



**Институт
биоинформатики**



**Центр геномной
биоинформатики
им Ф. Г. Добржанского**

Search for correlation of socioeconomic status and methylation profiles

Scientific advisor: Pavel Dobrynin

Student: Kirill Grigorev

Project premise

Published by Oxford University Press on behalf of the International Epidemiological Association
© The Author 2011; all rights reserved. Advance Access publication 20 October 2011

International Journal of Epidemiology 2012;41:62–74
doi:10.1093/ije/dyr147

EPIGENETIC EPIDEMIOLOGY

Associations with early-life socio-economic position in adult DNA methylation

Nada Borghol,^{1,2†} Matthew Suderman,^{1,2,3†} Wendy McArdle,⁴ Ariane Racine,^{1,2} Michael Hallett,³ Marcus Pembrey,^{5*} Clyde Hertzman,^{6*} Chris Power^{7*} and Moshe Szyf^{1,2*}

OPEN ACCESS Freely available online

PLOS ONE

Profiling of Childhood Adversity-Associated DNA Methylation Changes in Alcoholic Patients and Healthy Controls

Huiping Zhang^{1,5*}, Fan Wang^{1,5}, Henry R. Kranzler⁶, Hongyu Zhao⁴, Joel Gelernter^{1,2,3,5}

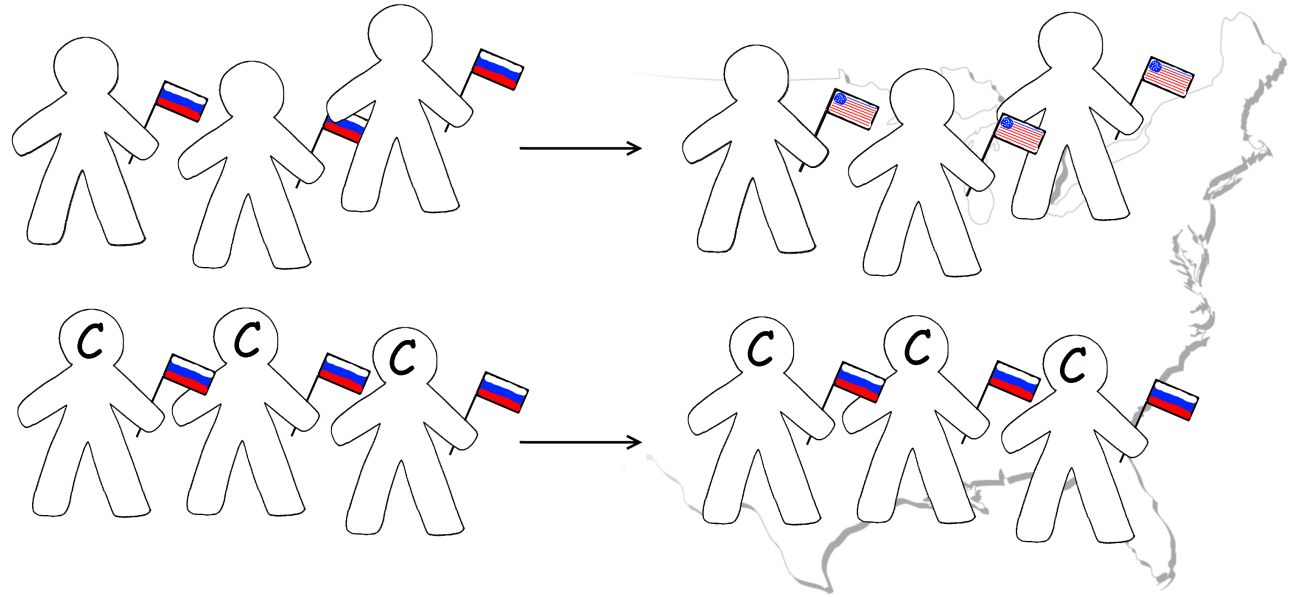
Childhood adversity and DNA methylation of genes involved in the hypothalamus–pituitary–adrenal axis and immune system: Whole-genome and candidate-gene associations

JOHANNA BICK^a, OKSANA NAUMOVA^{a,b}, SCOTT HUNTER^a, BAPTISTE BARBOT^a, MARIA LEE^a, SUNIYA S. LUTHAR^{a,c}, ADAM RAEFSKI^a, and ELENA L. GRIGORENKO^{a,c,d}

^aYale University; ^bVavilov Institute of General Genetics; ^cColumbia University and ^dMoscow State University

Project goal and experiment design

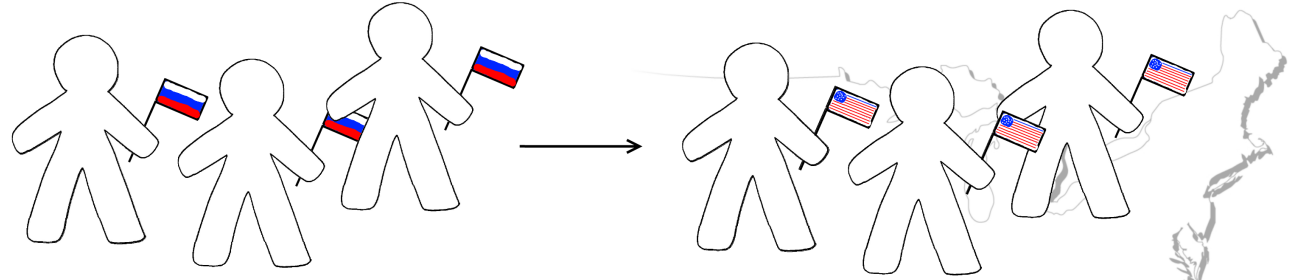
Detect systematic change in methylation patterns (if any)
in orphans moving from Russia to the U.S.



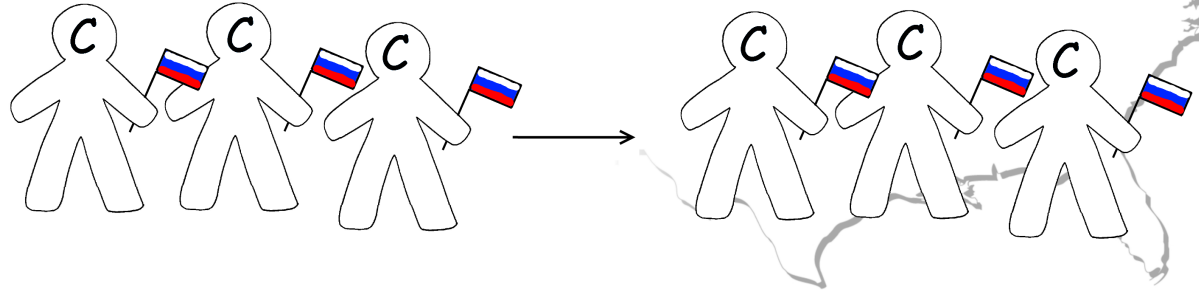
Project goal and experiment design

Detect systematic change in methylation patterns (if any) in orphans moving from Russia to the U.S.

Cases: Russian orphans adopted by U.S. families



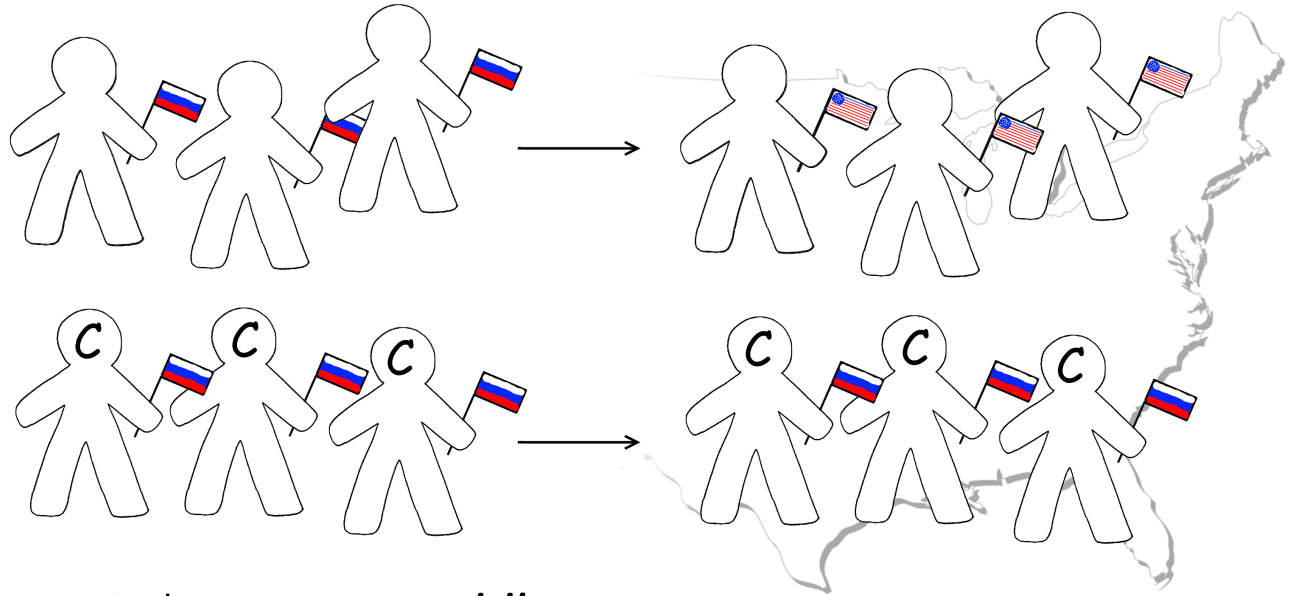
Controls: Russian children who moved to the U.S. with their biological parents.



Project goal and experiment design

Detect systematic change in methylation patterns (if any)
in orphans moving from Russia to the U.S.

Cases: Russian orphans
adopted by U.S. families

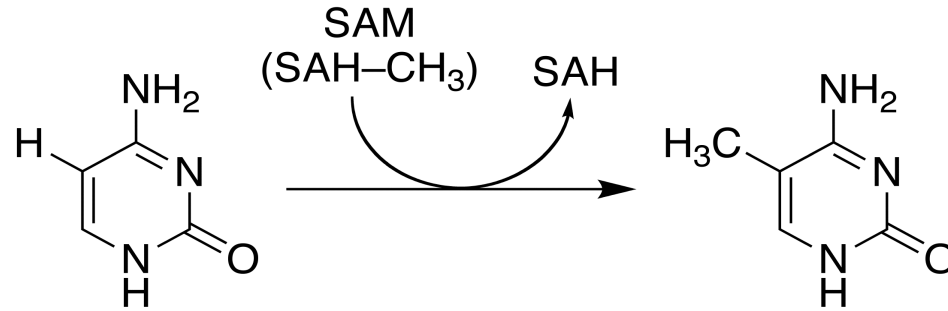


Controls: Russian children
who moved to the U.S.
with their biological
parents.

Subject age: **toddlers**

Time interval between sequencing: **6 months**

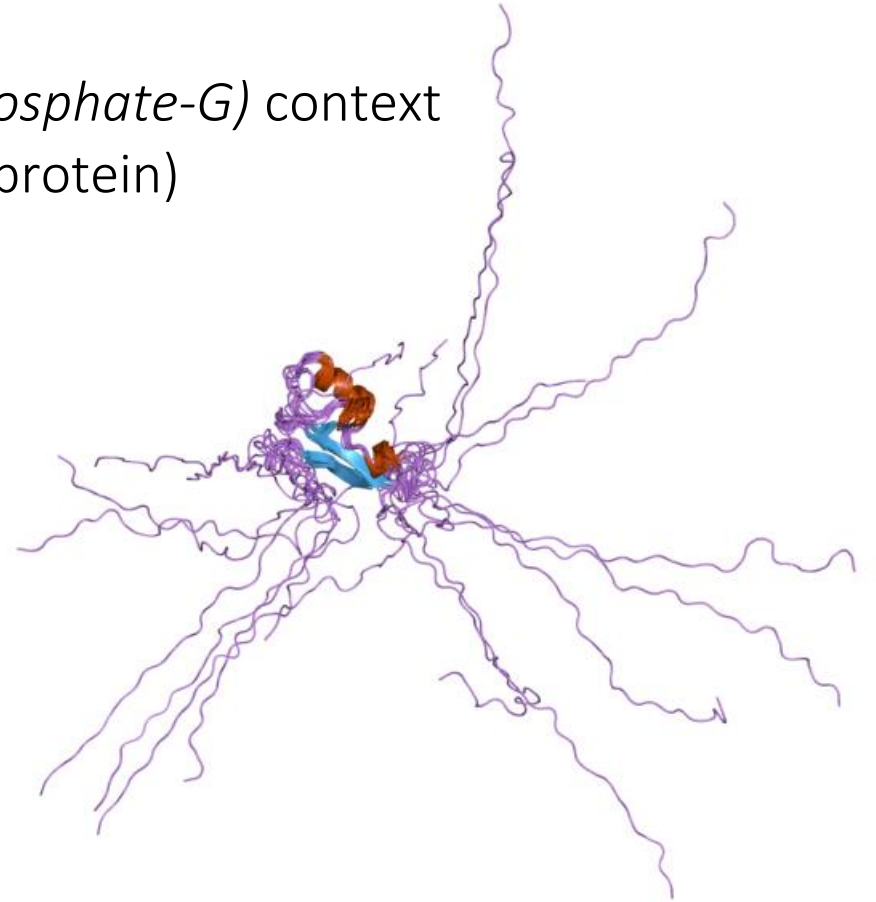
Cytosine methylation



- Typically occurs in CpG (*C-phosphate-G*) context
- Is involved in regulation of gene transcription

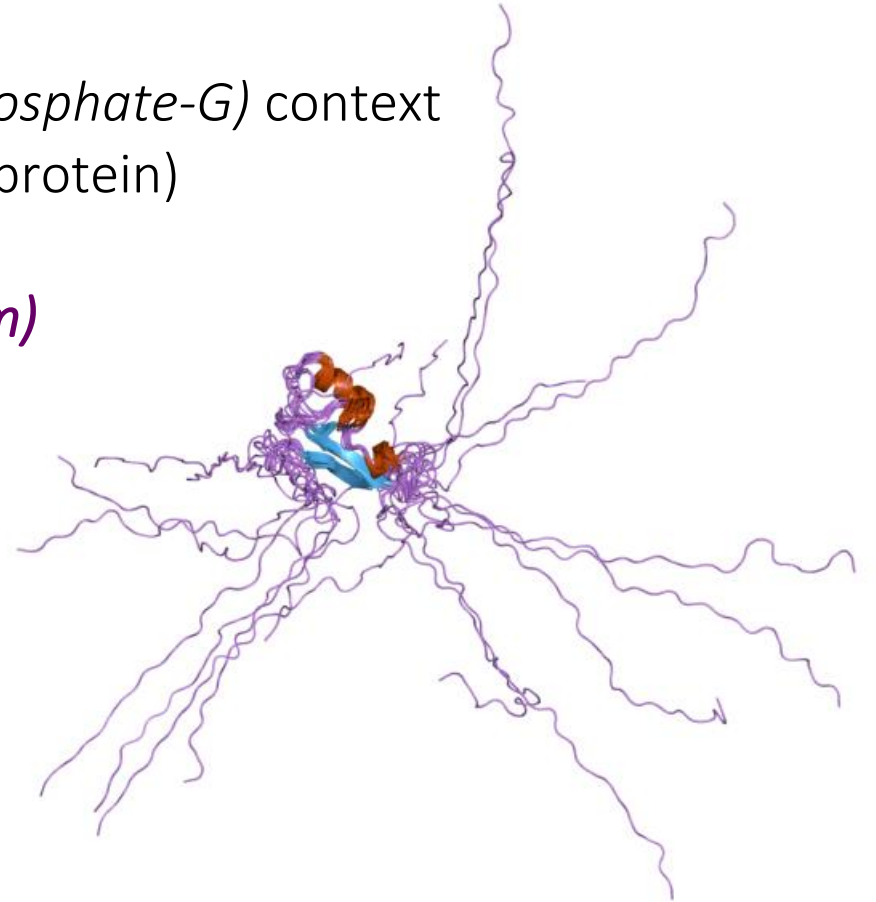
Cytosine methylation: MBD-Seq

1. Methylation typically occurs in CpG (*C-phosphate-G*) context
2. **MBD** = Methyl-CpG Binding Domain (in a protein)
3. Can use MBD in ChIP-seq
4. ???
5. Methylated region detection

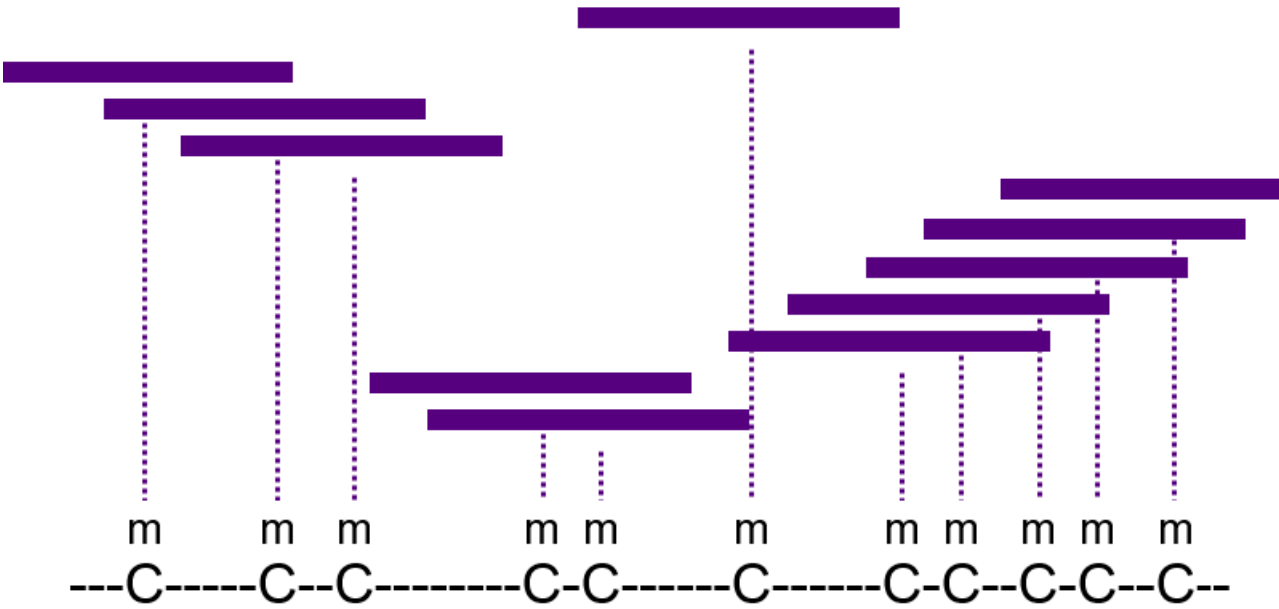


Cytosine methylation: MBD-Seq

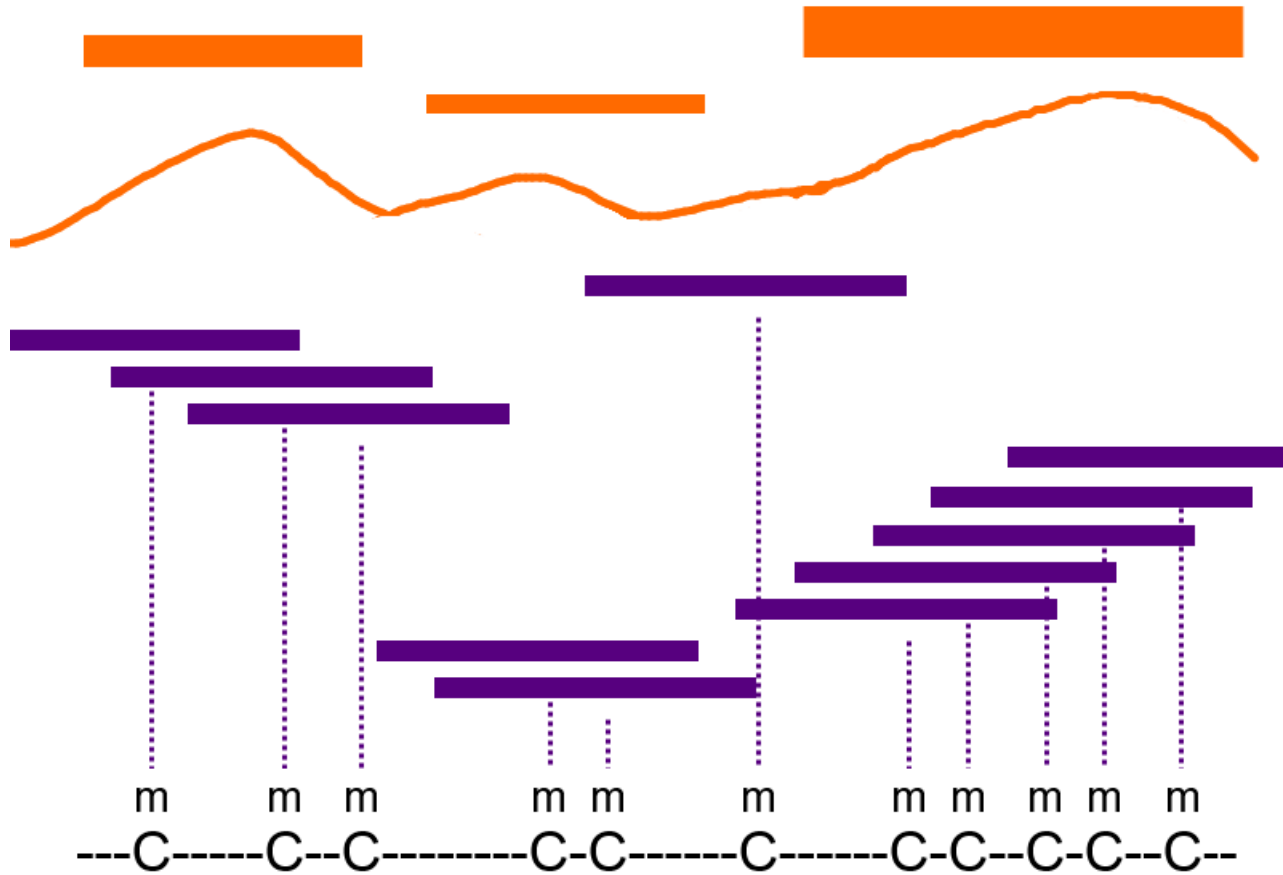
1. Methylation typically occurs in CpG (*C-phosphate-G*) context
2. **MBD** = Methyl-CpG Binding Domain (in a protein)
3. Can use MBD in ChIP-seq
4. ??? **Peak calling etc. (MACS, SICER, custom)**
5. Methylated region detection



Enrichment



Enrichment: regions the MACS2 way



Enrichment: interpretation

General idea

Find regions where enrichment changes:

- in the *same* direction for all *cases*
- in the *different* direction for all *controls*

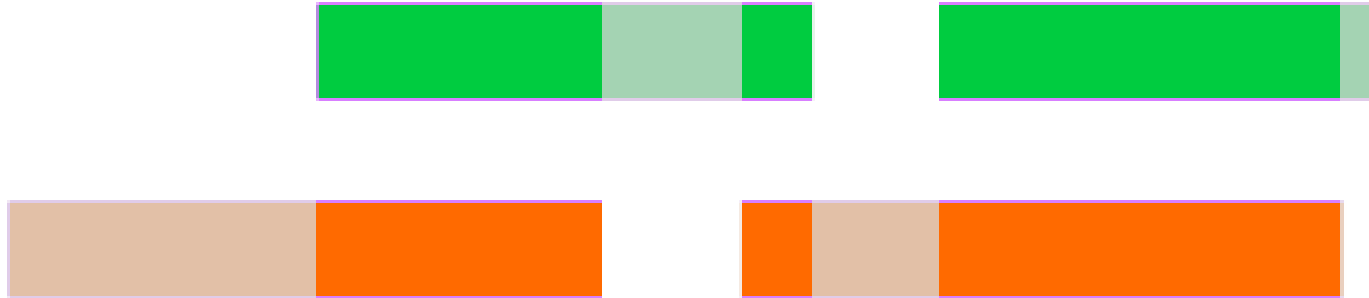


Enrichment: interpretation

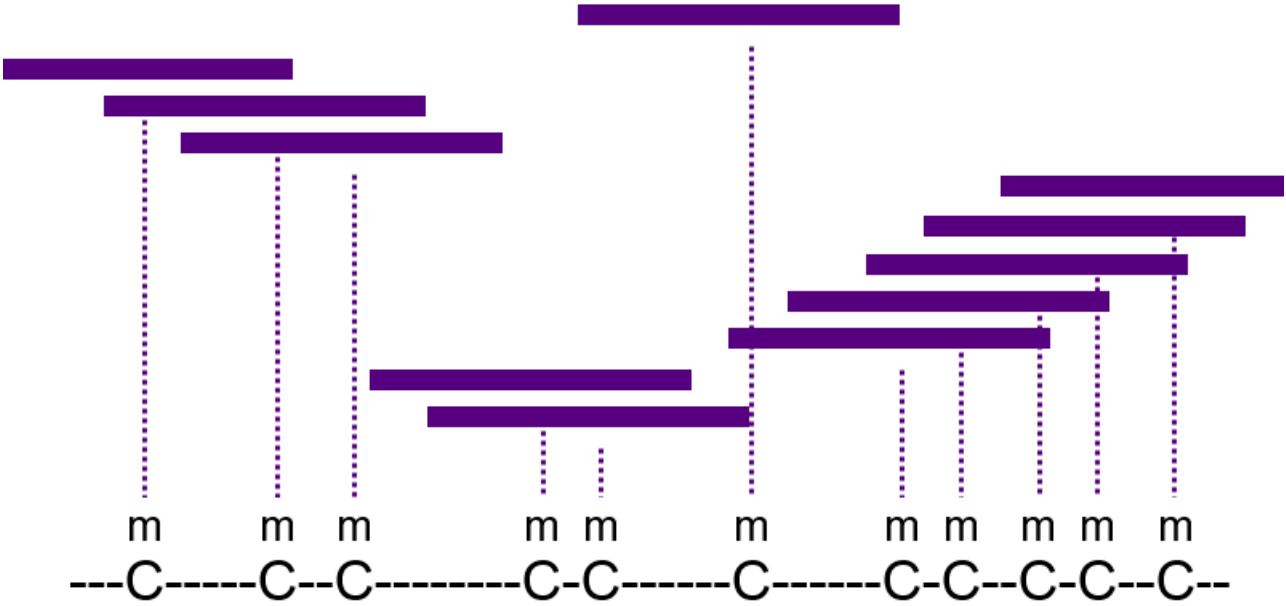
General idea

Find regions where enrichment changes:

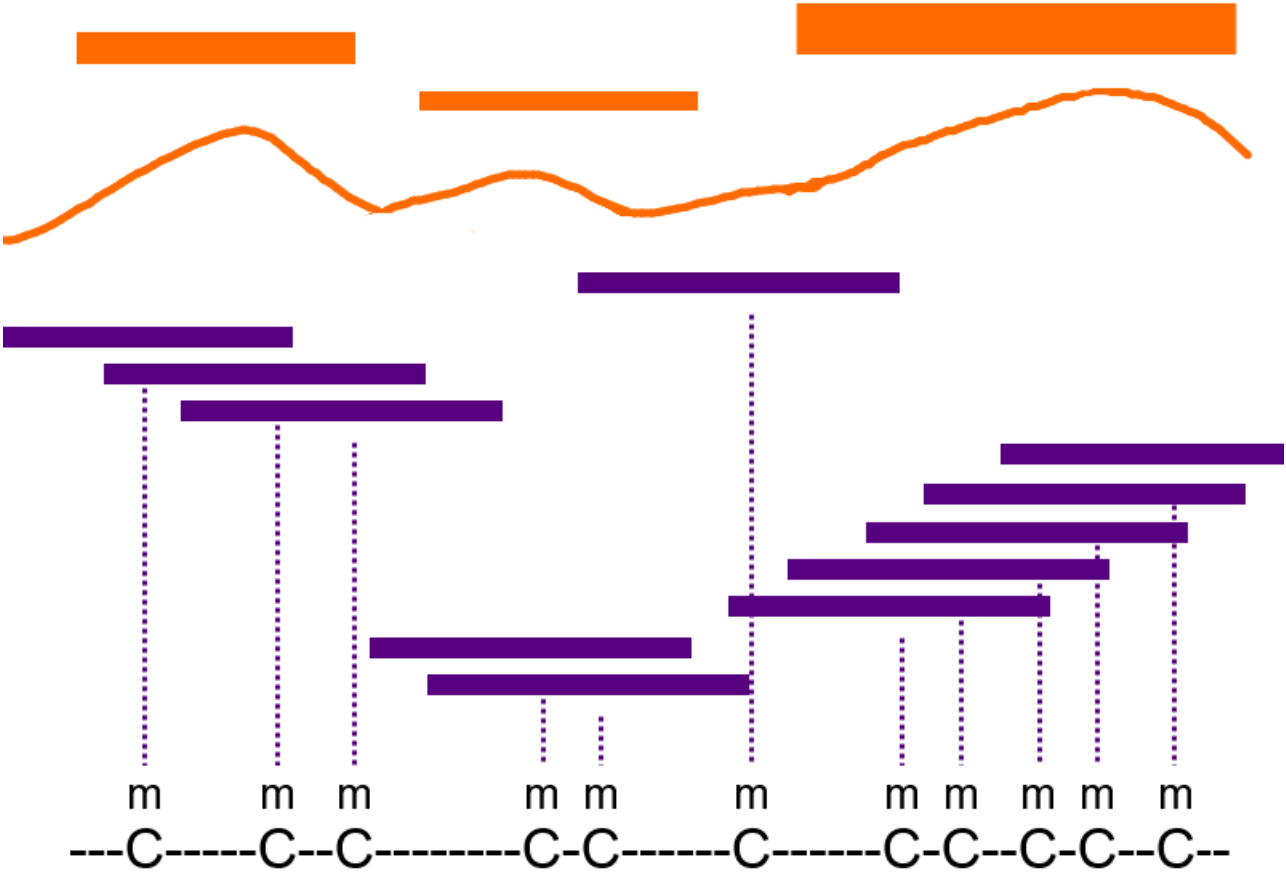
- in the *same* direction for all *cases*
- in the *different* direction for all *controls*



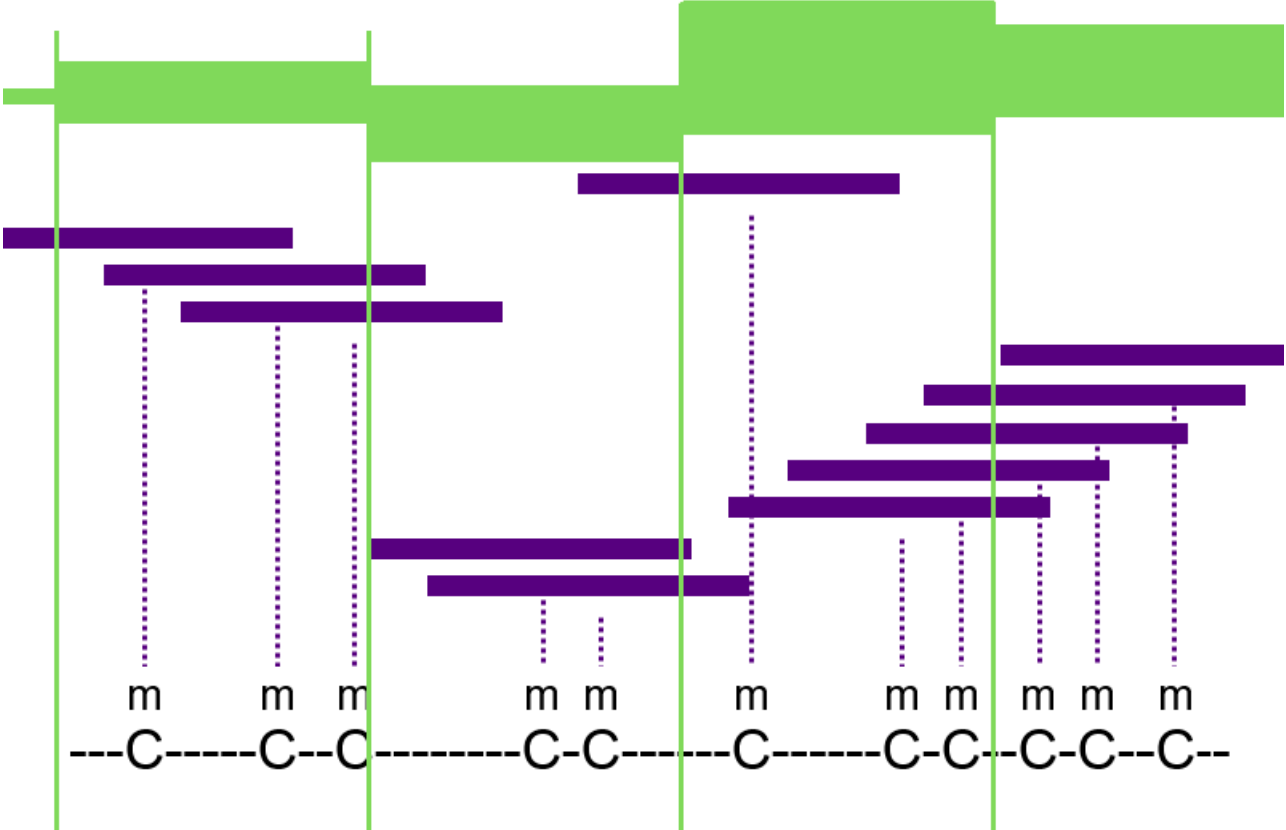
Enrichment: regions



Enrichment: regions the MACS2 way

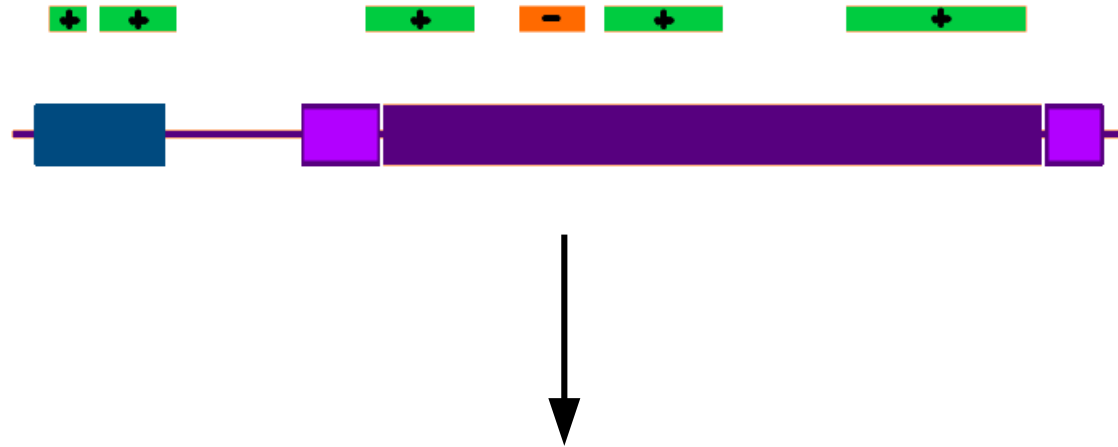


Enrichment: regions our way ©



Finding affected genes

Intersect regions and genes



genes with biggest amount of changed regions (*in uniform direction!*)
genes with biggest cumulative *significance* of changes

Finding affected genes

Examples:

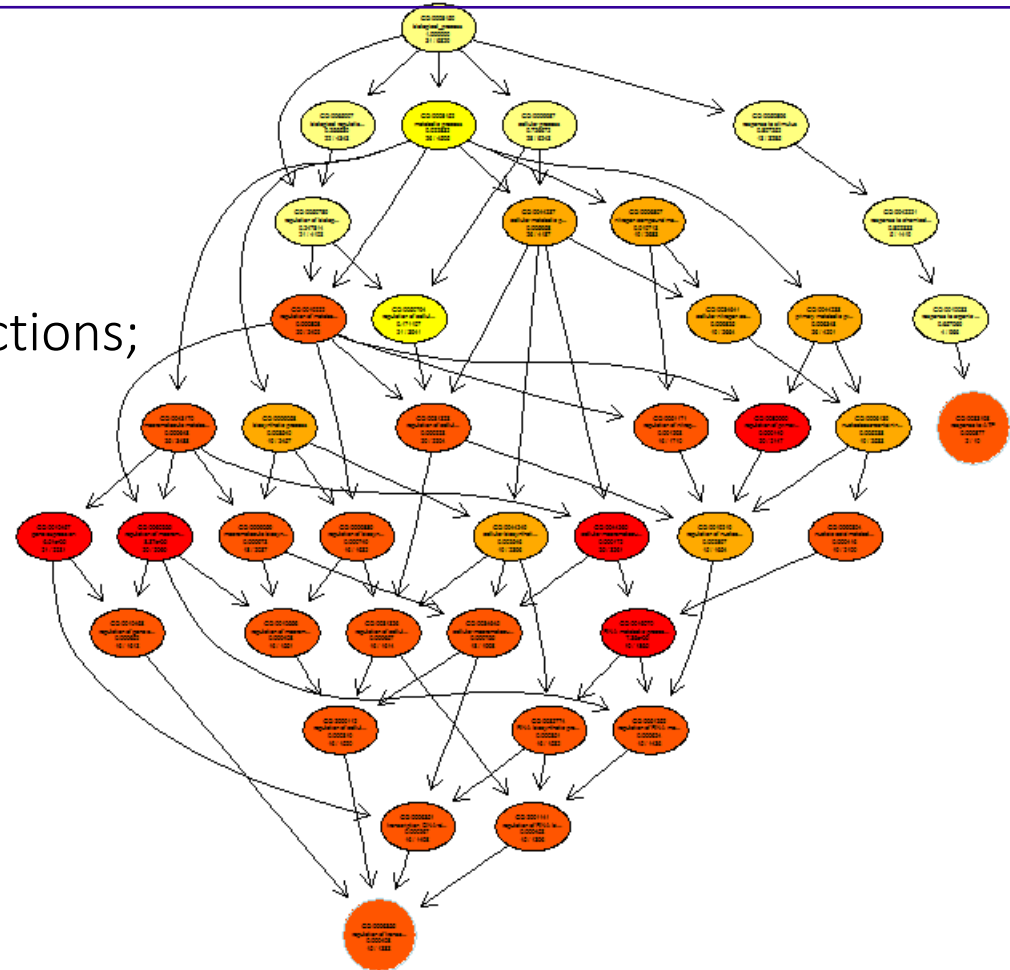
# gene id	region count	positions	significance
ENSG00000155093	15/-9	inside,	1.35778573742
ENSG00000153707	8 /-8	inside,	0.513472427213
ENSG00000179242	7 /-7	inside,	0.713335805813
ENSG00000196338	2 /-2	upstream,inside,	1.7097332516
ENSG00000267369	2 /-2	upstream,inside,	0.950590042702
ENSG00000259009	2 /-2	inside,	2.08073993732
ENSG00000204394	1 /-1	inside,	0.0405047542049

Affected gene clusters by function

Enter **Gene Ontology**

Reports functions for a gene;

Provides an XML file of relations of all functions;



Affected gene clusters by function

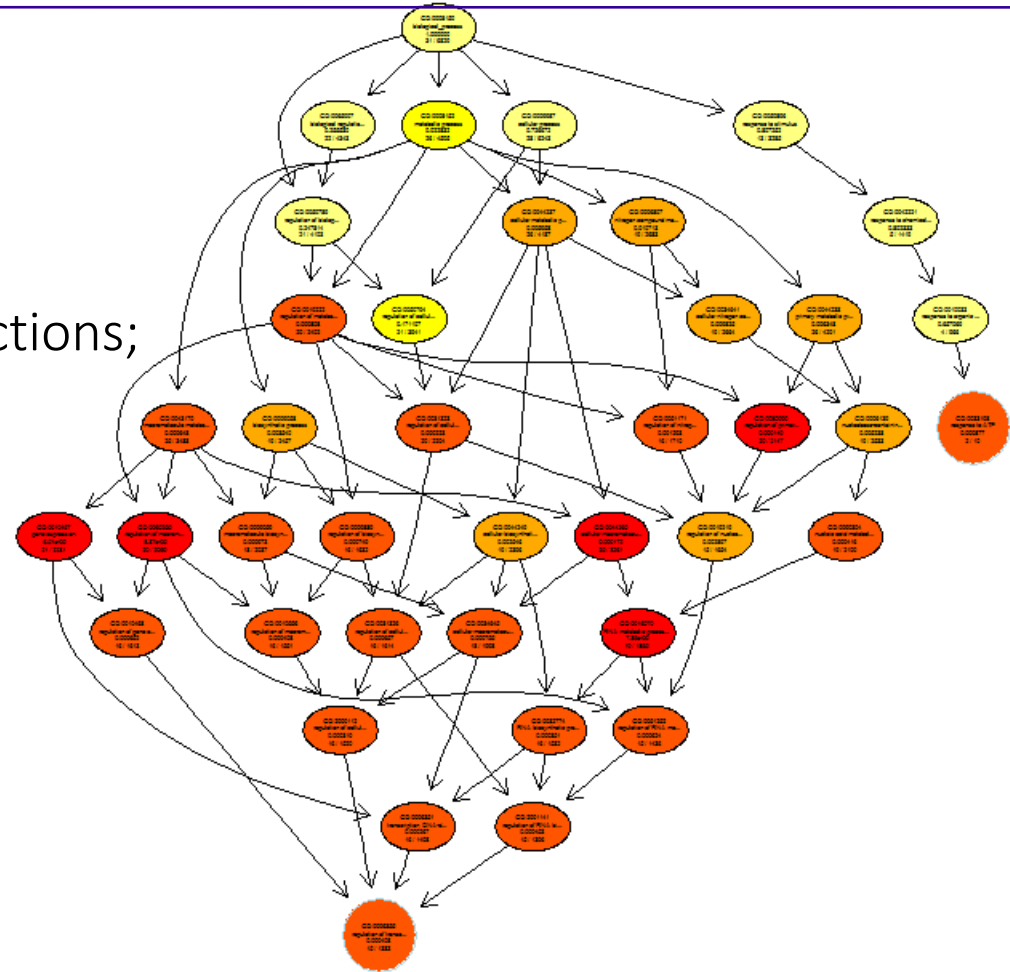
Enter **Gene Ontology**

Reports functions for a gene;

Provides an XML file of relations of all functions;

=> we can find full “ancestry” of functions for any gene

=> we can sort functions by frequency in our dataset



Affected gene clusters by function

Enter **Gene Ontology**

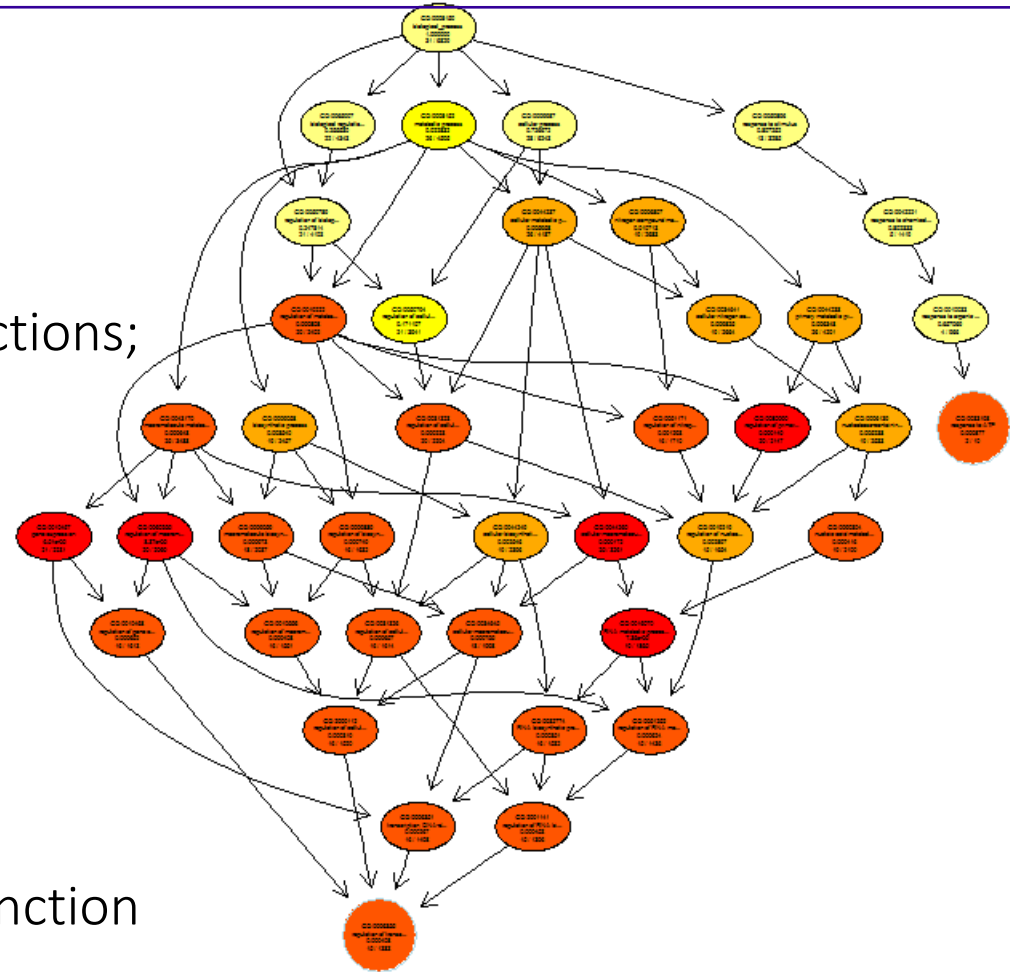
Reports functions for a gene;

Provides an XML file of relations of all functions;

=> we can find full “ancestry” of functions for any gene

=> we can sort functions by frequency in our dataset

=> we can find clusters with interesting function



Affected gene clusters by function

Examples of found clusters:

GO:0032502 (developmental process):	30 genes
GO:0048513 (organ development):	16 genes
GO:0009653 (anatomical structure morphogenesis):	13 genes
GO:0007417 (central nervous system development):	11 genes

Affected gene clusters by function

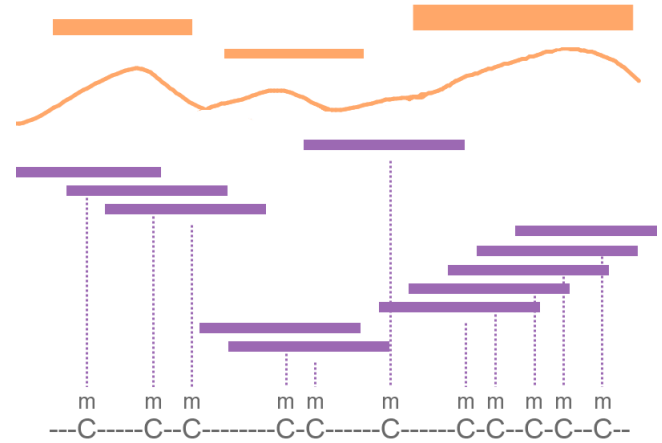
Examples of found genes:

- GO:0007417 => ENSG00000075213 (**SEMA3A**) [4 regions, 0.21 significance]
neuronal pattern development
- GO:0032502 => ENSG00000153707 (**PTPRD**) [8 regions, 0.51 significance]
neurite growth, ADHD / restless legs syndrome
- GO:0048513 => ENSG00000196498 (**NCOR2**) [3 regions, 0.91 significance]
transcription activity mediator

Conclusion

Results:

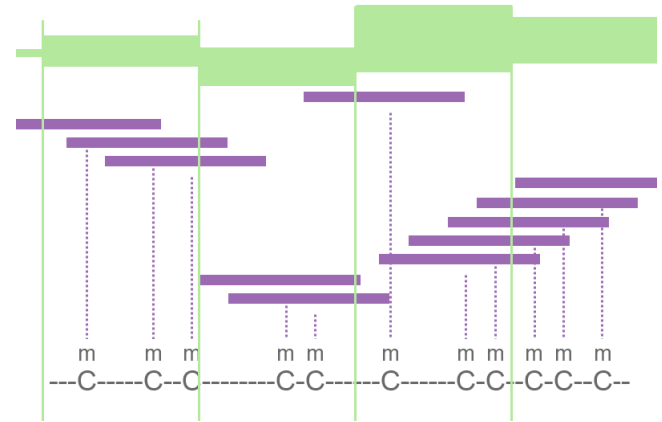
- A pipeline was created for detection of methylation profile changes;
- A successful proof-of-concept run was executed on a sample dataset;
- Significant change in methylation was found in a number of genes with important function



Conclusion

Future plans:

- Develop the new pipeline (based on the alternative idea)
- Apply both pipelines to the entire dataset, expand, compare
- Assess biological significance of obtained results



Orphans' methylomes



<http://bioinformaticsinstitute.ru>
<http://dobzhanskycenter.ru>