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 putative target of the humoral autoimmune response [1] and a major antigen in MS patients [2]. The immunoproteasome activities 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 14q1-24 proteasome genes were implicated previously in susceptibility to type 2 diabetes mellitus, cardiovascular 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 604H variant was observed to have a reduced risk of developing MS in HLA-A*02+ Italian families [6]. We have reported MS association with several alleles of proteasome genes [7] correlation between the SNPs of the PSMA3, PSMA6 and PSME5 genes and gene expression of these and other proteasome genes with type 1 diabetes mellitus [8].

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 innately 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.

Promoter and exon are coloured in white, 5'-UTR is coloured in grey; sequences of coding and non-coding genes are represented 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.

Multiple sclerosis related susceptible loci

To identify novel proteasome related MS susceptible loci

Conclusion

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

Related publications


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 bma-mrl264 originated from the X chromosome and potentially be differently expressed and differently involved in epigenetic network in females and males (data not shown).

The existence of a minor allele at the rs2277460 locus creates a binding site to the IRF4 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 CARPT proteins responsible for bone and muscle development.

Moreover, the rs2295827 and rs2348071 minor alleles could assist in sequence affinity to BRNS, LHXF, ME2F, and H-box2 of cartilage homeoproteins, with MEF2LS1.01 minor allele also potentially be differently expressed and differently involved in epigenetic pathways in females and males (data not shown).

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