Evaluation *in silico* of eventual functionality of 14q13.2 region proteasomal genes polimorfisms resulted in identification of novel candidate locus for association with multiple sclerosis (MS)

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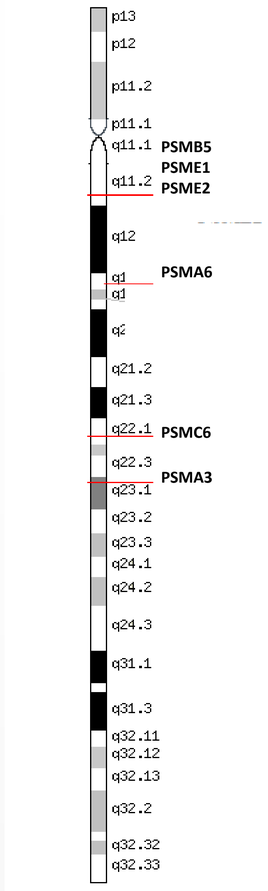
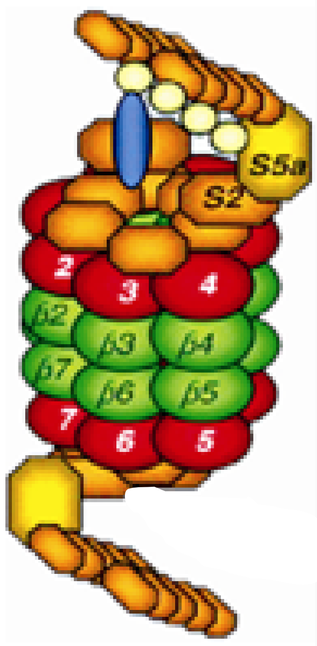
Chromosome 14



Proteosome



Proteasome activator subunit-1 (***PSME1***);

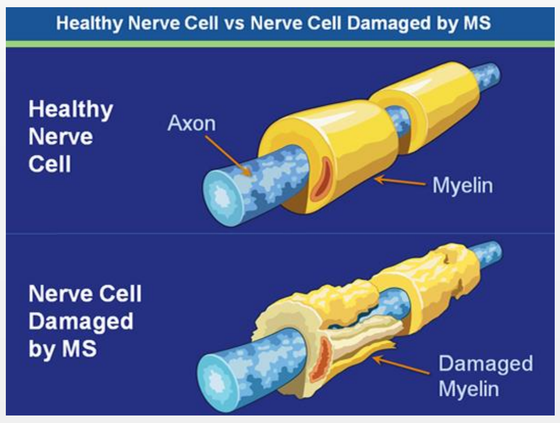
Proteasome activator subunit-2 (***PSME2***);

Proteasome (prosome, macropain) subunit alpha type-3 (***PSMA3***).

Proteasome subunit, beta type-5 (***PSMB5***);

Proteasome subunit alpha type-6 (***PSMA6***);

Proteasome 26S subunit ATPase type-6 (***PSMC6***);



Multiple sclerosis (MS)

is a chronic progressive disabling disorder of the central nervous system with considerable social impact and economical consequences. Disease is triggered by environmental factors in genetically predisposed subjects and it is immensely heterogeneous. Biomarkers that could predict disease predisposition, course, treatment response and risk of side effects would significantly assist to personalized management of MS patients. ***However, only few biomarkers have gone into clinical practice despite an extensive research over the last years.***

Possible links between proteasome functions and MS

Ubiquitin proteasome system (UPS) plays a crucial role in immunity and its deregulation and/or modulation may influence Multiple sclerosis (MS) development and progression. The 20S proteasome had been identified as a target of the humoral autoreactive immune response [1]. and a major autoantigen in MS patients [2]. Proteolytic activities of proteasomes are reduced in brain tissue of MS patients ([3]. Inhibition of proteasomes and lysosomal proteases involved in major histocompatibility complex II antigen presentation was shown to improve MS therapeutic efficacy [1, 4].

Region 14q13.2 association with autoimmune disorders

Genetic variations in the 14q11-24 proteasomal genes were implicated previously in susceptibility to autoimmunity, type 2 diabetes mellitus, cardio-vascular disorders, and population adaptation to environment [5]. It appears that there is large potential for some of these mutations to be also associated with multiple sclerosis. Modulation of UPS efficiency could be influenced by polymorphisms in the genes encoding UPS related proteins. The immunoproteasome *PSMB9* codon 60HH variant was observed to have a reduced risk of developing MS in HLA-A*02+ Italian females [6]. We have reported MS association with several alleles of proteasome genes [7]. correlation between the SNPs of the *PSMA3*, *PSMA6* and *PSMC6* genes and gene expression of these and other proteasome genes with type 1. diabetes mellitus [8].

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Goal **To identificate of novel proteasome related MS susceptible loci**

Conclusion

The 14q13.2 region proteasomal genes polimorfisms specific sequences functional motifs potentially could significantly affect Ubiquitin proteasome system (UPS) functionality and be involved in multiple sclerosis (MS) cause and progression.

Related publications

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Results

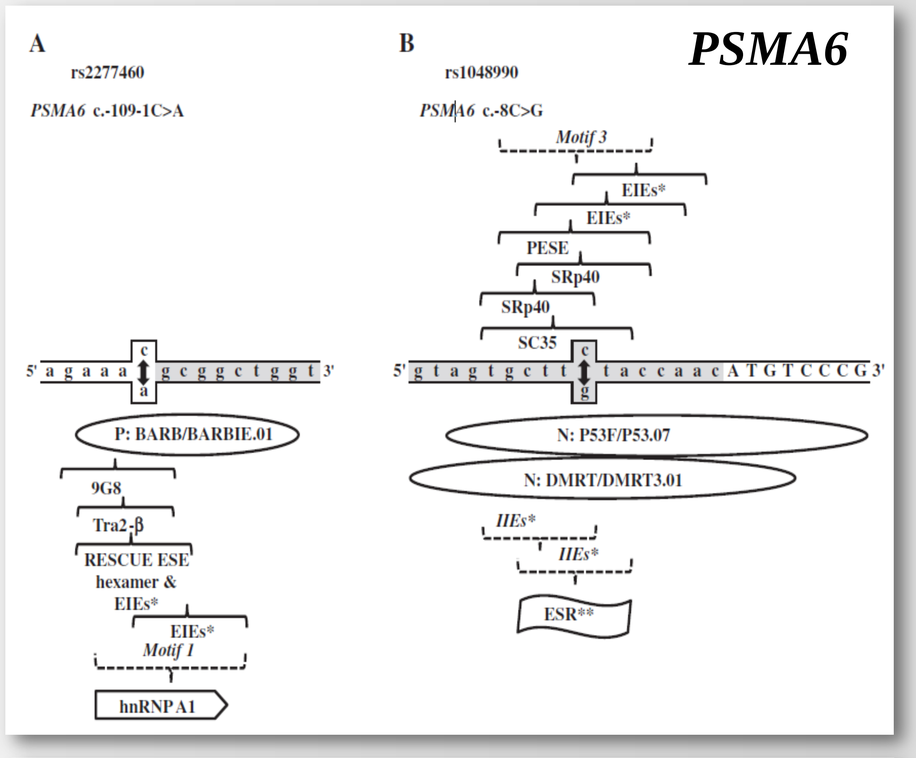

Fig. 1. Consequences of the rs2277460 (Panel A) and rs1048990 (Panel B) nucleotide substitutions on functional potential of corresponding genomic regions of the PSMA6 gene.

BARB/BARBIE.01 — barbiturate-inducible element; P53F/P53.07 — tumour suppressor p53; DMRT/DMRT3.01 — double sex and mab-3 related TF 3. Splicing enhancers are indicated by solid up-directed horizontal braces; splicing silencers are indicated by interrupted down-directed horizontal braces; splicing enhancer and silencers motifs are abbreviated according to Human Splicing Finder Version 2.4 at http://www.umd.be/HSF.
Other abbreviations: ESR — exonic splicing regulatory sequence. Asterix (*) indicates situation when several splicing signals of the same type could occupy the sequence and overlap each other.

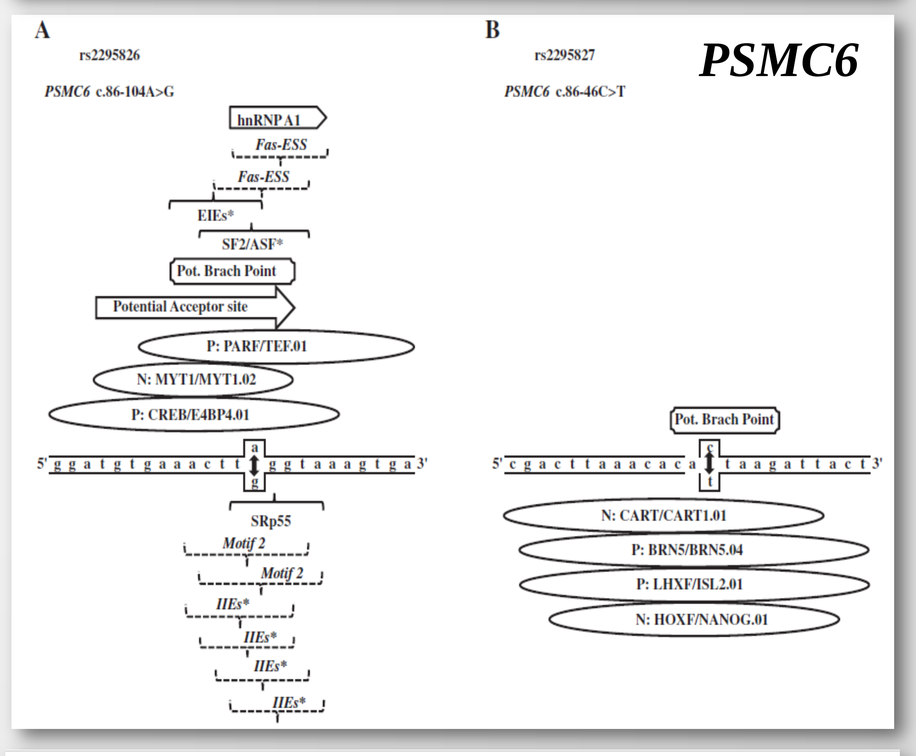

Fig. 2. Consequences of the rs2295826 (Panel A) and rs2295827 (Panel B) nucleotide substitutions on functional potential of corresponding genomic regions of the PSMC6 gene.

CREB/E4BP4.01–E4BP4, bZIP domain, transcription repressor; MYT1/MYT1.02–MyT1 zinc finger TF involved in primary neurogenesis; PARF/TEF.01–thyrotrophic embryonic factor; CART/CART1.01–Cart-1 cartilage homeoprotein 1; BRN5/BRN5.04–POU class 6 homeobox 1 (POU6F1); LHXF/ISL2.01–ISL LIM homeobox 2; HOXF/NANOG.01–Homeobox TF Nanog. “Pot. Branch Point” means potential branch point.

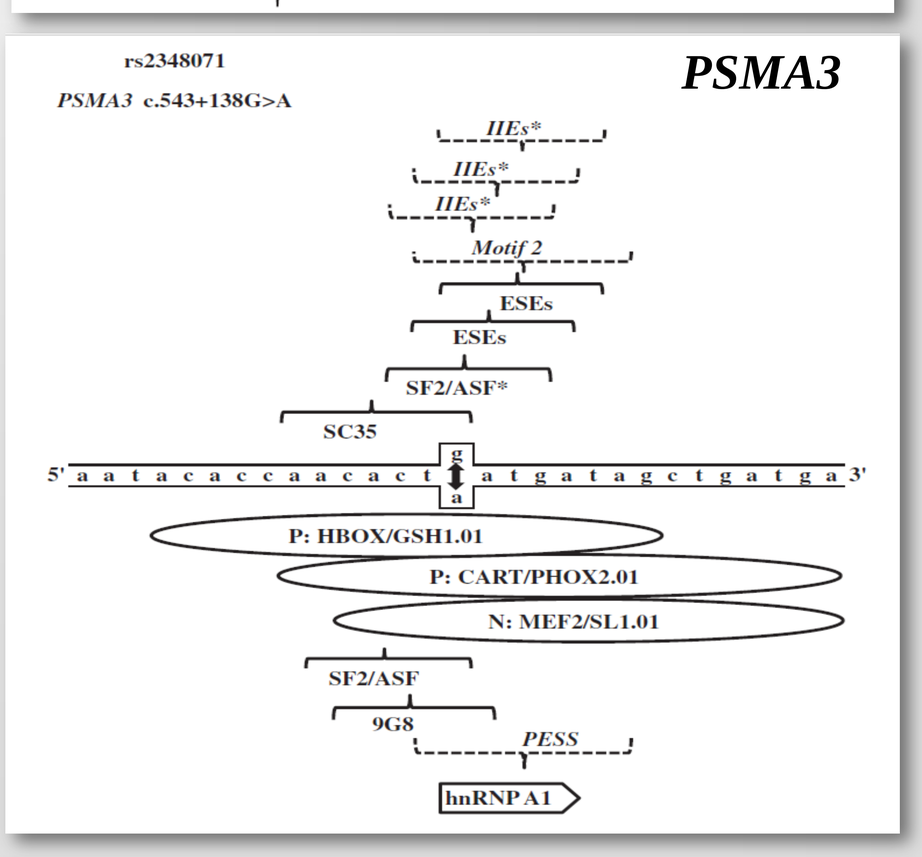

Fig. 3. Consequences of the rs2348071 nucleotide substitutions on functional potential of corresponding genomic regions of the PSMA3 gene.

HBOX/GSH1.01–Homeobox TF Gsh-1; Cart/PHOX2.01–Phox2a (ARIX) and Phox2b of cartilage homeoproteins family; MEF2/SL1.01–member of the RSRF related to serum response factors. Other abbreviations are the same as in Figs. 2.

Promoter and exon are coloured in white, 5′-UTR is coloured in grey; sequences of coding and noncoding genes' regions are presented by capital and small letters respectively. Positive and negative DNA strands are indicated by capital letters P and N respectively. The transcription factors family and matrix names are separated by symbol of division and given according to MatInspector, Release 7.4 online tool at www.genomatix.de

Discussion

The major allele of the **rs2295826** potentially assists to sequence affinity for TFs of CREB, MYT1, and PARF families known to be involved in regulation of multiple physiological processes and control of the circadian clock[1-2].CREB related TFs are especially interesting with respect of MS pathogenesis, as they are known to be essential for osteoblast differentiation and function [1], and they have been implicated in immune response [2]. It is of interest that expression of CREB, MYT1, and PARF proteins potentially could share the same epigenetic mechanism of regulation by hsa-miR-1264 originated from the X chromosome and potentially be differently expressed and differently involved in epigenetic network in females and males (data not shown).
The presence of a minor allele at the **rs2277460** locus creates a binding site to the BARBIE box proteins reported to be involved in signal transduction pathways during development [4]and modulation of innate immunity [5]. Sequences having minor alleles at the **rs2295827** and **rs2348071** sites can potentially bind CART proteins responsible for bone and cartilage development [6].
Moreover, the rs2295827 and rs2348071 minor alleles could assist in sequence affinity to BRN5, LHXF, MEF2, and HBOX factors known to mediate transcriptional control of neuronal differentiation [7-10] and HOXF family NANOG.01 factor generally involved in signal transduction pathways during development [11]. Similar to TFBSs, patterns of predicted splicing signals are allele specific.
The **rs2295826** and **rs2348071** loci create a number of allele-specific targets for splicing enhancers and silencers. Nucleotide substitutions at the **rs2277460, rs2295826**, and **rs2348071** define affinity of corresponding sequences to the hnRNP A1 known as alternative splicing repressor [12] and factor facilitating processing of specific microRNAs[13].

Acknowledgements

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