

The 61st International Scientific Conference of Daugavpils University

Possible functionality of genetic variations in polyA microsatellite of *PSMA6* promoter in association with autoimmune disease development in Latvians

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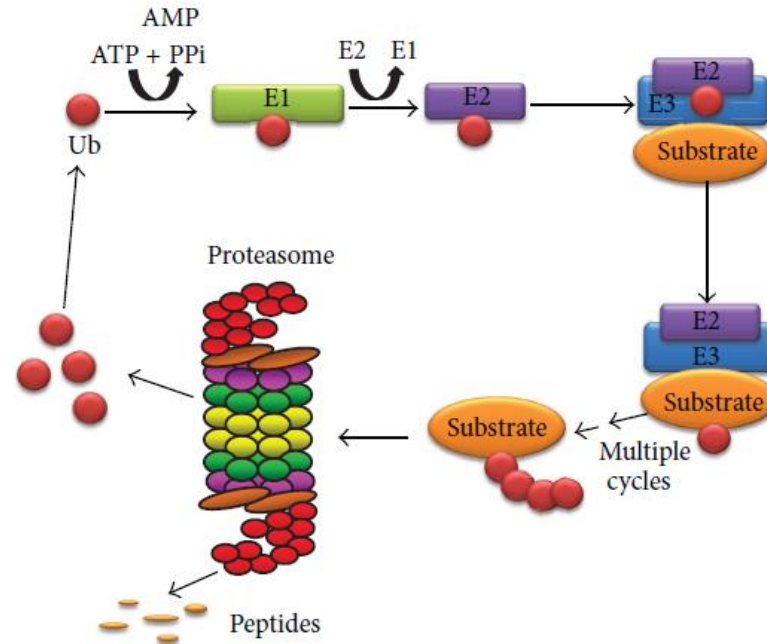


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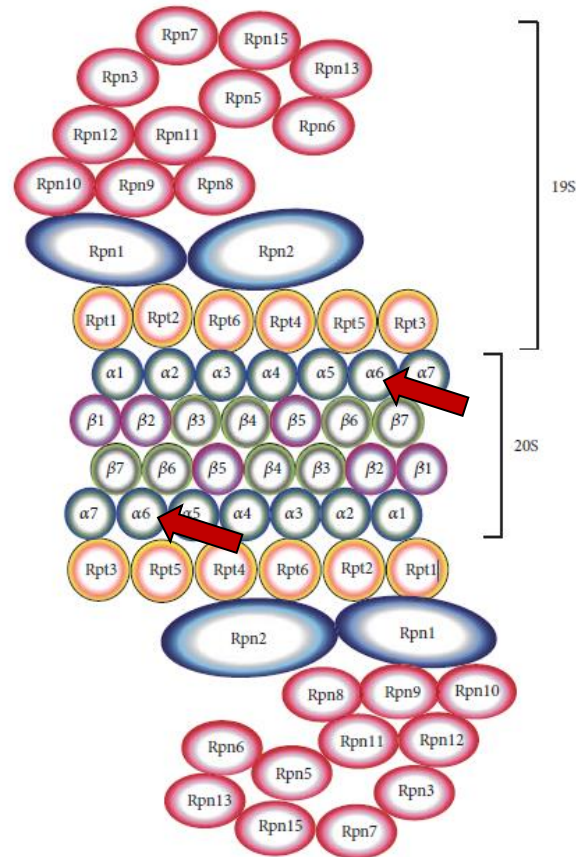
Ubiquitin - proteasome system

- ▶ Main non-lysosomal proteolysis pathway
- ▶ UPS participates in cell cycle regulation, cell differentiation, abnormal and removal of abnormal and misfolded intracellular proteins, and generation of antigenic peptides

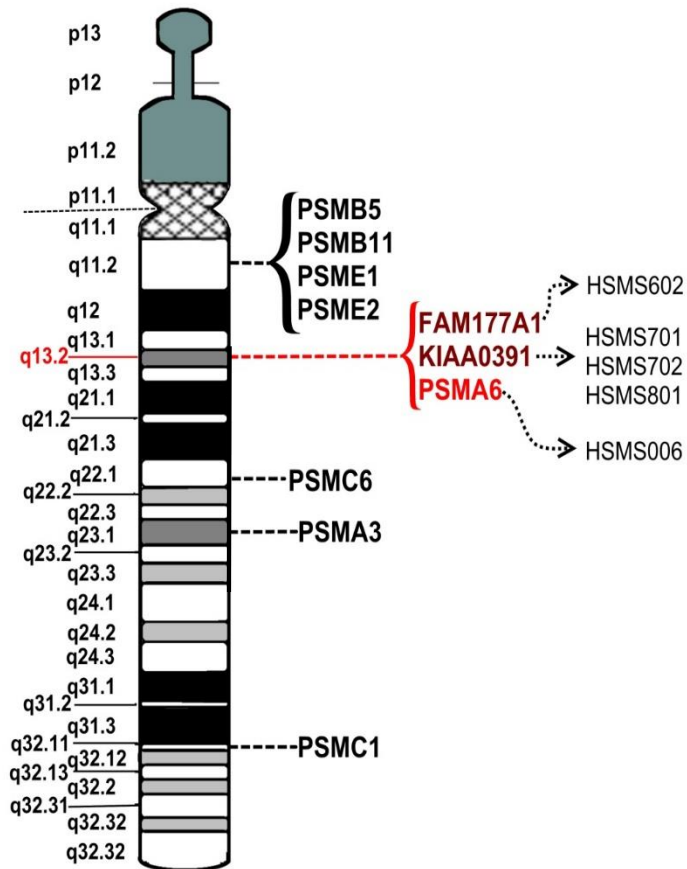


26S proteasome

- ▶ Multicatalytic enzyme complex, expressed in nucleus and cytoplasm of all eukaryotic cells (~20 000 per cell);
- ▶ 2000 kDa; consists of 20S core and one or two 19S regulatory subunits;
- ▶ Core is a cylinder consisting of two outer α and two inner β rings each made of 7 subunits ($\alpha 1$ - $\alpha 7$ and $\beta 1$ - $\beta 7$).



PSMA6



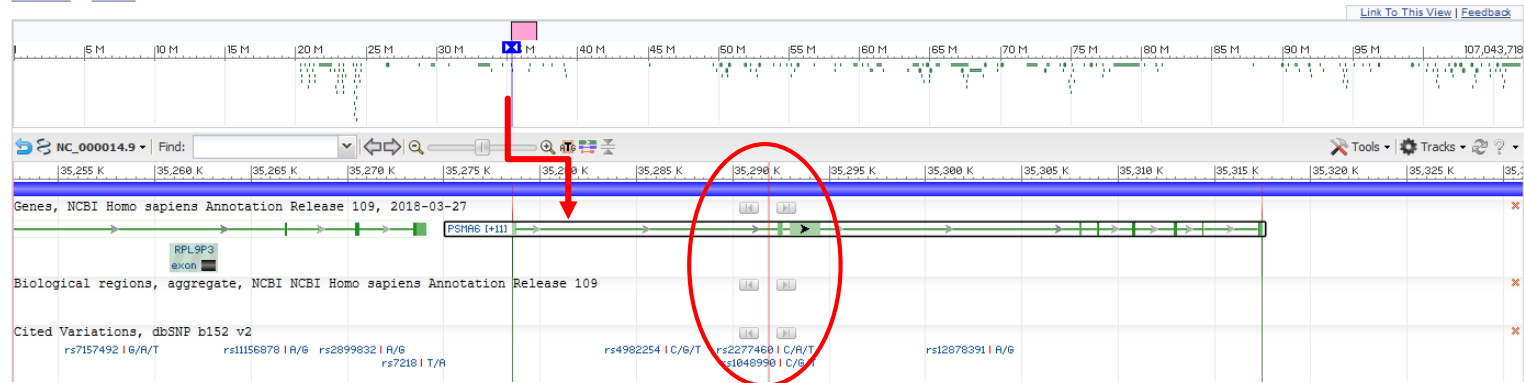
- ▶ Proteasome subunit alpha type 6;
- ▶ Human chromosome 14 region 14q13.2;
- ▶ Polymorphisms in proteasomal genes, including *PSMA6*, have been associated with increased risk or resistance of Type 1 and 2 *diabetes mellitus*, Greave's disease, juvenile idiopathic arthritis, myocardial infarction, obesity, bronchial asthma and multiple sclerosis.

Studied poly(dA:dT) tract

Homo sapiens chromosome 14, GRCh38.p12 Primary Assembly

NCBI Reference Sequence: NC_000014.9

[GenBank](#) [FASTA](#)



Studied poly(dA:dT) tract

Ref. (NC_000014.9)

rs113987343

PSMA6 c.-655An

GAAACTCTGTCTC**AAAAAAAAAAAAAAAAAAAAAAAAAAAA**GACTAAA

A = 24

(1.) (2.)

(3.)

GAAACTCTGTCTC**CACAC**AAAAAAAAAAAAAAAAAAAAAAAA**CAA**GACTAAA

1. rs200541481 (-/CA)
2. rs200298313 (-/C)
3. rs71640264 (C/A)

Studied poly(dA:dT) tract

- ▶ In previous fragment length analysis studies an association between rs200541481 and autoimmune disease susceptibility was detected.
- ▶ Genotyping results have shown a complete linkage disequilibrium between rs71640264 and a juvenile idiopathic arthritis and bronchial asthma associated locus rs2277460 (*PSMA6c*.-110C>A)
- ▶ Association between rs200298313 and autoimmune diseases have not been detected.

GAAACTCTGTCT**(1.)** **(2.)** CAC**(3.)** AAAAAAAAAAAAAAAAAAAAAAA**(3.)** CAA GACTAAA

1. rs200541481 (-/CA)
2. rs200298313 (-/C)
3. rs71640264 (C/A)

Aim of the current study

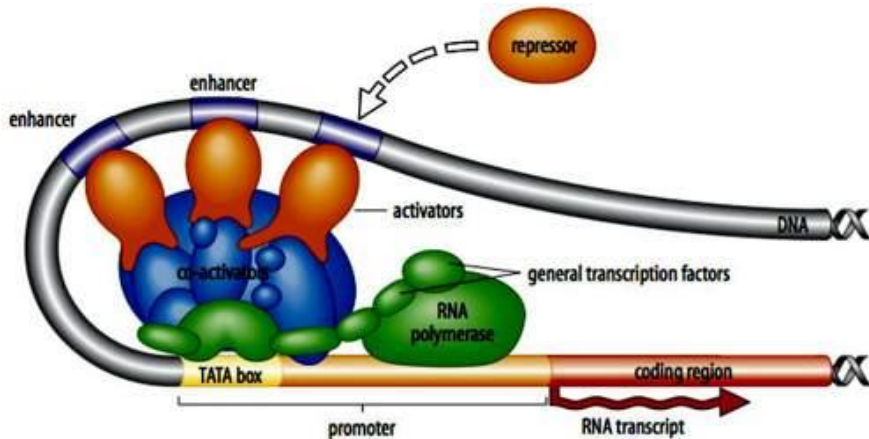
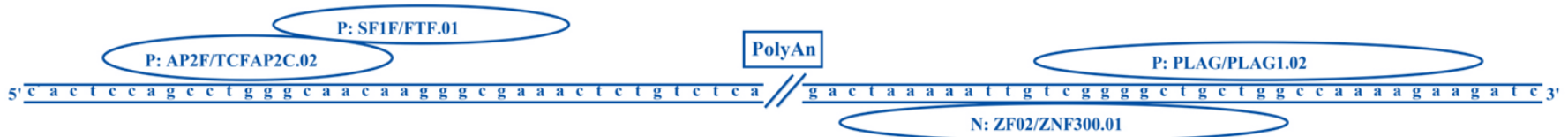
To evaluate the functionality of genetic variations in *PSMA6* poly(dA:dT) tract *in silico*.

Methods

- ▶ Putative transcription factor binding site analysis with MatInspector, Release 10.1 in data base Genomatix;
- ▶ DNA secondary structure modeling in MFOLDROOT;
- ▶ Analysis of DNA bending in bend.it

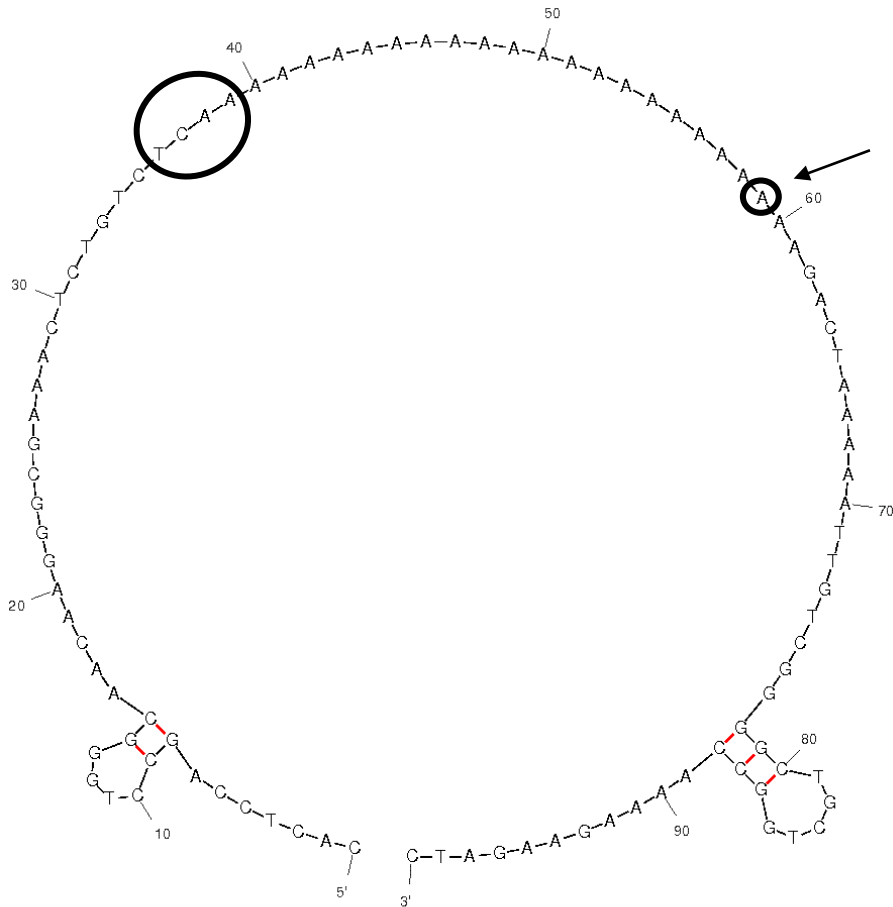
The screenshot displays the 'bend.it[®] Server' web application. The page header includes logos for 'intrexon', 'THE RNA INSTITUTE COLLEGE OF ARTS AND SCIENCES UNIVERSITY AT ALBANY State University of New York', and 'FAZMÁNY PÉTER CATHOLIC UNIVERSITY - UNIVERSITY OF NATIONAL EXCELLENCE FACULTY OF INFORMATION TECHNOLOGY AND BIONICS'. The main content area features a navigation menu with links to 'Bioinformatics services', 'Introduction', 'Input form', 'Theory', 'Tips', 'Examples', 'Tables', 'Standalone version', and 'References'. Below the navigation is a small diagram of a DNA double helix being bent. The main text describes the server's function: 'This server predicts DNA curvature from DNA sequences. The curvature is calculated as a vector sum of dinucleotide geometries (roll, tilt and twist angles) using the BEND algorithm of Godsell and Dickerson, and expressed as degrees per helical turn (10.5°/helical turn = 1°/basepair)'. It also provides information on the calculation's accuracy and the types of results generated, such as 1-D sequence plots, 2-D plots, and ASCII output. The footer contains logos for 'NIH' and 'Agency for Science, Technology and Research'.

Putative transcription factor binding sites

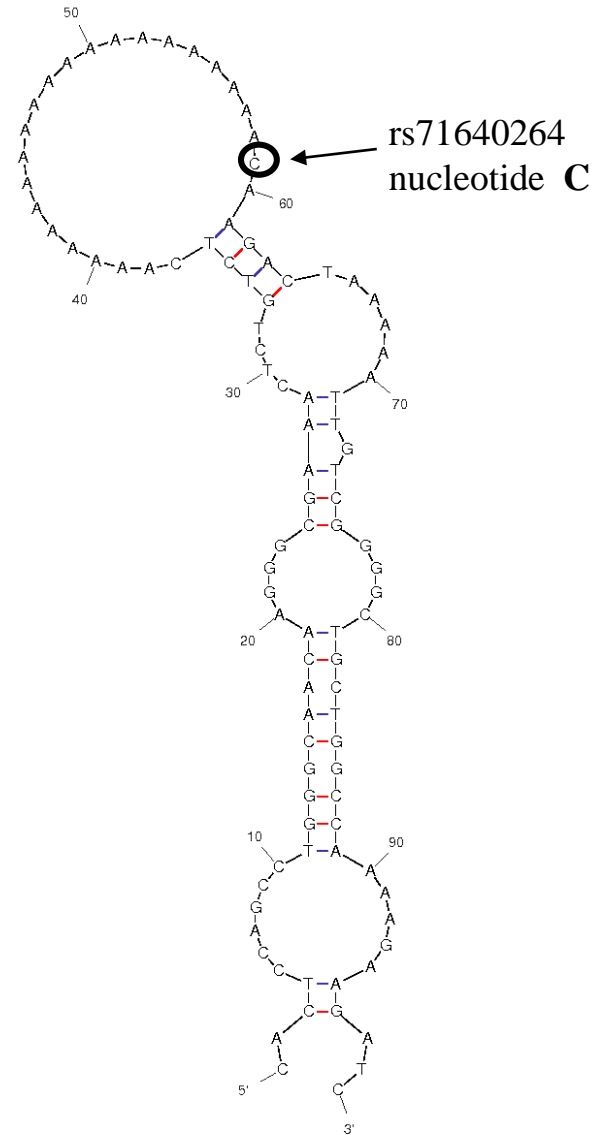


- ▶ Proteins that bind to specific DNA sequences in order to control the transcription rate of a specific gene

DNA Secondary structures



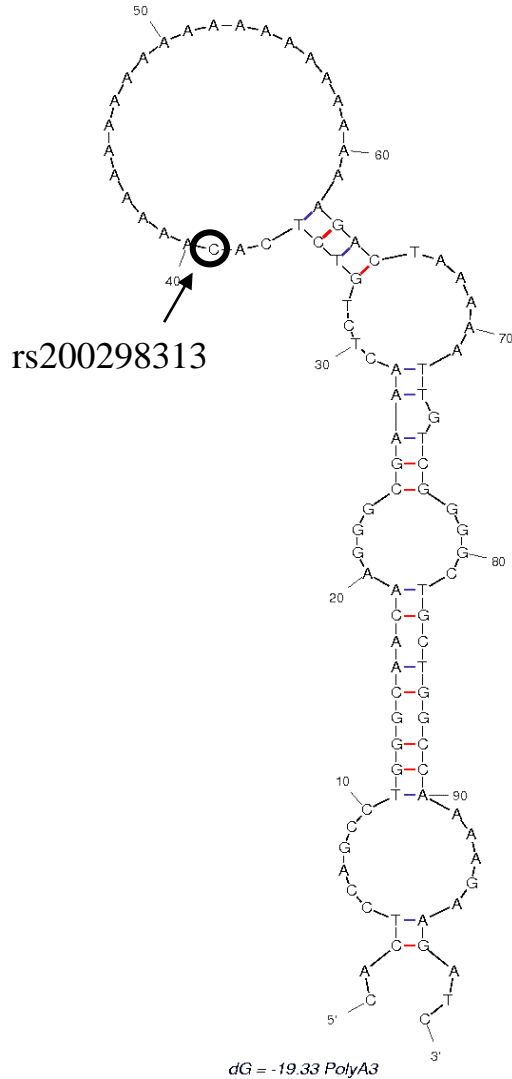
$dG = -3.37$ PolyA1



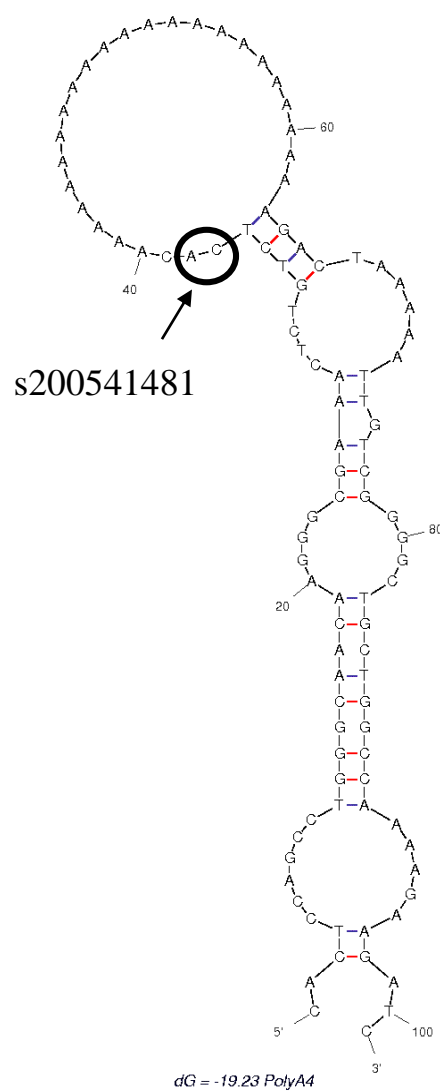
$dG = -19.43$ PolyA2

DNA Secondary structures

Output of sr_graph (9)
model_uil.37



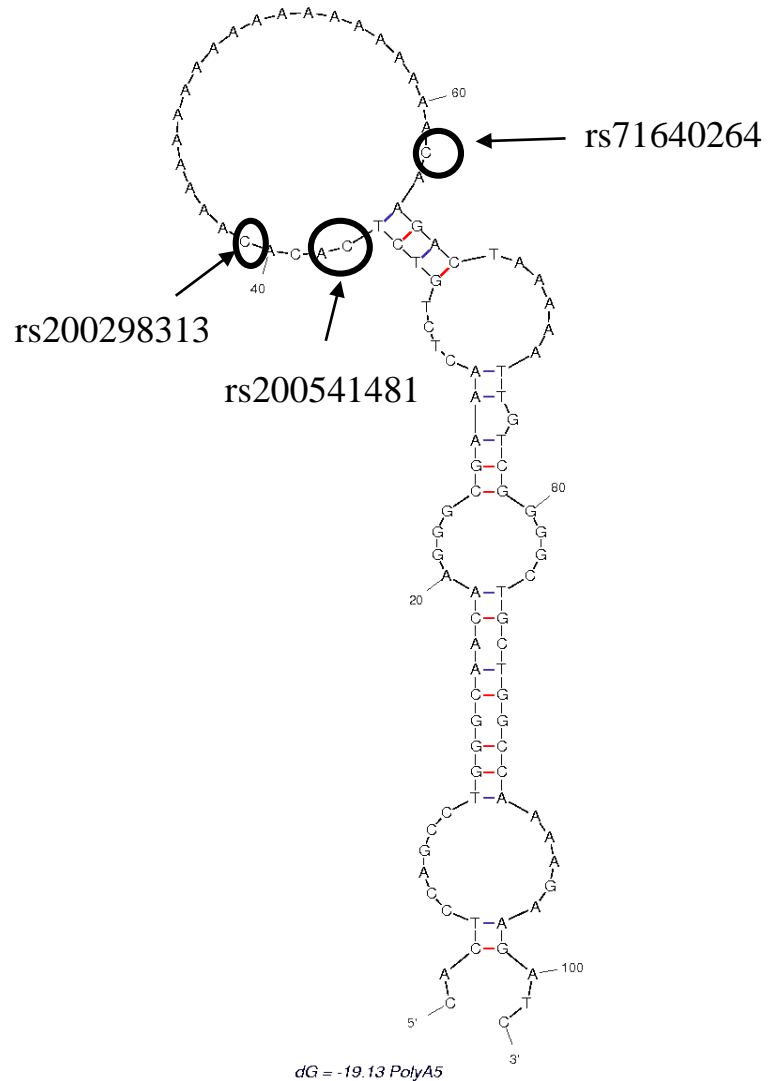
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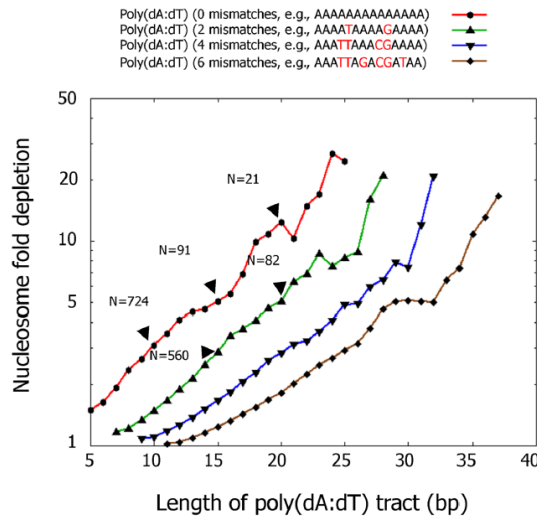
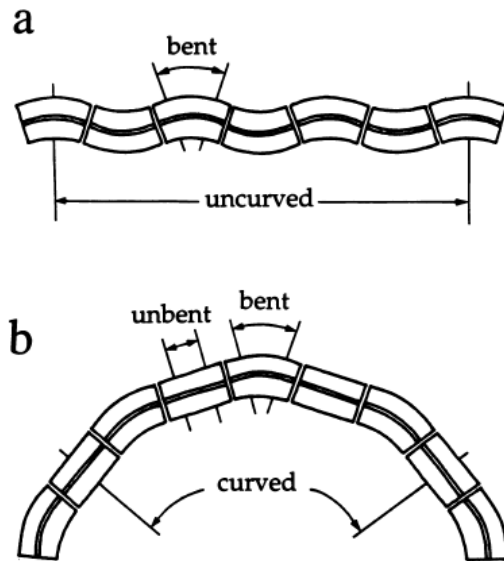
DNA Secondary structures

Output of tr_graph ©
midq_uni_4.7



DNA bendability and curvature

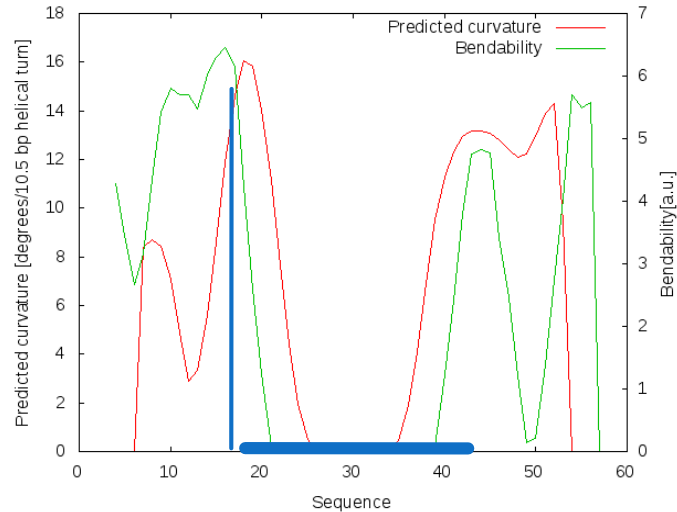
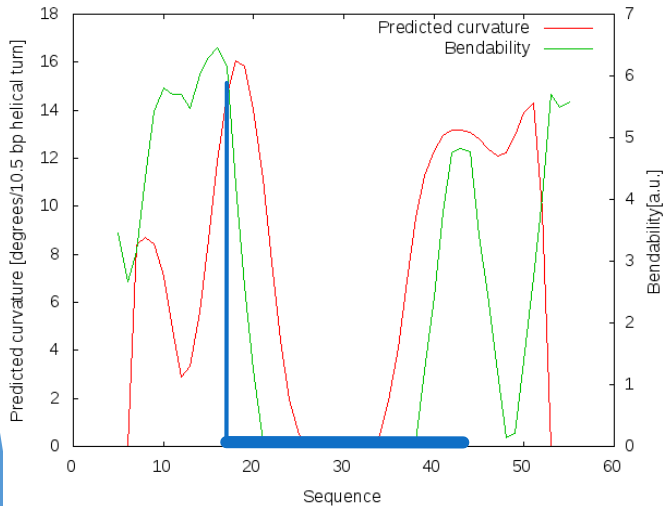
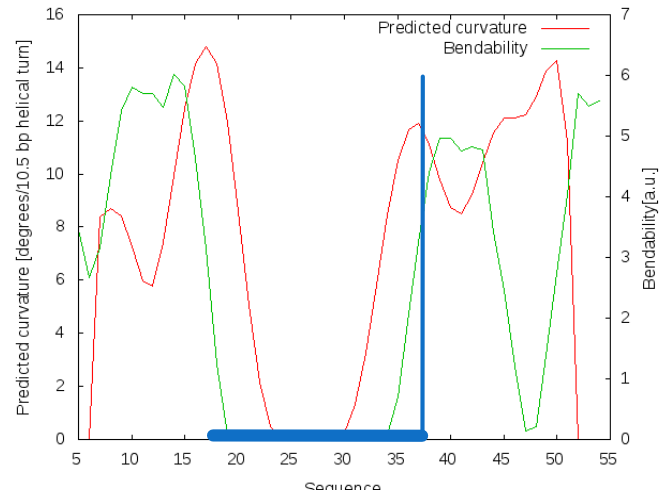
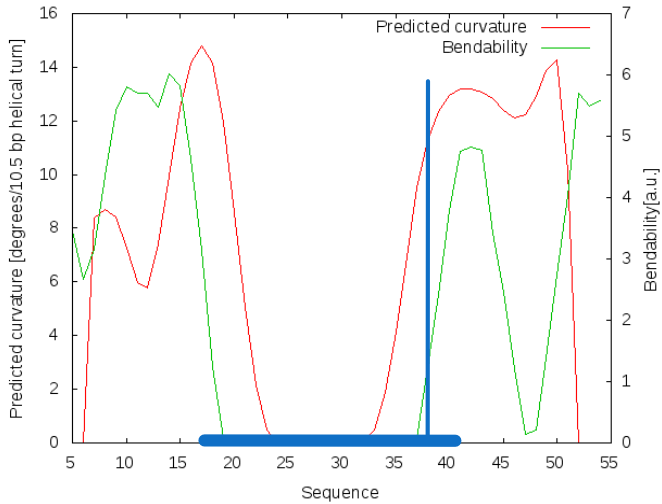
- ▶ Affects nucleosome positioning, chromatin organisation and genome functioning in general;
- ▶ Important for replicational and transcriptional regulation; facilitate gene activation by nucleosome exclusion



Goodsell, D. S., Dickerson, R. E. (1994). Bending and curvature calculations in B-DNA. *Nucleic Acid Research*.

Segal, E., Widom, J. (2009). Poly(dA:dT) Tracts: Major Determinants of Nucleosome Organization. *Curr Opin Struct Biol*.

Effect of studied variations on DNA curvature and bendability



Conclusions

- ▶ In polyA tract region of *PSMA6* gene promoter there are four putative transcription factor binding sites that are not affected by studied variations.
- ▶ Single nucleotide polymorphism rs71640264 (C/A) creates two new putative transcription factor binding sites (SRF and AREB6) in 3' end of the studied polyA tract, while the studied insertions rs200541481 (-/CA) and rs200298313 (-/C) have no effect on putative transcription factor binding sites.
- ▶ rs200541481 (-/CA), rs200298313 (-/C) and rs71640264 (C/A) may have a pronounced effect on DNA secondary structure thus changing binding of gene expression regulating elements.
- ▶ rs71640264 (C/A) may have an effect on DNA curvature and bendability at the 3' end of the studied polyA tract, which makes the sequence more curved and can affect the binding of gene expression regulating elements.
- ▶ rs71640264 (C/A) may have an effect on disease development through functional changes both in DNA structure and mechanical characteristics as well as in putative transcription factor binding sites.

Thank you for the attention!

The study was funded from the European Regional Development Fund project No. 1.1.1.1/16/A/016 "Identification of proteasome related genetic, epigenetic and clinical markers for multiple sclerosis".

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