Association analysis between proteasome gene polymorphisms and circulating proteasome concentration in multiple sclerosis patients in Latvia

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BACKGROUND

- **Ubiquitin proteasome system** is the main proteolytic pathway of an eukaryotic cell, and proteasome is the main component of this system (Fig. 1). Proteasomal gene variations are well known to be associated with different diseases such as myocardial infarction, bronchial asthma, juvenile idiopathic arthritis (Sjakste et al. 2016).
- **Multiple sclerosis** (MS) is a chronic inflammatory disease of the central nervous system, which leads to large focal lesions in the white matter of the brain and spinal cord (Fig. 2), characterized by primary demyelination (Fig. 3) with a variable extent of axonal loss (Lassmann 2018).
- Changes in **circulating proteasome concentration** have been associated with oncological and autoimmune disease development (Sixt and Dahlmann 2008).
- We observed an association between SNPs in proteasomal genes *PSMA6* (**rs2277460**) and *PSMC6* (**rs22795826** and **rs22795827**) and increased MS risk in Latvian population. Also, these SNPs had a potential effect on secondary structure of the surrounding DNA region. Thus, it was assumed that these variations might have an effect on circulating proteasome concentration.

The aim of the current study was to evaluate possible associations between proteasomal gene polymorphisms and circulating proteasome concentration in multiple sclerosis patients in Latvia.

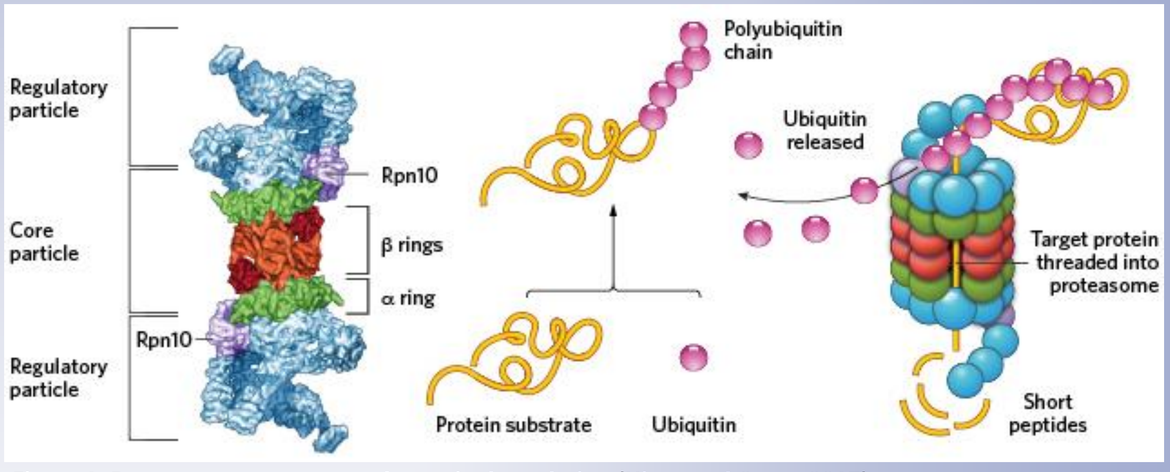


Figure 1. Proteasome structure and protein degradation (Hines and Crews 2017)

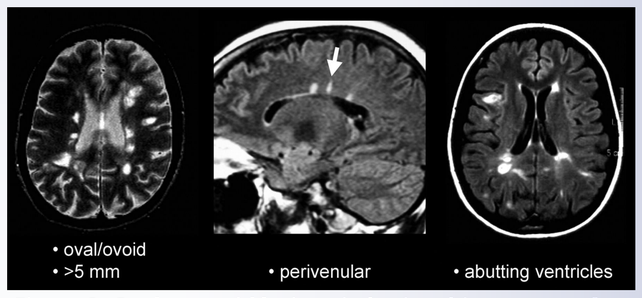


Figure 2. Oval or ovoid lesions in brain white matter of three multiple sclerosis patients (Bakshi et al. 2004)

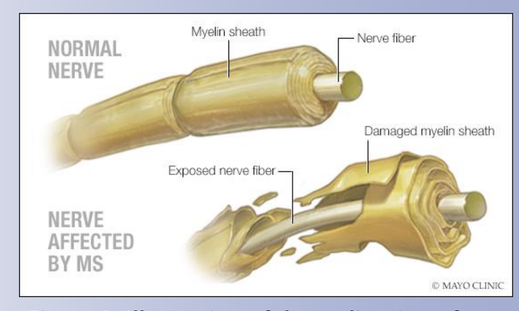
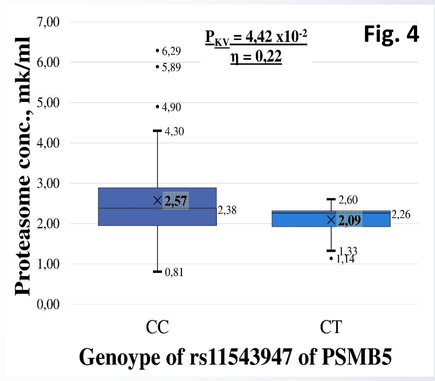
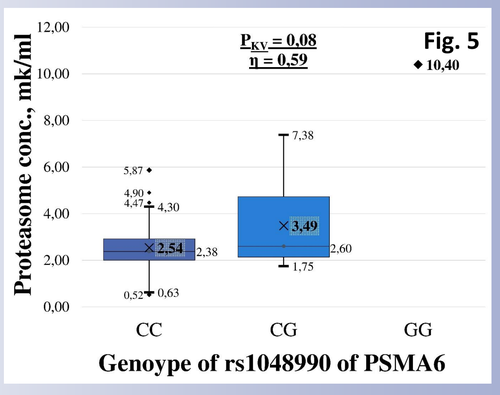


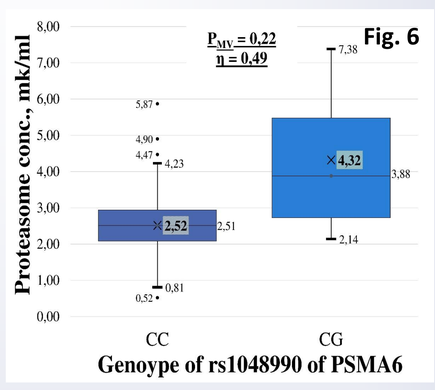
Figure 3. Illustration of demyelination of nerves in MS (Mayo Clinic informative illustration)

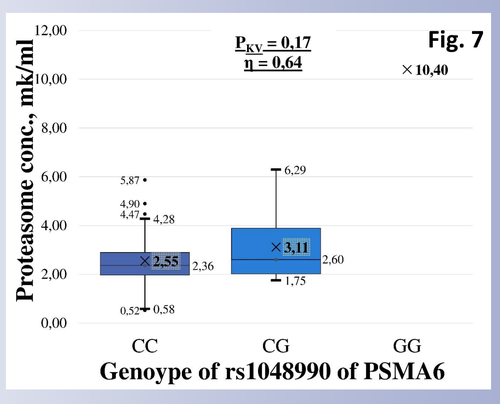
METHODS

Circulating proteasome concentration was detected with Enzo Life Sciences Proteasome ELISA kit (BML-PW0575-0001) following the protocol of manufacturer. For statistical analysis previously acquired genotyping data of *PSMB5* (rs11543947), *PSMA6* (rs2277460 and rs1048990), *PSMC6* (rs2295826 and rs2295827) and *PSMA3* (rs2348071) in Latvian MS population were used. Difference in median or mean of proteasome concentration between single genotypes or dominant homozygous and genotypes carrying the rare allele were calculated with T-test, ANOVA, Mann-Whitney or Kruskal-Wallis test depending on groups and data normality. Data were analysed in total MS collection and stratified by gender or type of the disease – RRMS (remitting relapsing) or SPMS (secondary progressive).









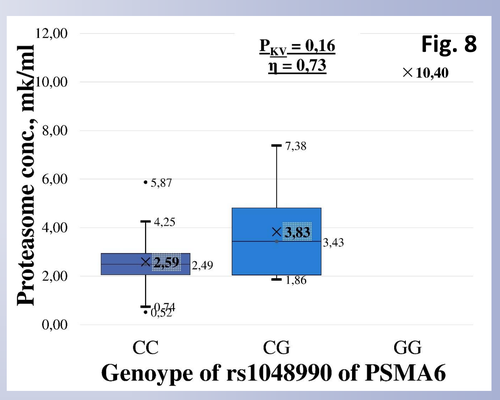


Figure 4. Circulating proteasome concentration in association with *PSMB5* (rs11543947) genotypes of RRMS patients. Figure 5. Circulating proteasome concentration in association with *PSMA6* (rs1048990) genotypes of total MS collection. Figure 6. Circulating proteasome concentration in association with *PSMA6* (rs1048990) genotypes of MS male patients. Figure 7. Circulating proteasome concentration in association with *PSMA6* (rs1048990) genotypes of MS female patients. Figure 6. Circulating proteasome concentration in association with *PSMA6* (rs1048990) genotypes of SPMS patients.

RESULTS

Only statistically significant difference in circulating proteasome concentration was detected between *PSMB5* gene rs11543947 genotypes of RRMS, but the low eta (η) value (0.22) indicated on a low association between genotypes and proteasome concentration (Fig. 4). Interestingly that, although in *PSMA6* gene rs1048990 genotypes of total MS collection as well as in Females, Males and SPMS (Fig. 5, 6, 7 and 8) statistically significant differences in proteasome concentration were not detected, η values indicated on average to strong association between genotypes and proteasome concentration.

CONCLUSIONS

In order to acquire statistically more significant data groups of MS patients should be increased. *PSMA6* rs1048990 genotypes could be associated with differences in circulating proteasome concentration.

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