



UNIVERSITY OF LATVIA
INSTITUTE OF
BIOLOGY



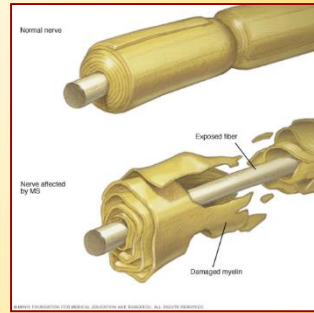
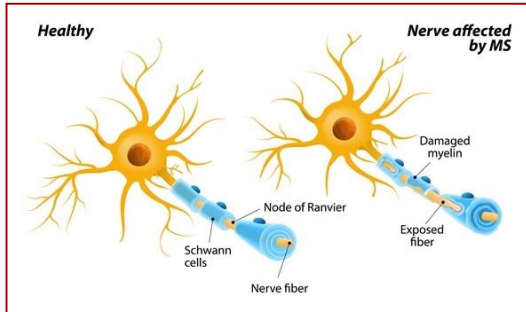
Meta and bioinformatics analysis of SNP of proteasome genes as possible molecular markers for multiple sclerosis case/control study in Latvian population

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Multiple sclerosis

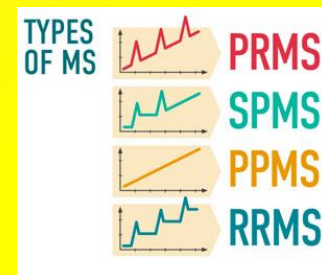
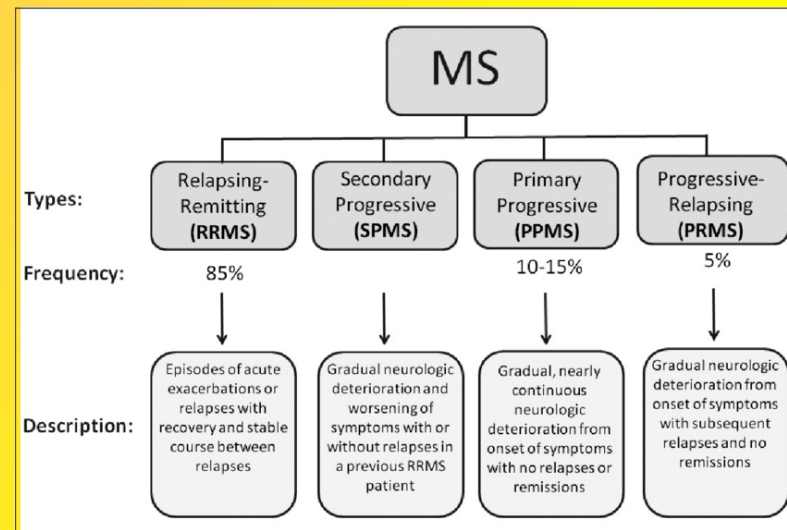


Multiple sclerosis (MS) involves an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system (CNS: brain, spinal cord and optic nerves). Therefore MS is **autoimmune inflammatory disease**.

Within the CNS, the immune system causes **inflammation that damages myelin** — the fatty substance that surrounds and insulates the nerve fibers — as well as the nerve fibers themselves, and the specialized cells that make myelin. When myelin or nerve fibers are damaged or destroyed in MS, **messages** within the CNS are **altered** or **stopped** completely.

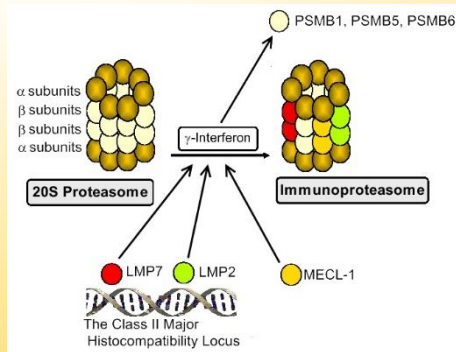
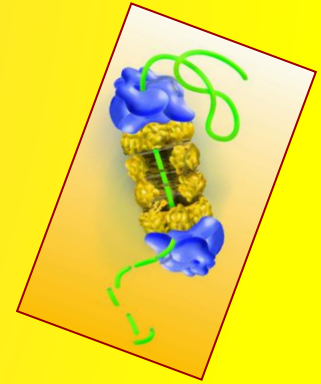
Damage to areas of the CNS may produce a variety of **neurological symptoms** that will vary among people with MS in **four** disease courses (**types**) and severity.

The cause of MS is not known, but it is believed to **involve genetic susceptibility**, abnormalities in the immune system and environmental factors that combine to trigger the disease.



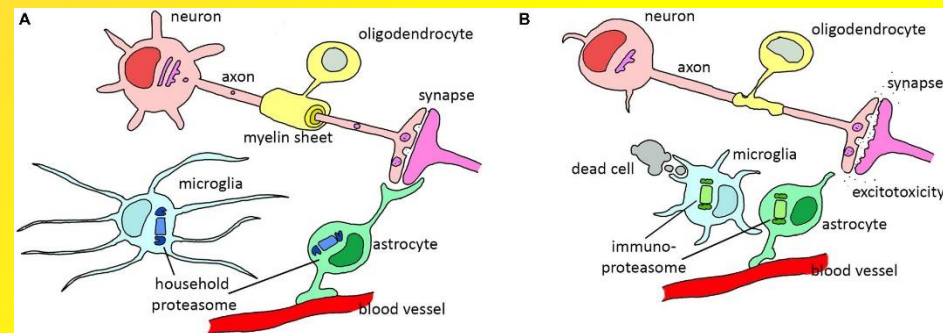
Possible links between proteasome and multiple sclerosis

Proteasomal system: Proteasomes, the multicatalytic 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 PSMB5, PSMB6 and PSMB1 by LMP2 (PSMB8), LMP7 (PSMB9) and MECL-1 (PSMB10) (multicatalytic endopeptidase complex subunit), respectively, and forms **immunoproteasome**. Expression of LMP2 and LMP7 genes is decreased in patients with autoimmune diseases.

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 of the study

To determine the prevalence and possible **functionality** **SNPs** of **proteasome** gene to analyze their usability as **molecular markers** for **multiple sclerosis binding study** in the Latvian population.

Materials and methods

Six SNPs of proteasomal genes:

1. PSMB8 (LMP7) - proteasome subunit beta 8:

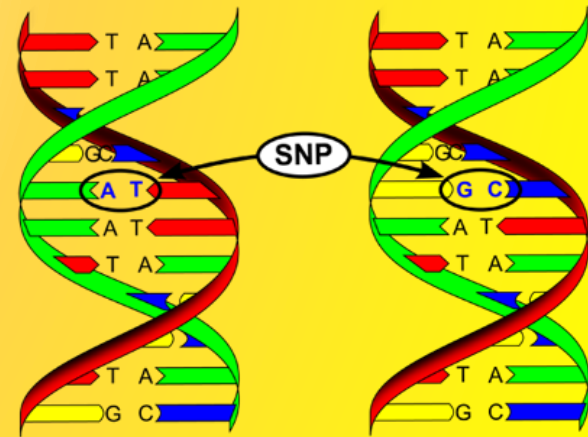
- I. rs2071543 > NM_004159.4:c.135+427C>A (Gln49Lys)
- II. rs9357155 > NM_148919.3:c.537+63C>T (G>A)
- III. rs9275596 > NT_167246.1:g.4138777T>C

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 bendability > 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>)

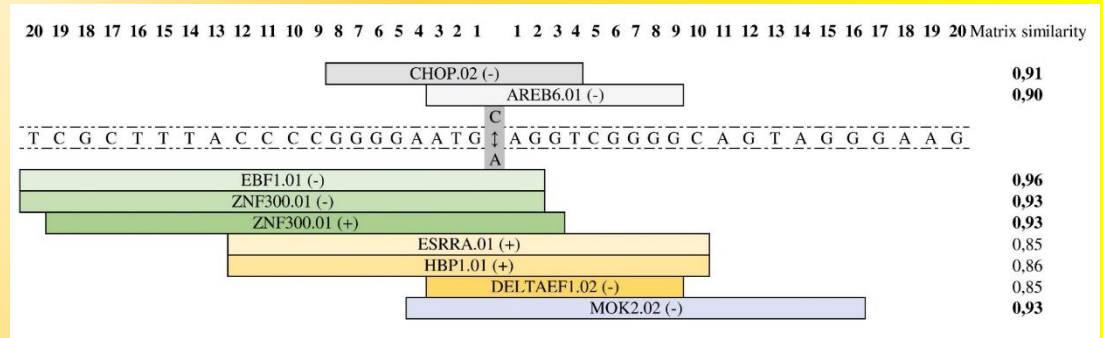


Results

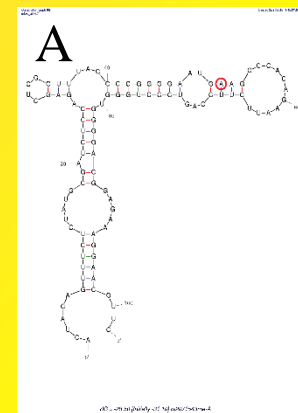
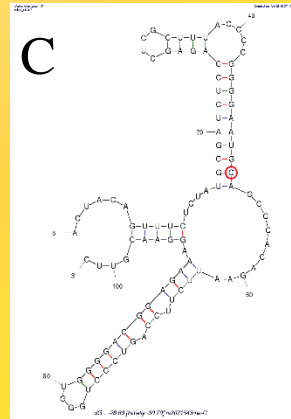
PSMB8 - rs2071543: NM_004159.4:c.135+427C>A (Gln49Lys)

MAF in EUR: 0.15

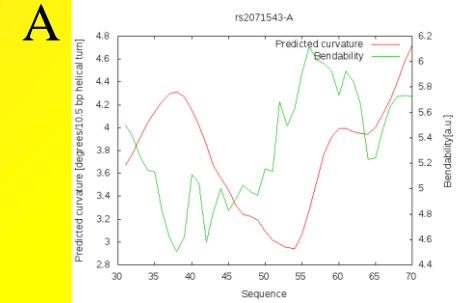
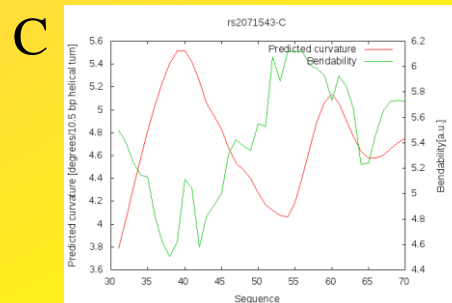
Transcription factor binding site



RNA secondary structure



DNA bendability (green line) in areal decreases at change of nucleotide C>A

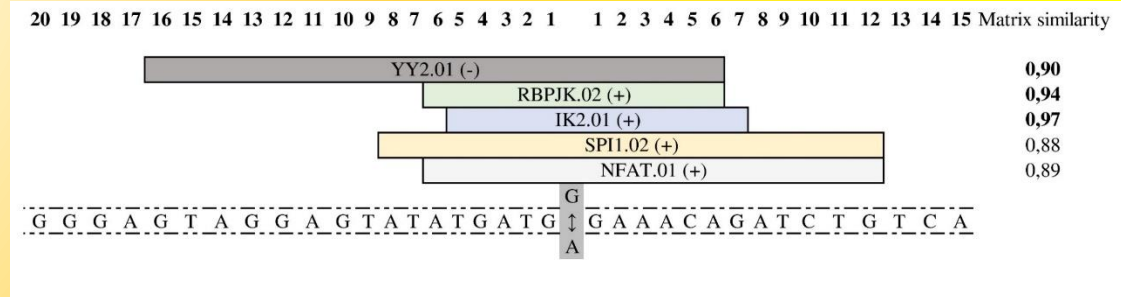


Results

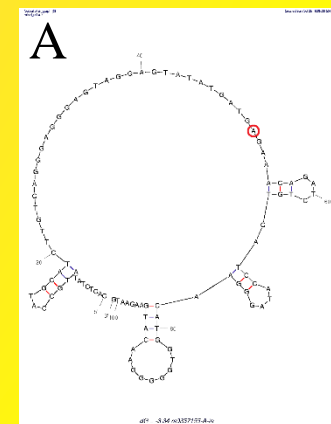
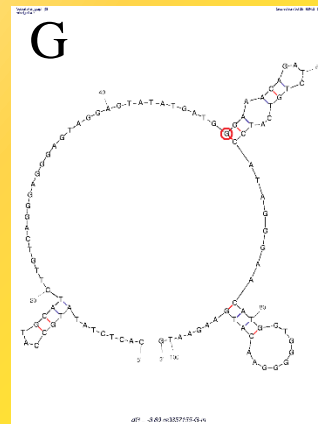
PSMB8 - rs9357155: NM_148919.3:c.537+63C>T (G>A)

MAF in EUR: 0.31

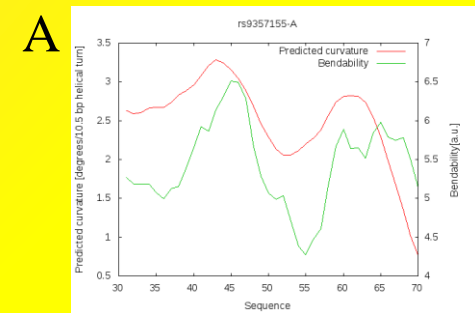
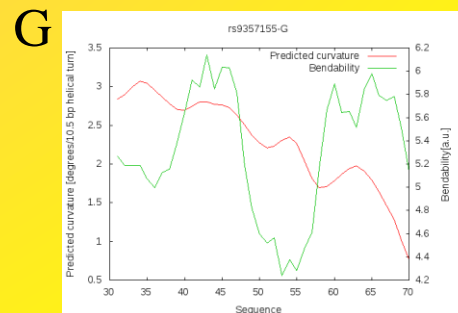
**Transcription factor
binding site**



**DNA secondary
structure**



**DNA bendability (green line) in
areal increases at change of
nucleotide G>A**

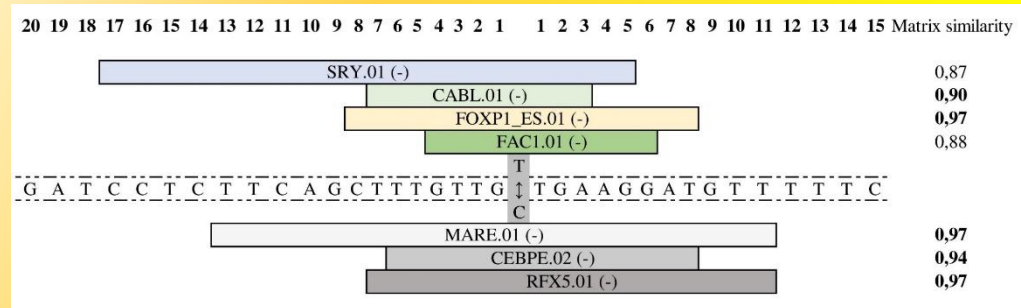


Results

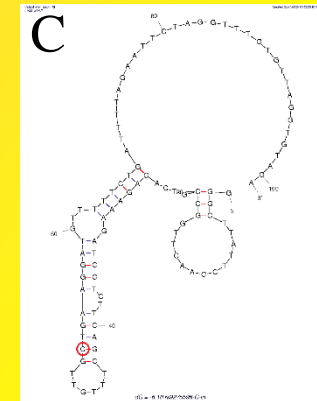
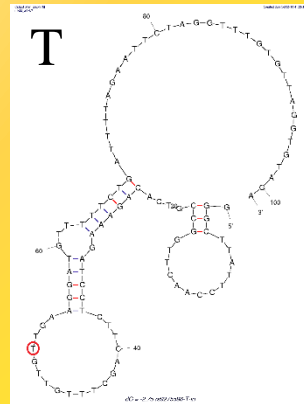
PSMB8 - rs9275596 > NT_167246.1:g.4138777T>C

MAF in EUR: 0.14

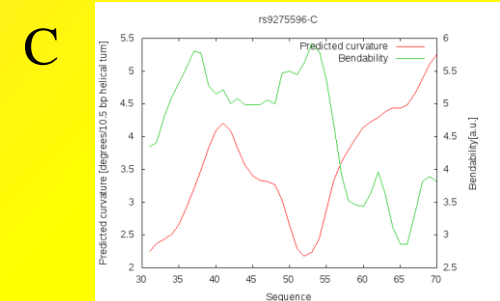
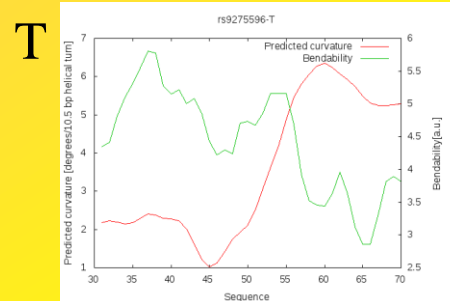
**Transcription factor
binding site**



**DNA secondary
structure**



**DNA bendability (green line) in
areal increases at change of
nucleotide T>C**

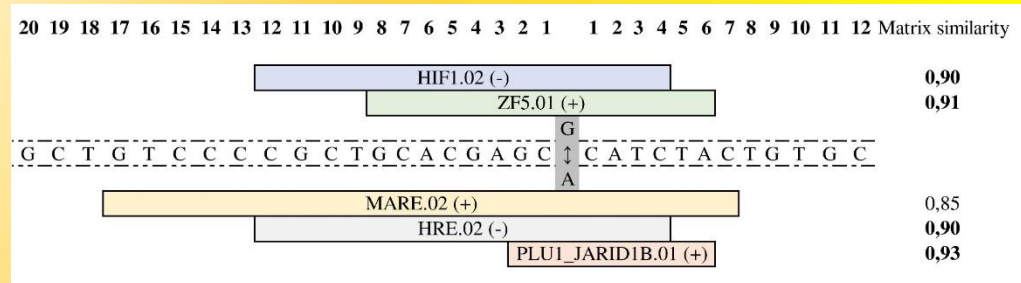


Results

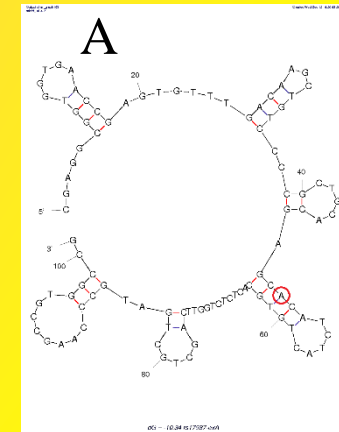
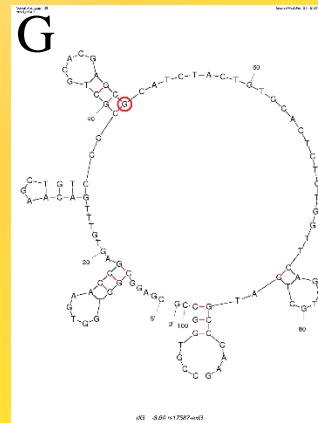
PSMB9 - rs17587 > NM_002800.4:c.179G>A

MAF in EUR: 0.27

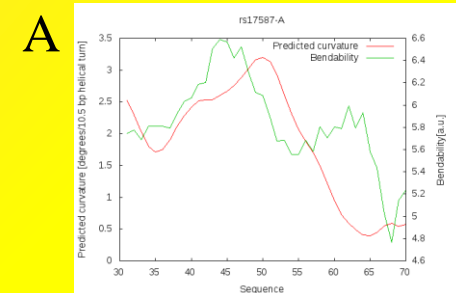
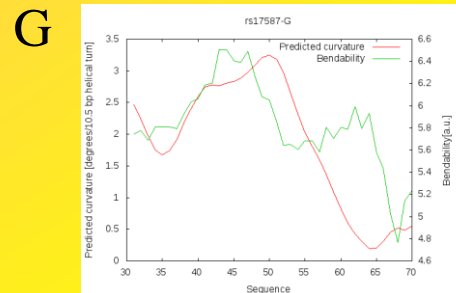
Transcription factor
binding site



DNA secondary
structure



DNA bendability (green line) in
areal **no difference** at change of
nucleotide G>A



Results

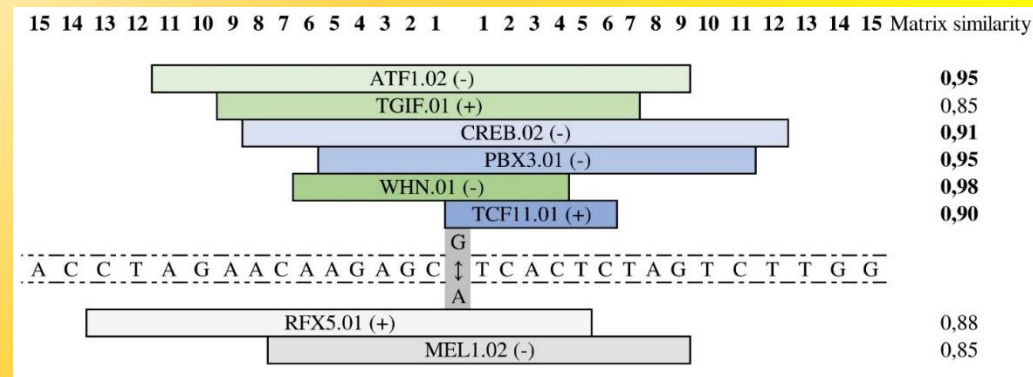
PSMD9 - rs74421874: NM_002813.6:c.454-460G>A and
rs3825172: NM_002813.6:c.454-437C>T

in complete **linkage disequilibrium**

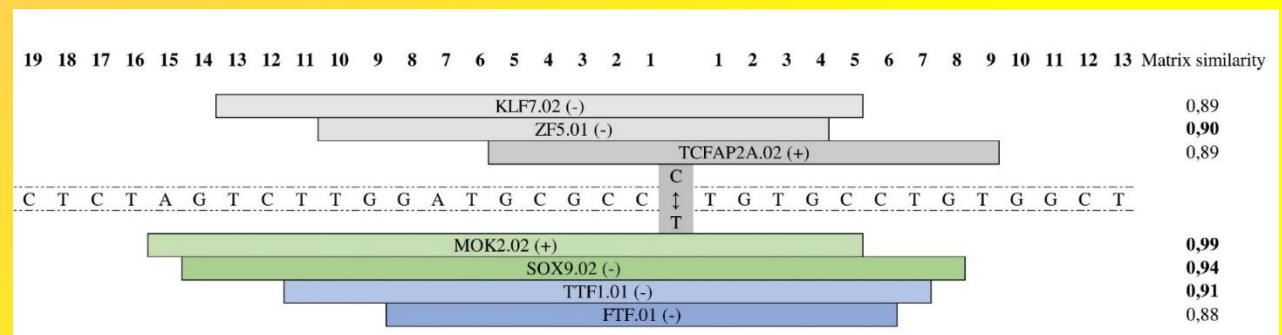
with MAF in EUR: 0.31 for both SNPs (between are 23 bp)

Transcription factor binding site

rs74421874



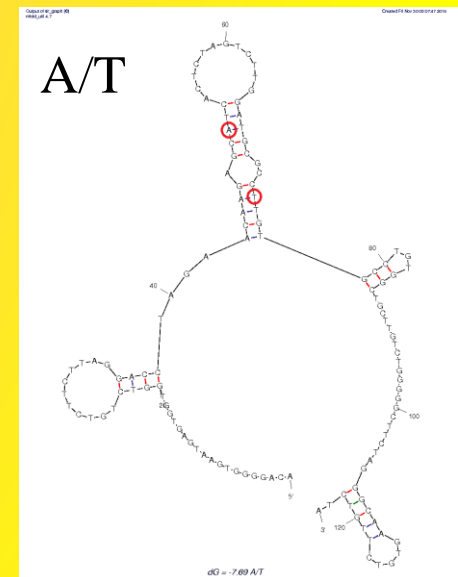
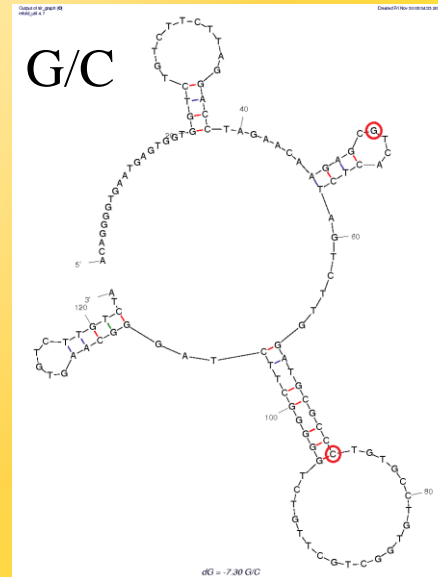
rs3825172



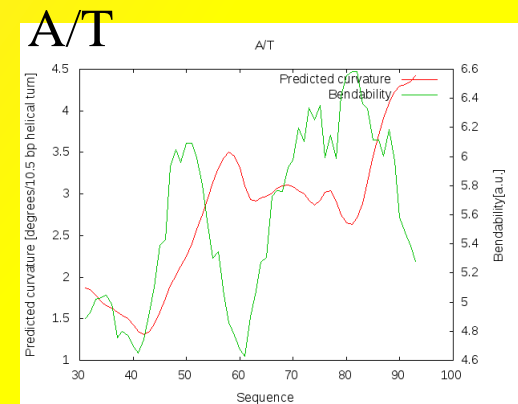
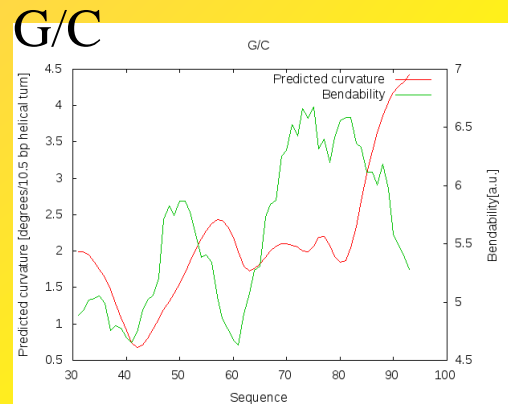
Results

**PSMD9 - rs74421874: NM_002813.6:c.454-460G>A and
rs3825172: NM_002813.6:c.454-437C>T**

**DNA secondary
structure**



**DNA bendability (green
line) in areal increases at
change of nucleotide
G/C>A/T**



Conclusions

Meta and bioinformatic analysis of selected SNPs of PSMB8 (rs2071543, rs9357155 and rs9275596) , PSMB9 (rs17587) and PSMD9 (rs74421874 and rs3825172) **illustrate possibility** of using them as molecular markers of **multiple sclerosis** by genotyping in association study.

Thank you for your attention!

