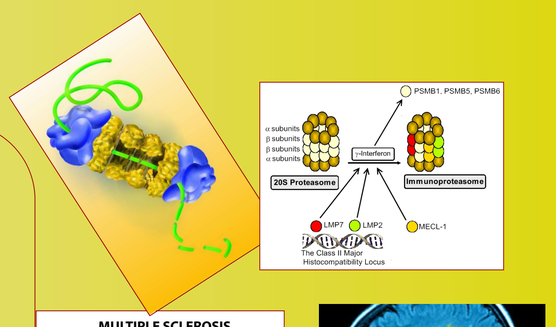
Computational assessment of candidate SNP markers of proteasomal genes for multiple sclerosis association studies in Latvian population

I. TRAPINA[1], **G.MELKUS, N. PARAMONOVA**[1], **N.SJAKSTE**[2]

[1]Institute of Biology, University of Latvia; [2] Faculty of Medicine, University of Latvia

Background



Proteamol 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 disregulation and/or modulation may influence the development and progression of different diseases.

Multiple sclerosis 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 fibres, the nerve fibres themselves, and the specialized cells that make myelin, thus leading to neurodegeneration and disabilities.

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

Aim

Utilize several computational methods for the effective assessment of several proteasomal gene SNPs as candidate markers for future genotyping in the Latvian population to discover medically relevant associations with multiple sclerosis

Materials and methods

Six SNPs of proteasomal genes:

1. PSMB8 (LMP7) - proteasome subunit beta 8:
   I. rs2071543 > NM_004159.4:c.135+427C>A (Gln49Lys)
   II. rs9357155 > NM_148919.3:c.537+63C>T (G>A)
   III. rs9275596 > NT_167246.1:g.4138777T>C
2. PSMB9 (LMP2) - proteasome subunit beta 9
   I. rs17587 > NM_002800.4:c.179G>A
3. PSMD9 - proteasome 26S subunit, non-ATPase 9
   I. rs74421874 > NM_002813.6:c.454-460G>A
   II. rs3825172 > NM_002813.6:c.454-437C>T

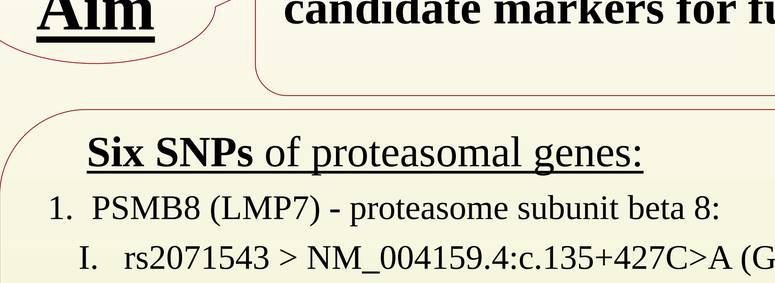
- ✓ **Meta analyze of scientific literature**
- ✓ **Bioinformatical tools:**
  - **Transcription factor binding site > MatInspector** (http://www.genomatix.de) with identity 1,00 of core and >0,85 of matrix
  - **DNA bendabilty > bent.it (**Vlahovicek et al., 2003; http://pongor.itk.ppke.hu/dna/bend_it.html#/bendit_form)
  - **DNA and/or RNA secondary structure > Mfold** (Zuker 2003, http://unafold.rna.albany.edu/?q=mfold/DNA-Folding-Form)

Results

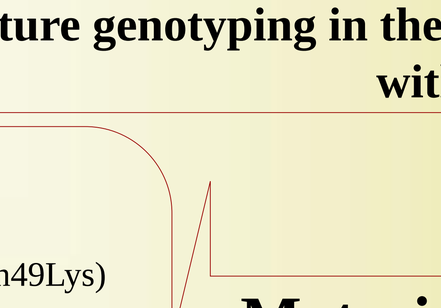
PSMB8 (LMP7)

rs2071543 - MAF in EUR: 0.15

Transcription factor binding site



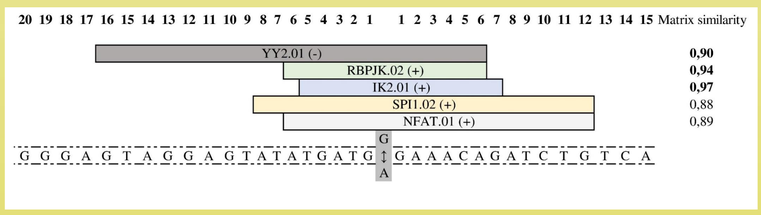
RNA secondary structure



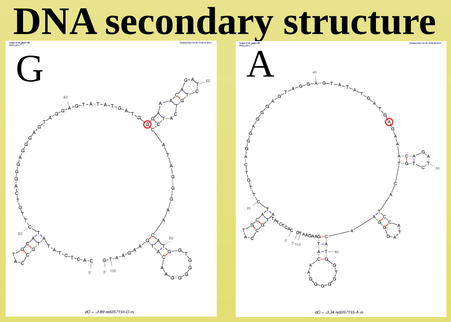
DNA bendabilty in areal **decreases** at change of nucleotide C>A

rs9357155 - MAF in EUR: 0.31

Transcription factor binding site



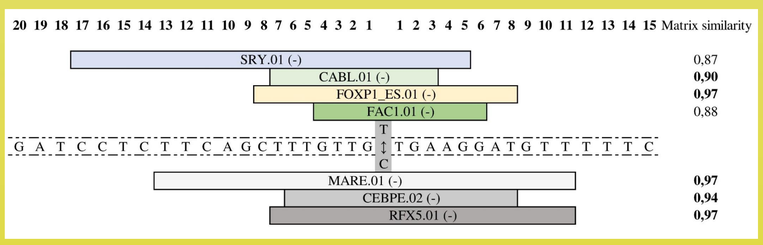
DNA secondary structure



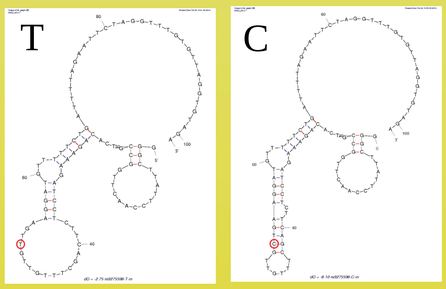
DNA bendabilty in areal **increases** at change of nucleotide G>A

rs9275596 - MAF in EUR: 0.14

Transcription factor binding site



DNA secondary structure

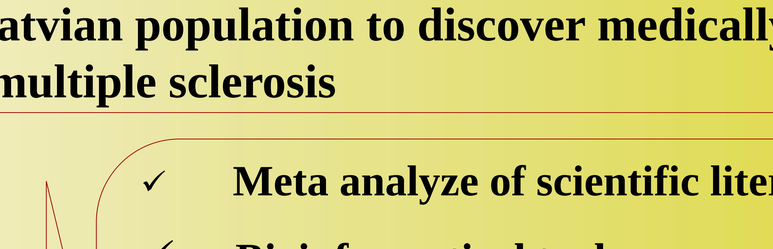


DNA bendabilty in areal **inreases** at change of nucleotide T>C

PSMB9 (LMP2)

rs17587 - MAF in EUR: 0.27

Transcription factor binding site



DNA secondary structure

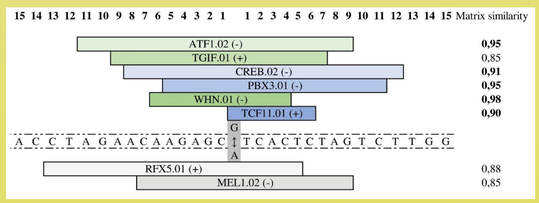
DNA bendabilty in areal **not change** at change of nucleotide G>A

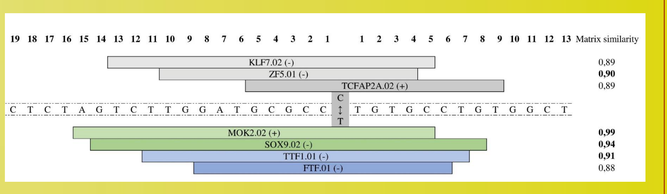
PSMD9

rs74421874 **rs3825172**

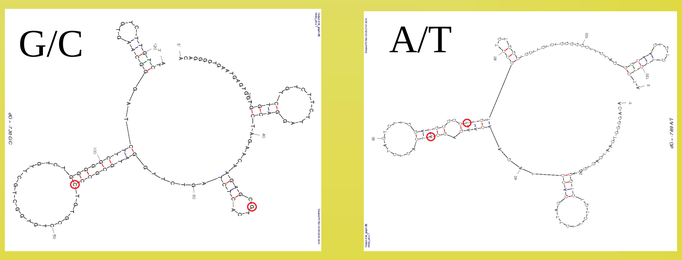
in complete linkage disequilibrium with MAF in EUR: 0.31 for both SNPs

Transcription factor binding site





DNA secondary structure



DNA bendabilty in areal **inreases** at change of nucleotide G>A and C>T, or GC > AT

MAF – minor allele frequency; EUR – European population;

Conclusion

- ✓ **Literature about chosen SNPs of *PSMB8*, *PSMB9*, and *PSMD9* illustrate their potential as markers for multiple sclerosis.**
- ✓ **Computational analyses highlight that chosen SNPs may be functionally relevant in their corresponding genes through modulating the binding of transcription factors via structural and sequence changes.**

Acknowledgements

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Ilva Trapina e-mail: ilva.trapina@lu.lv