1048990 (c.-8C>G) of *PSMA6* **can be risk** form for **respond** to **interferon therapy** of MS patients.



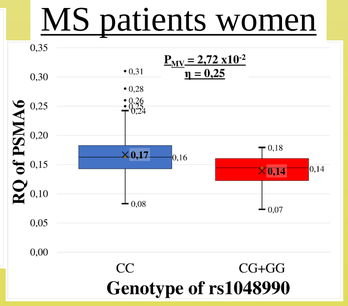


Expression level of PSMA6 depending on genotype of rs1048990

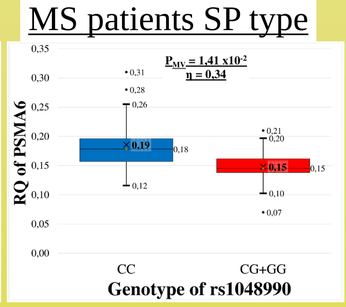
MS patients



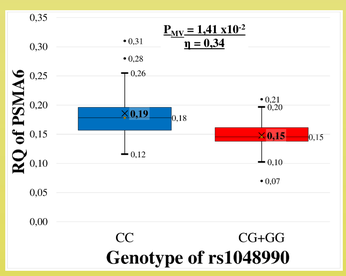
MS patients women



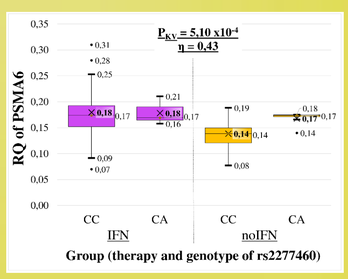
MS patients SP type

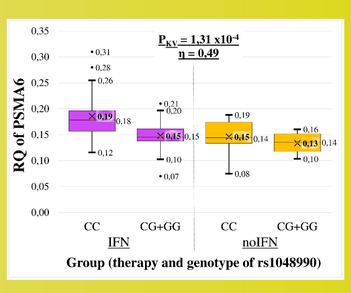


Heterozygote genotype of rs1048990 (c-8C>G) **for MS women or SP type patients** are **risk form** for expression of *PSMA6* gene.



Heterozygotes genotype of rs1048990 (c-8C>G) for MS patients **with interferon therapy** are **risk** for expression of genes**.**





Heterozygotes genotype of rs2277460 (c.-110C>A) increase expression of PSMA6 gene for MS patients without INF therapy, but **heterozygotes genotype** of rs1048990 (c-8C>G) decrease expression for MS patients.

Conclusion

- We **provide** evidence that variations of PSMA6 gene may contribute to the risk of multiple sclerosis in Latvians.
- **Results suggest** that IFN therapy increases transcription of genes of 20S proteasome α type subunits.
- Our **results prove** that the investigated polymorphisms potentially may be usable biomarkers for MS risk in clinical practice.

Acknowledgements

ERAF SAM Nr. 1.1.1.1/16/A/016 project “Determination of proteasome-related genetic, epigenetic and clinical markers for multiple sclerosis”; UL research project “The study of biomarkers and natural compounds for the diagnosis and personalized treatment of acute and chronic disease”

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