



**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

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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}

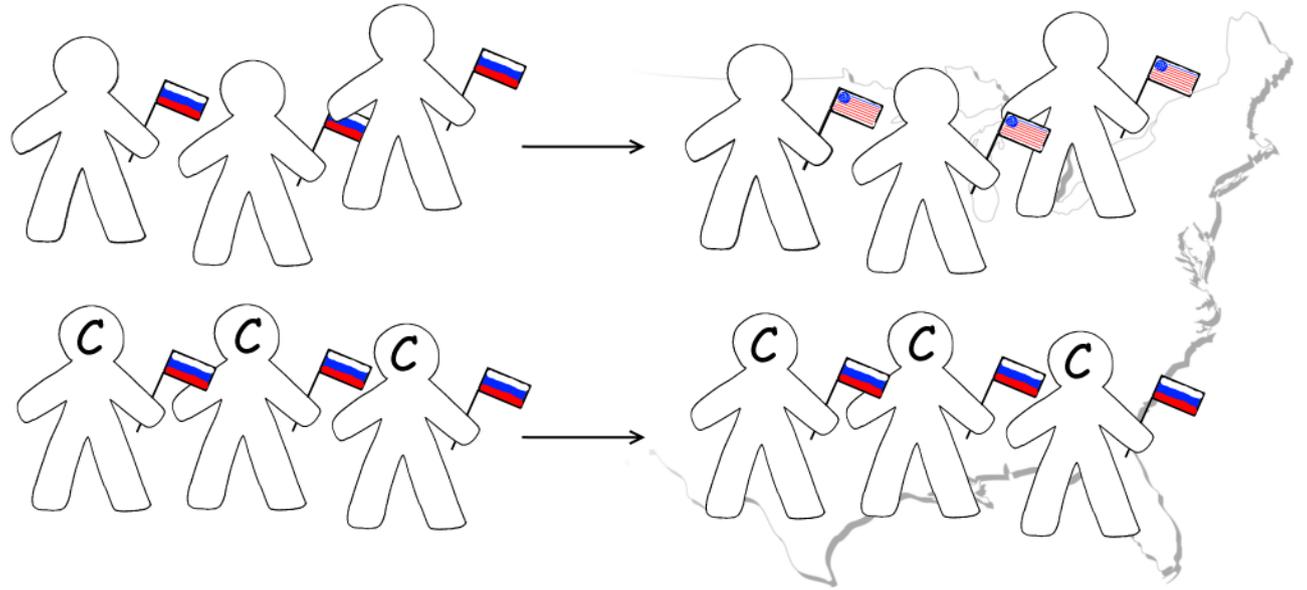
Childhood adversity and DNA methylation of genes involved in the hypothalamus–pituitary–adrenal axis and immune system: Whole-genome and candidate-gene associations

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

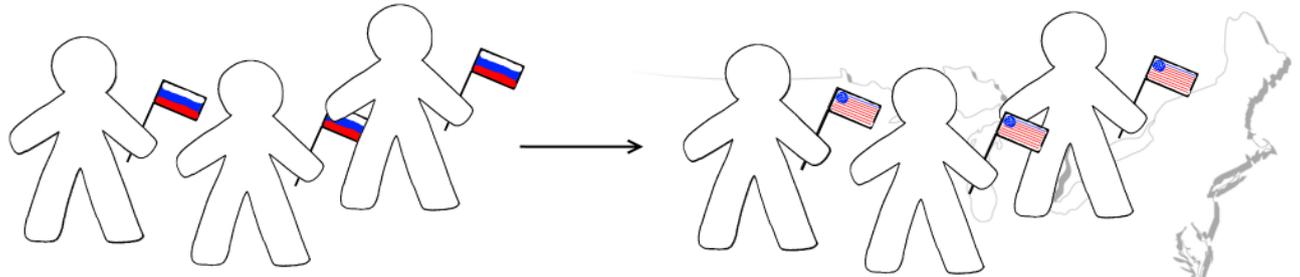
Detect systematic change in methylation patterns (if any)
in orphans moving from Russia to the U.S.



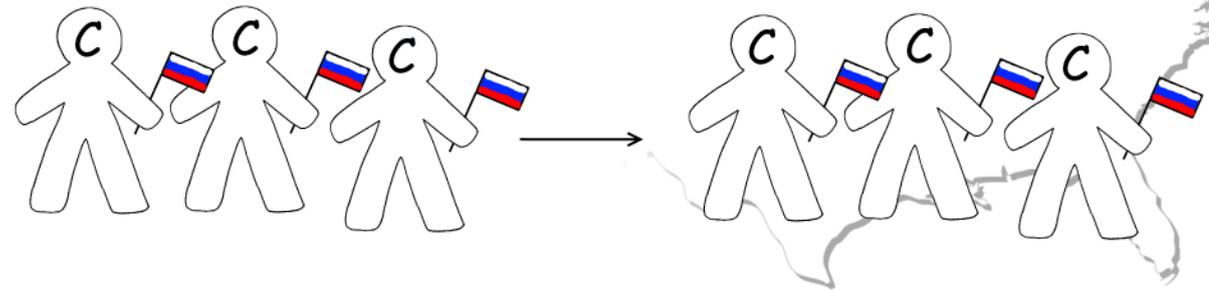
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Cases: Russian orphans adopted by U.S. families



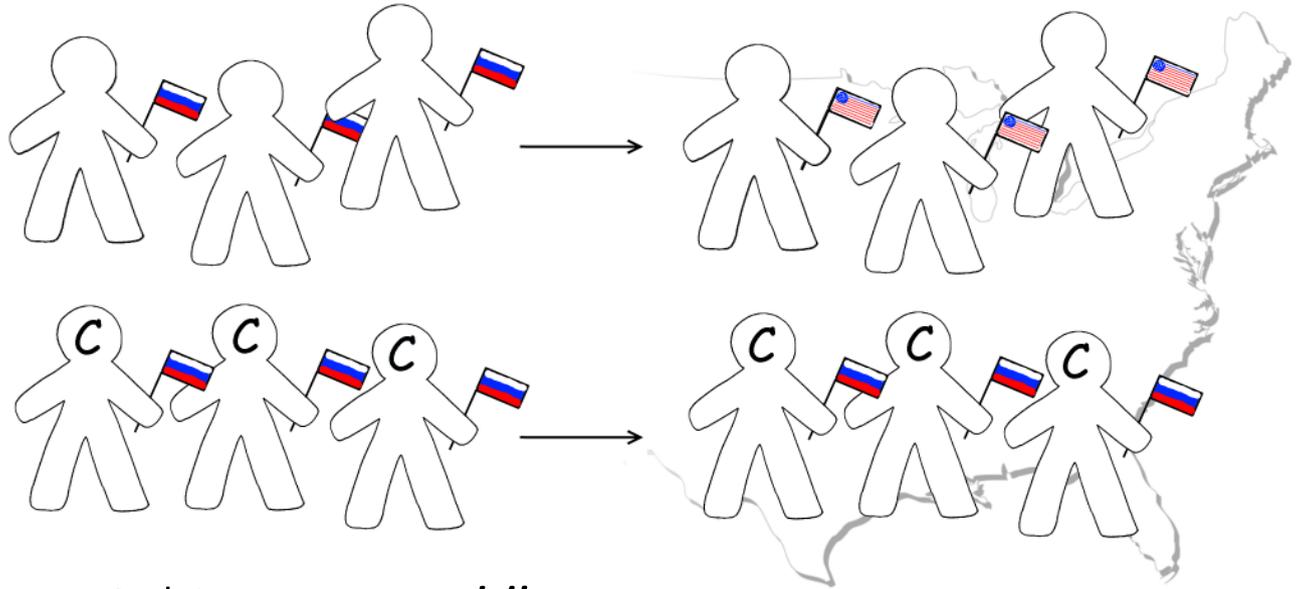
Controls: Russian children who moved to the U.S. with their biological parents.



Project goal and experiment design

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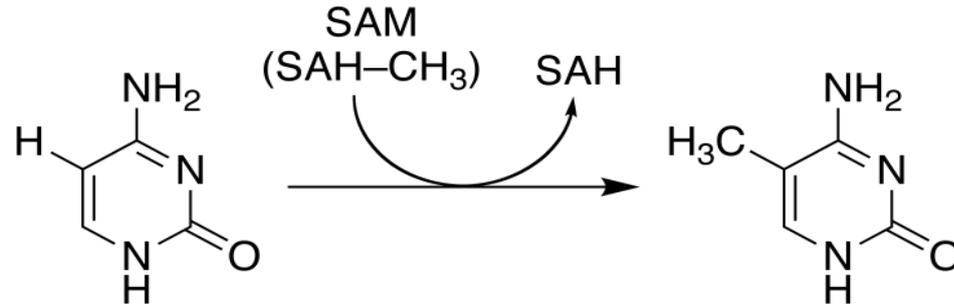


Controls: Russian children
who moved to the U.S.
with their biological
parents.

Subject age: **toddlers**

Time interval between sequencing: **6 months**

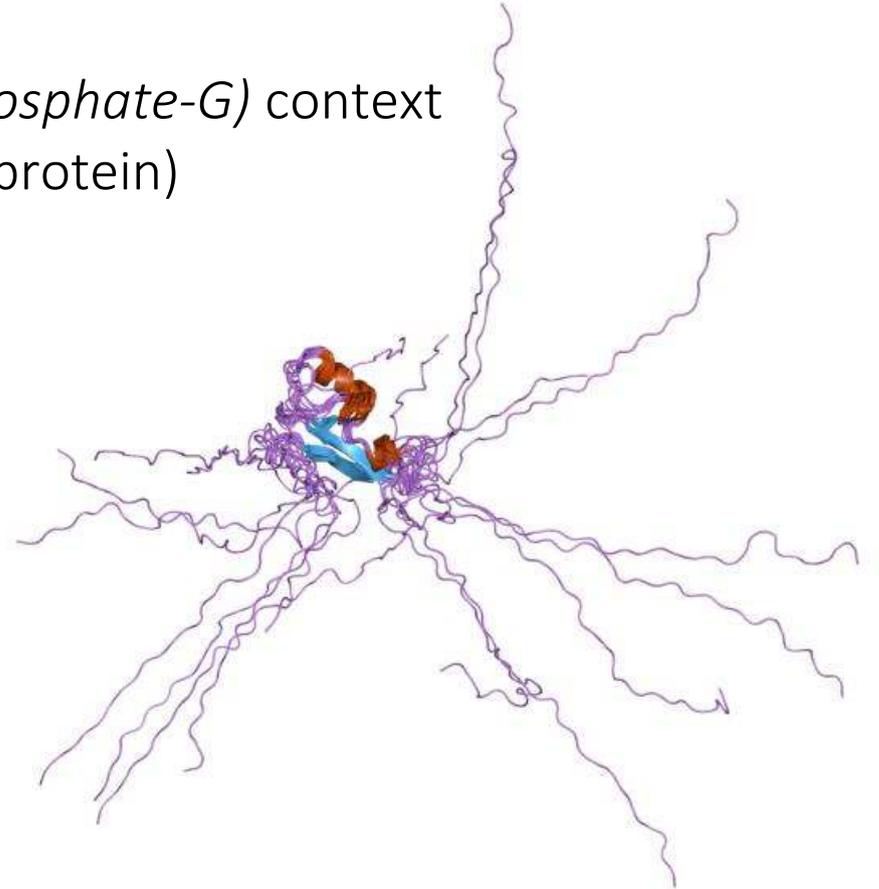
Cytosine methylation



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

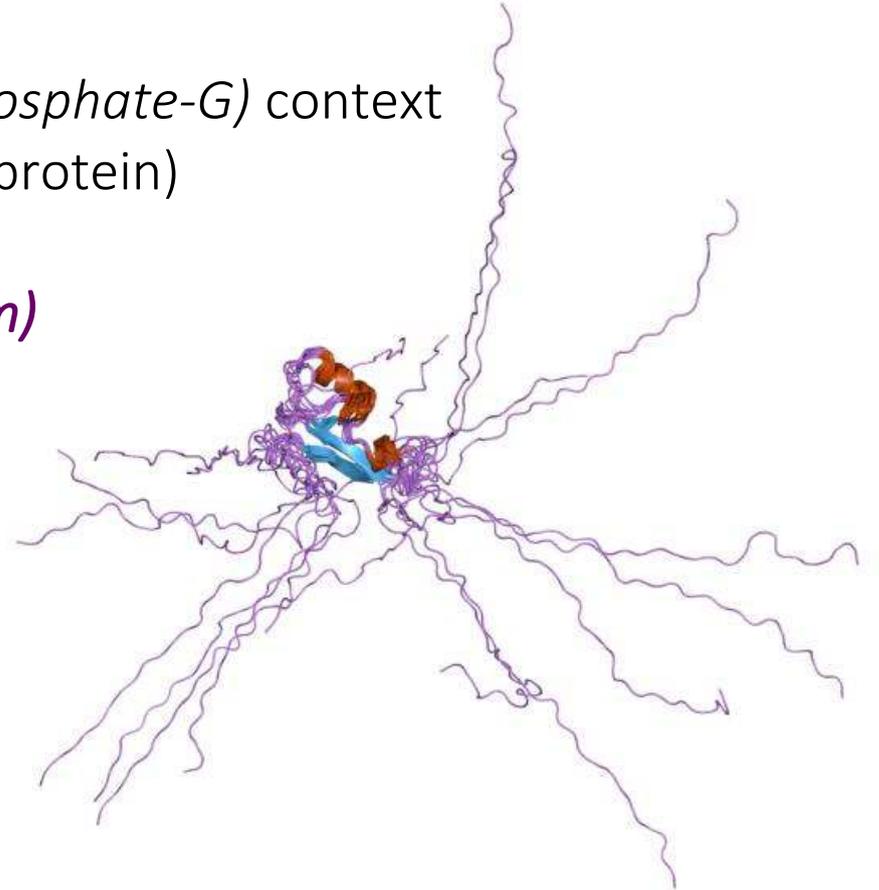
Cytosine methylation: MBD-Seq

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

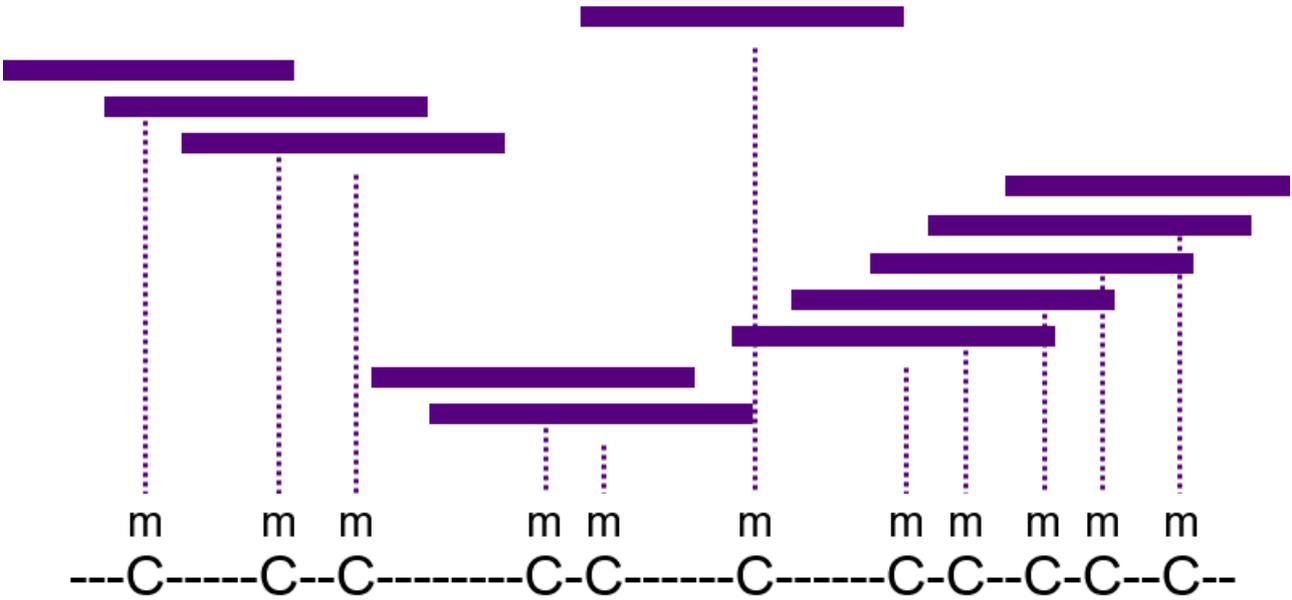


Cytosine methylation: MBD-Seq

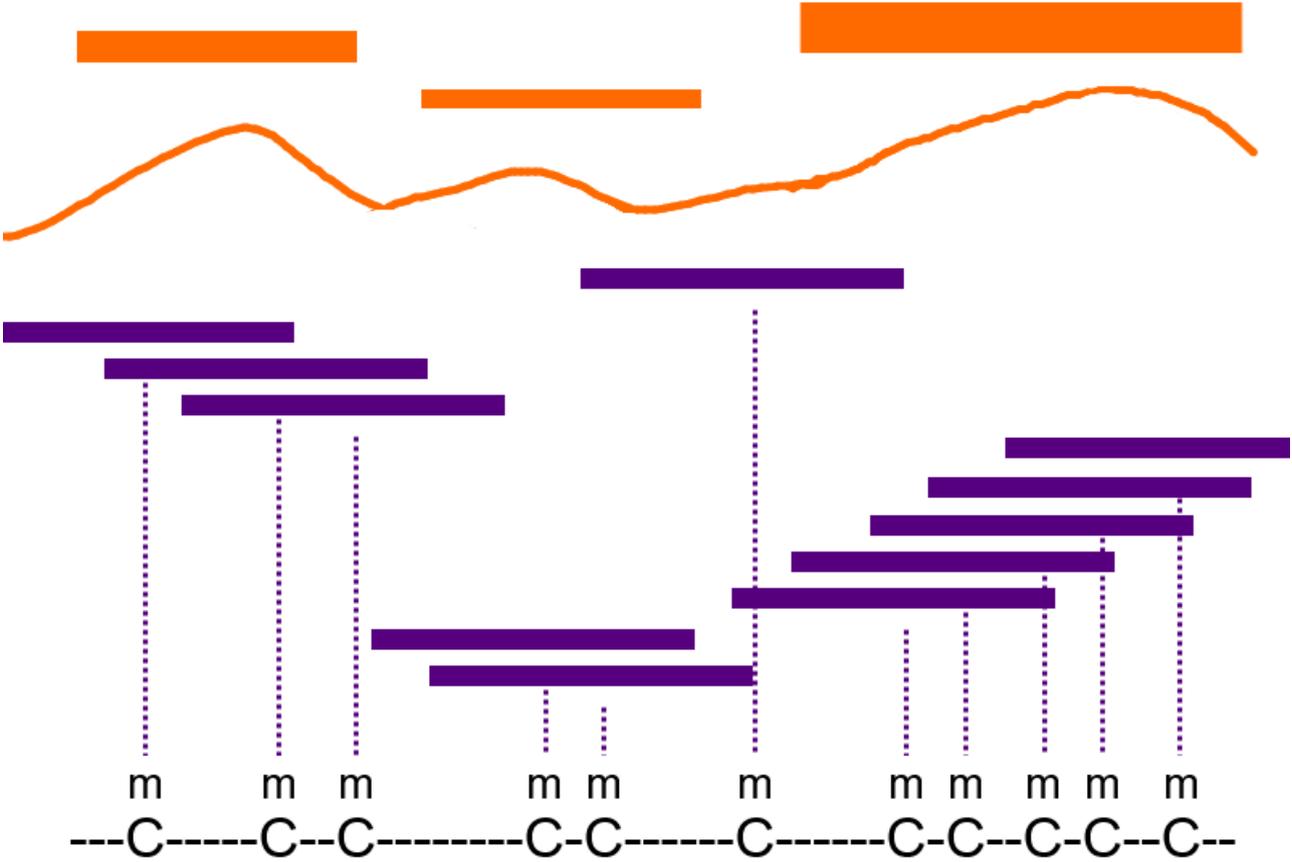
1. Methylation typically occurs in CpG (*C-phosphate-G*) context
2. **MBD** = Methyl-CpG Binding Domain (in a protein)
3. Can use MBD in ChIP-seq
4. ??? **Peak calling etc. (MACS, SICER, custom)**
5. Methylated region detection



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*

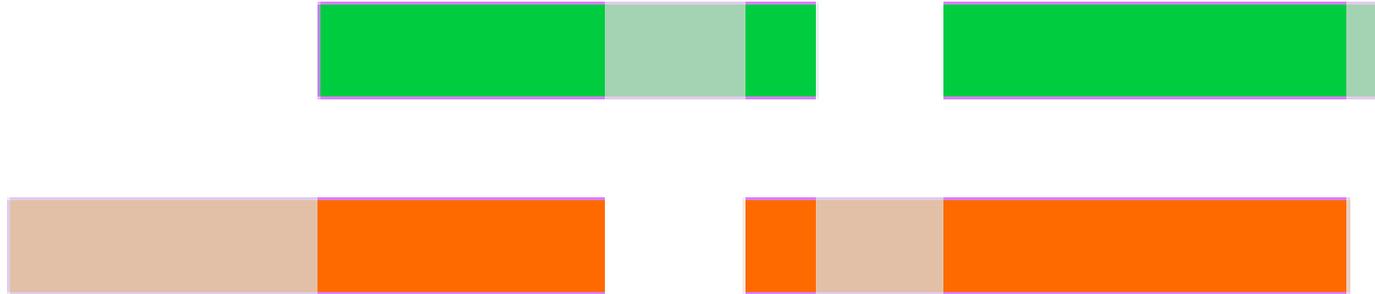


Enrichment: interpretation

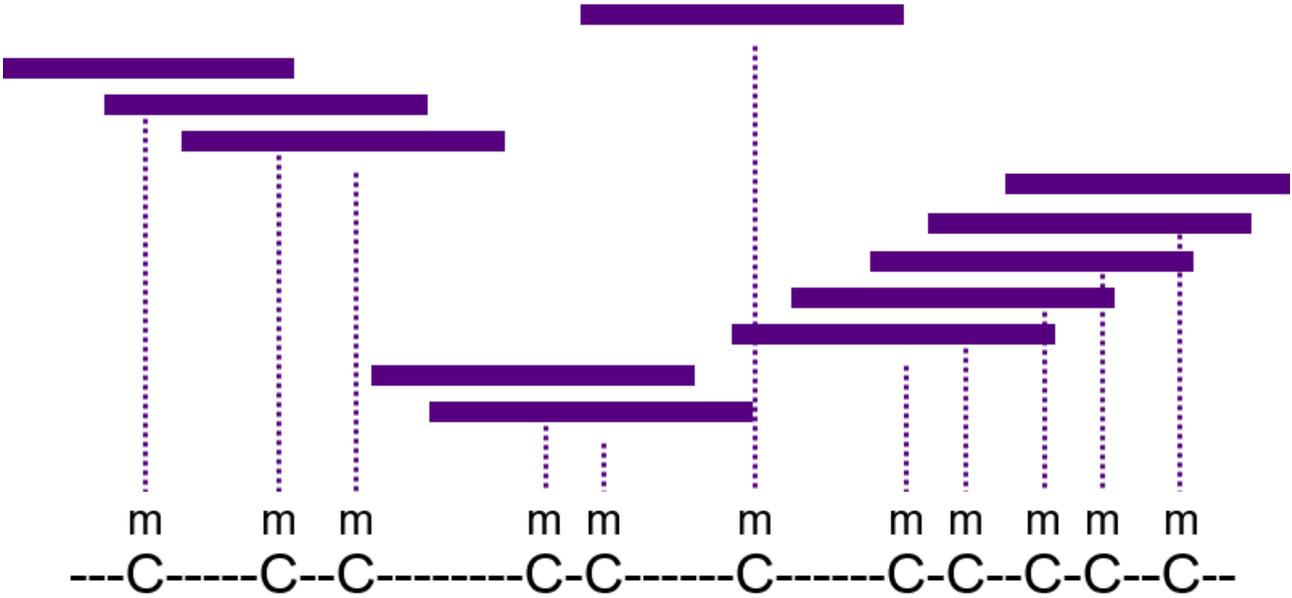
General idea

Find regions where enrichment changes:

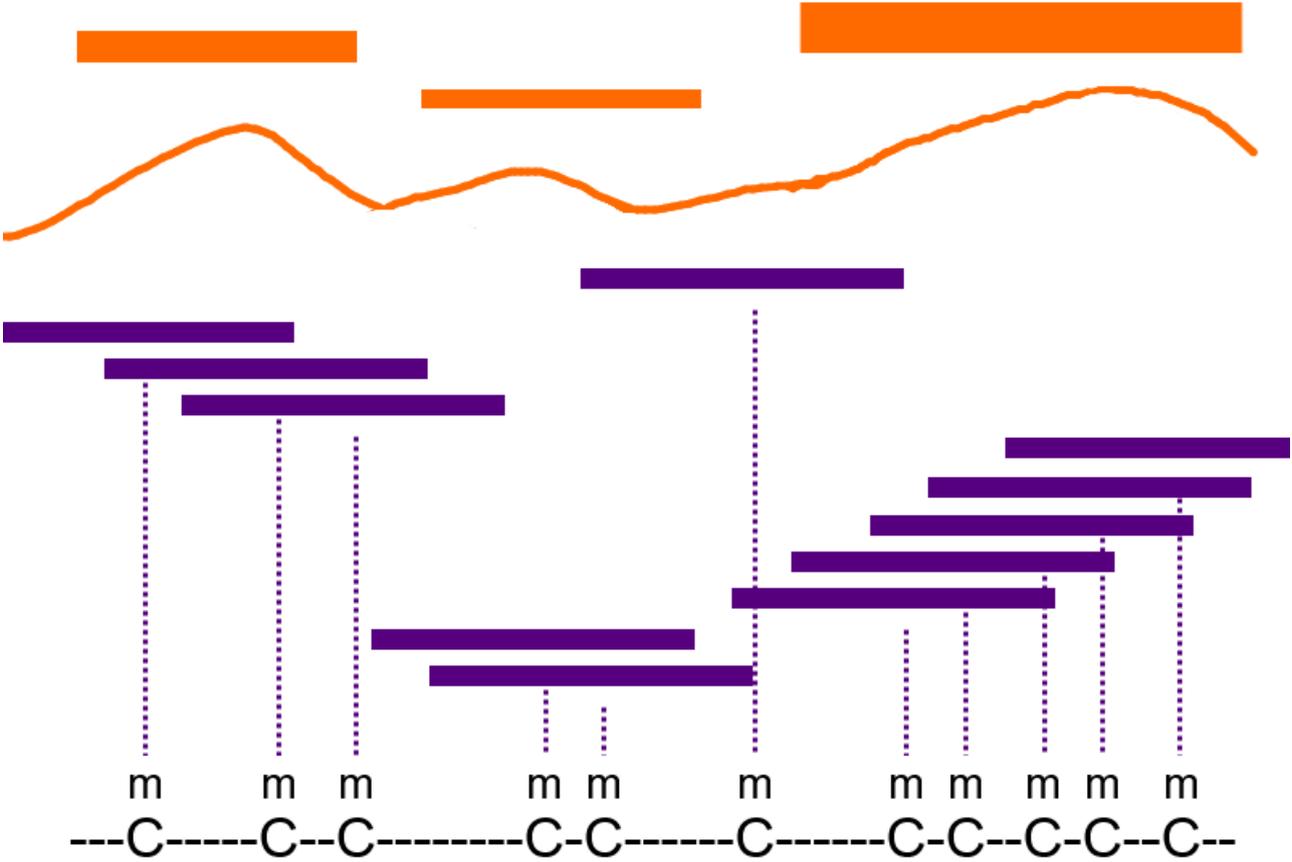
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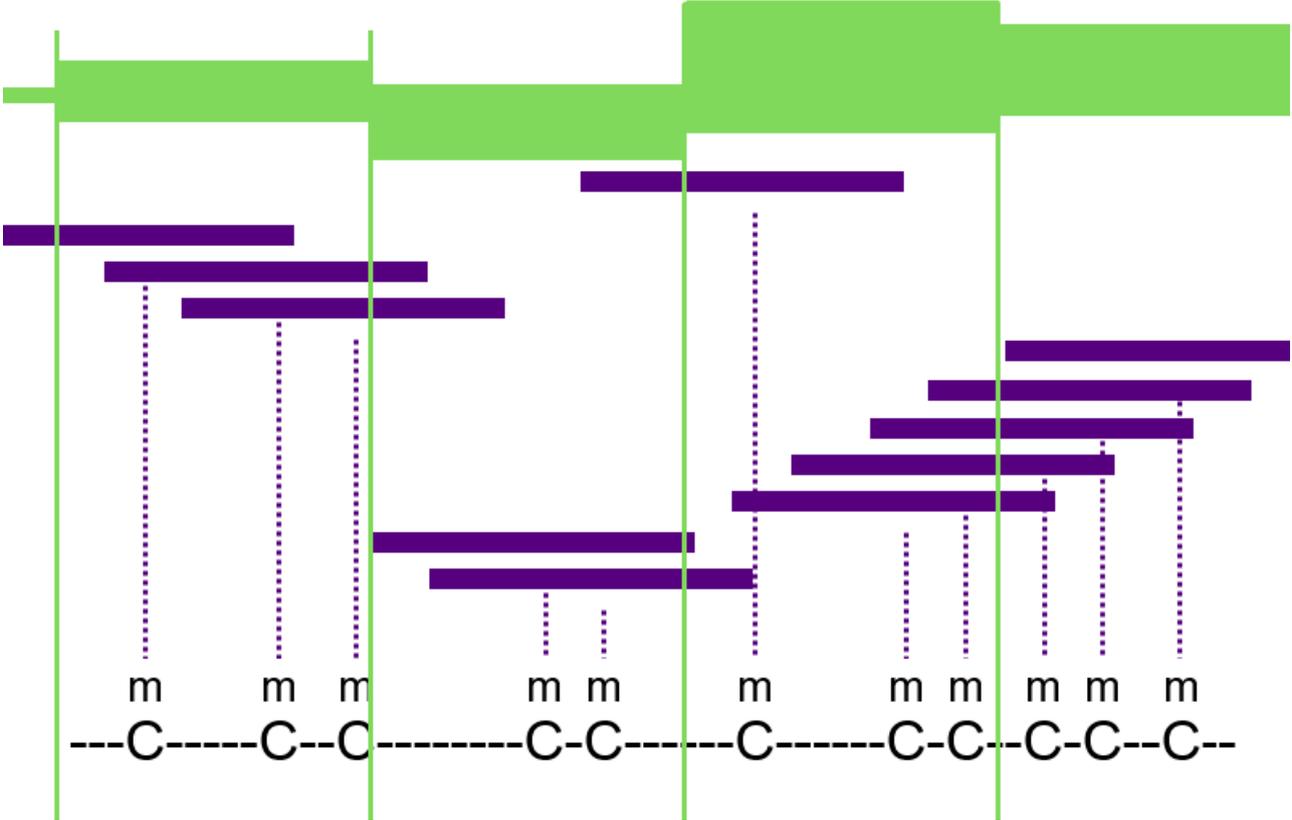
Enrichment: regions



Enrichment: regions the MACS2 way

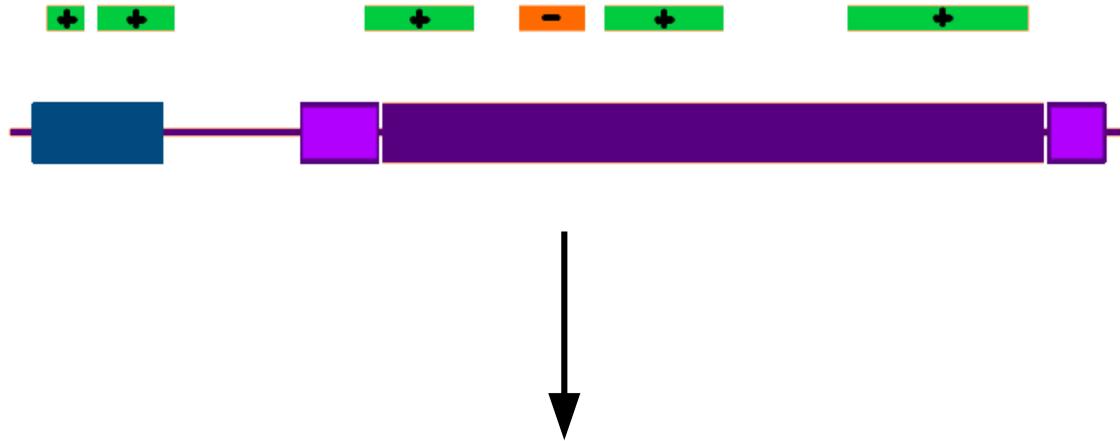


Enrichment: regions our way ©



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

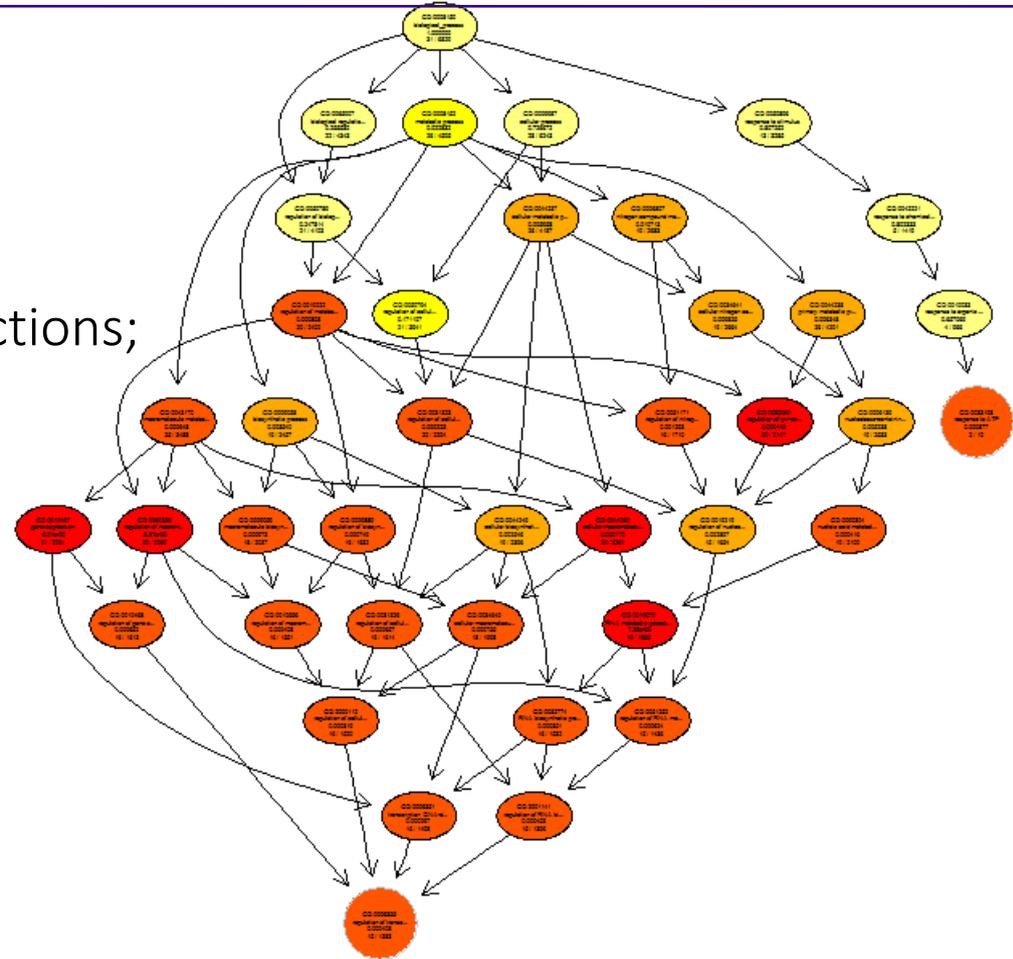
Affected gene clusters by function

Enter **Gene Ontology**

Reports functions for a gene;

Provides an XML file of relations of all functions;

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



Affected gene clusters by function

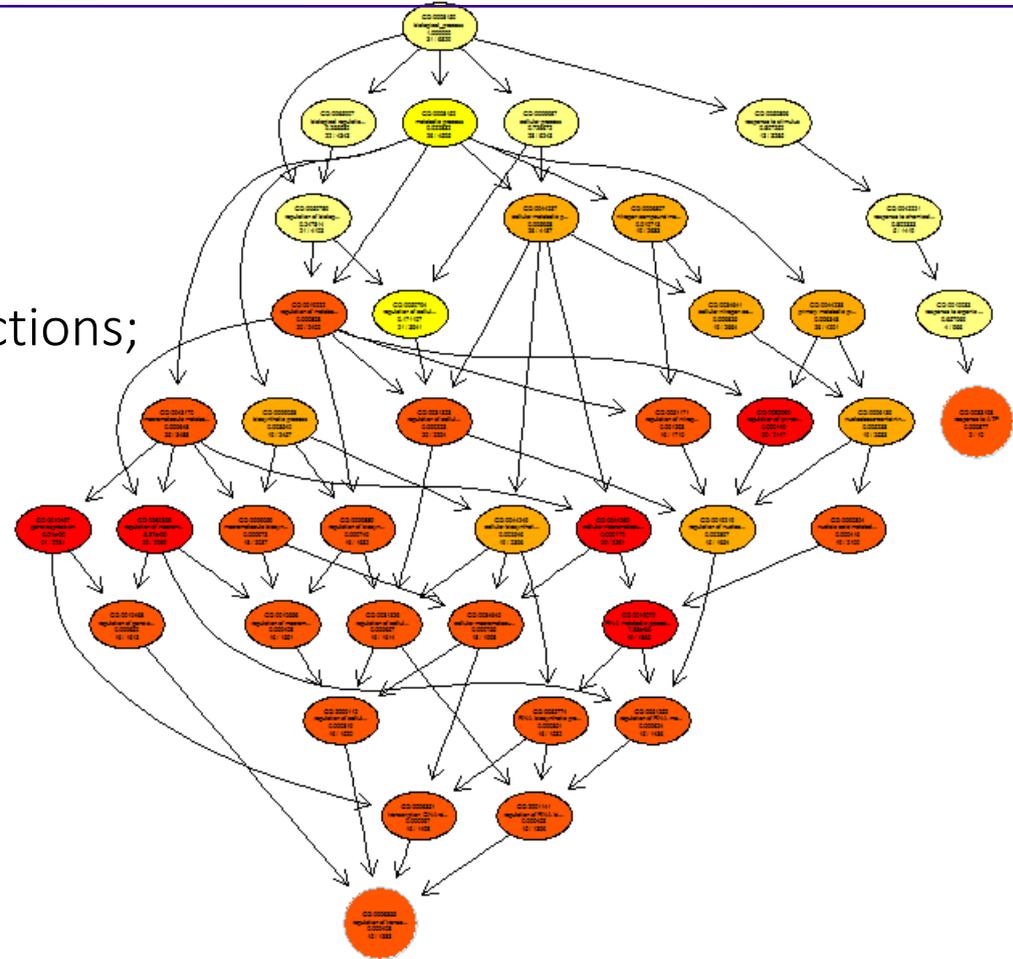
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Affected gene clusters by function

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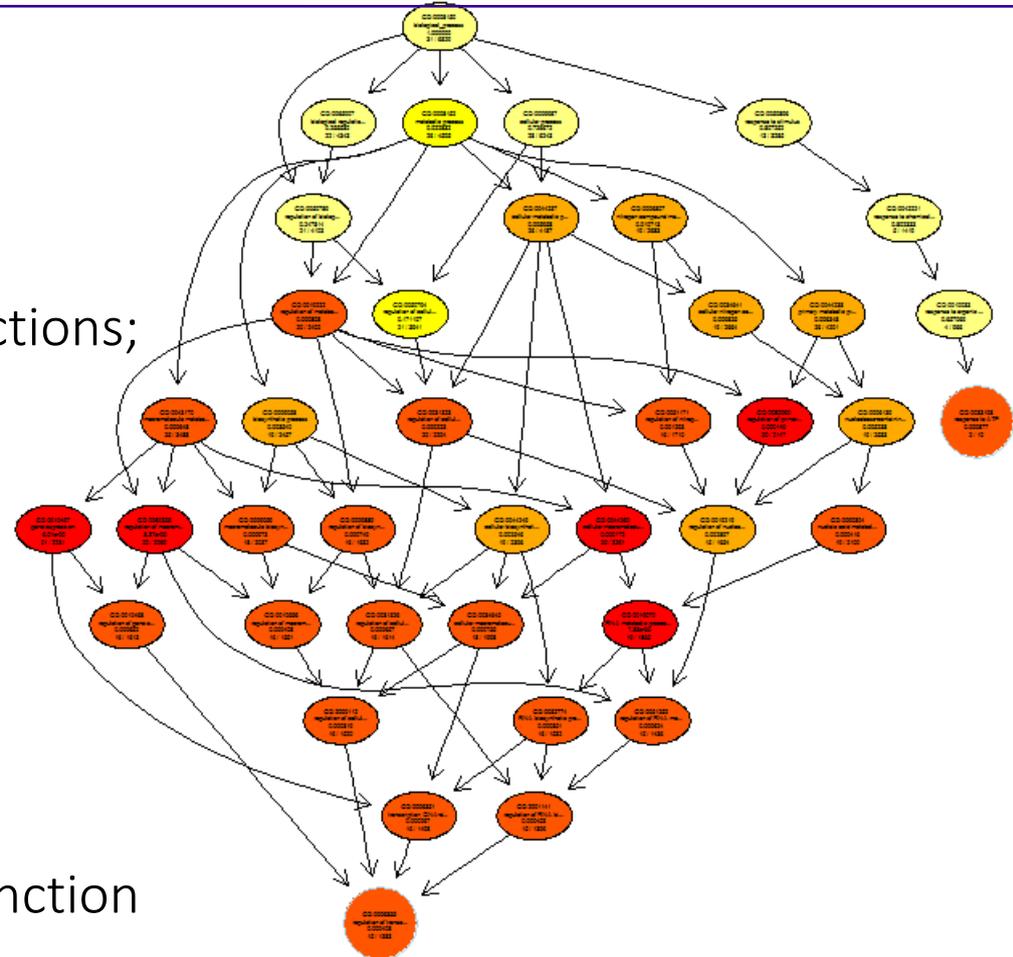
Reports functions for a gene;

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

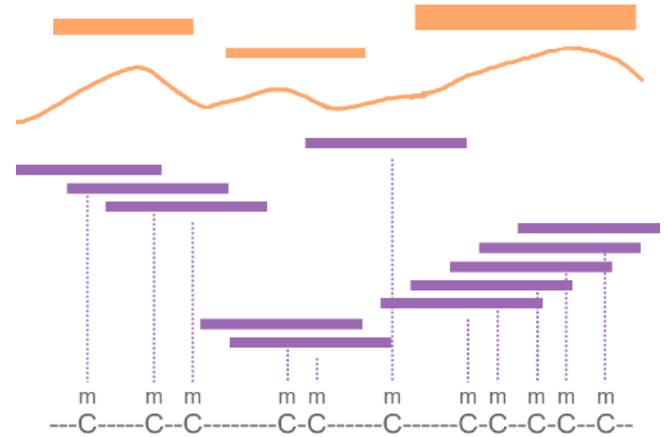
Examples of found genes:

- 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:

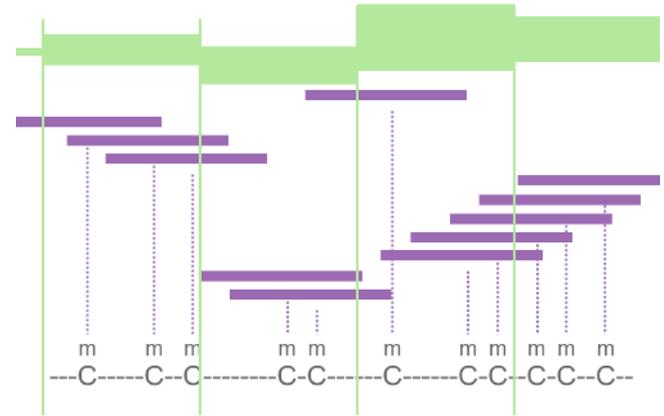
- A pipeline was created for detection of methylation profile changes;
- A successful proof-of-concept run was executed on a sample dataset;
- Significant change in methylation was found in a number of genes with important function



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>