

Unveiling sex- differences: Exploring Methylation and Gene Expression in Multiple Sclerosis

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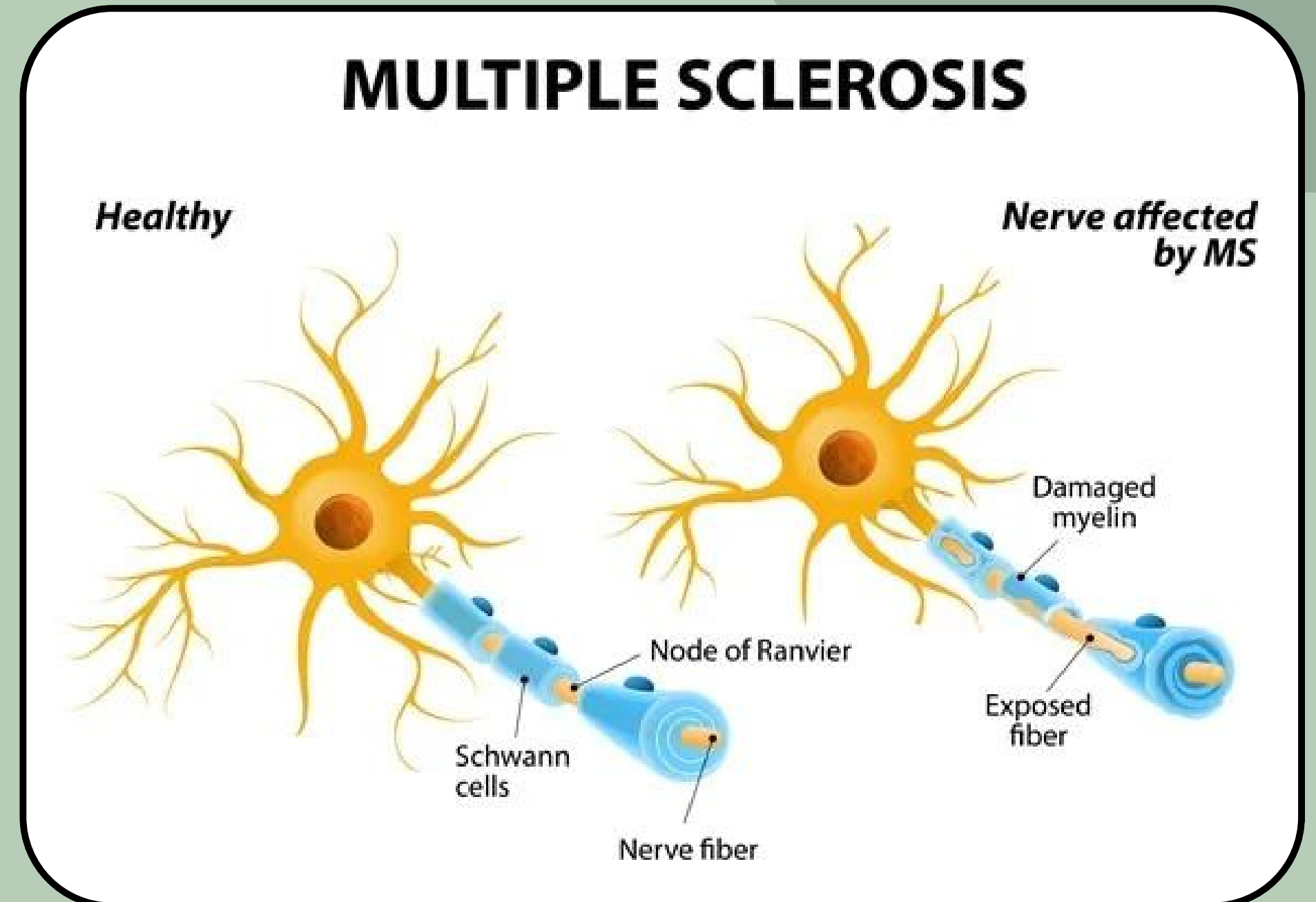


I/ Multiple Sclerosis: Pathogenesis and Sex Differences

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1/ Chronic autoimmune disease of the central nervous system.

2/ Most common non-traumatic disabling disease in young adults.



Multiple Sclerosis

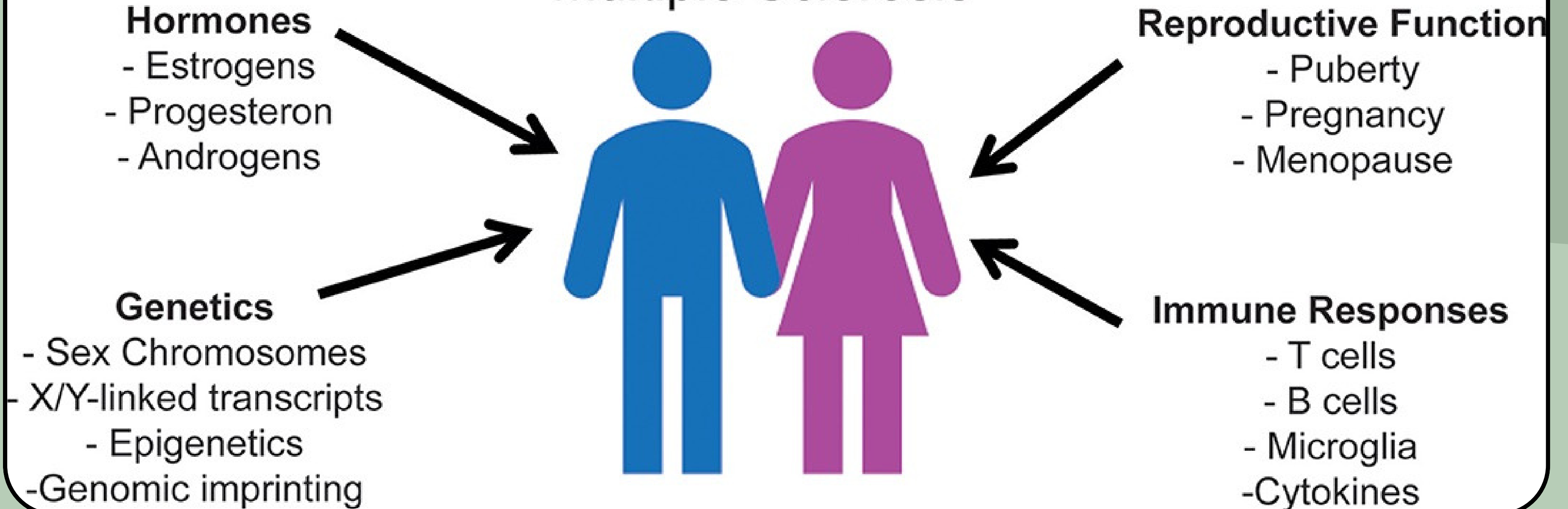
DataSet and Pipeline

Results

Sex differences in MS

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Sex Differences in Multiple Sclerosis



Multiple Sclerosis

DataSet and Pipeline

Results

Sex differences in MS

Estrogen - Tends to increase the activation of immune cells, intercellular signaling and the production of antibodies.

Progesterone and Androgens - Generally tend to suppress and/or weaken the immune system's activity.

Testosterone - Has immunosuppressive effects that may lead to lower immune reactivity in males, potentially increasing susceptibility to infections compared to females.

f:m ratio even in 1900, now ~ 3:1

Migration from low-risk (near the equator) to high-risk areas (in northern latitudes) or vice versa influences an individual's risk of developing MS.

DataSet

4 males vs 5 females

- 2 brain samples from each patient (lesion-non lesion)

- EPIC Methylation Array
- RNASeq

What we compared

- Male vs. Female
 1. lesion vs. lesion
 2. non-lesion vs. non-lesion
- Female

lesion vs. non-lesion
- Male

lesion vs. non-lesion

Pipelines

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RNAseq

FastQC

cutadapt

FeatureCounts

STAR

DEseq2

gProfiler

We used MonSda which :

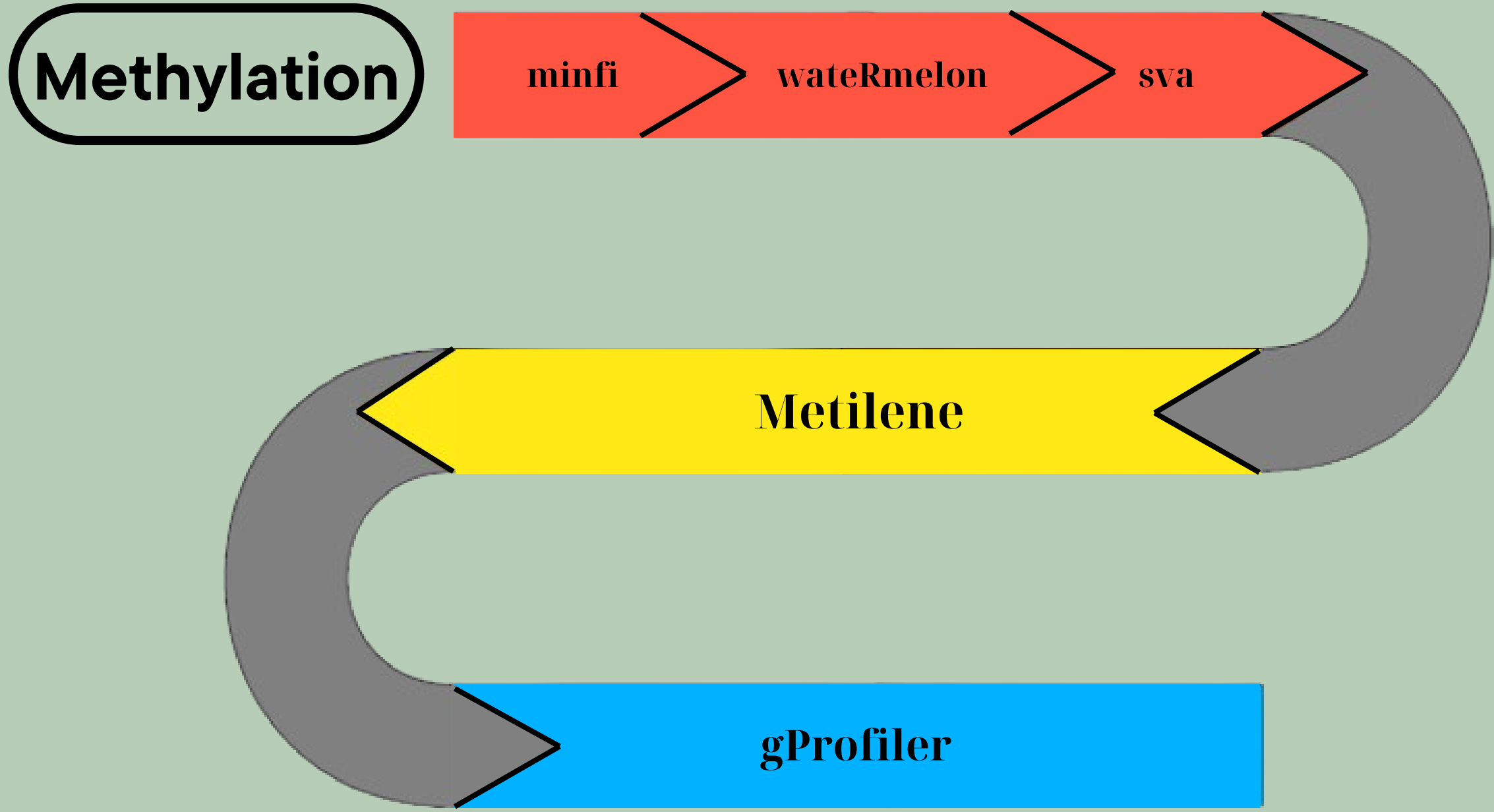
- Automates HTS analysis
- Data download and preprocessing
- Mapping and postprocessing/analysis
- Cut-off DESeq2: adj. p-value < 0.05 , $\log_2FC > 0.5$

Multiple Sclerosis

DataSet and Pipeline

Results

Pipelines



Methylation

The preprocessing steps were carried out by the authors of the original study.

We used metilene :

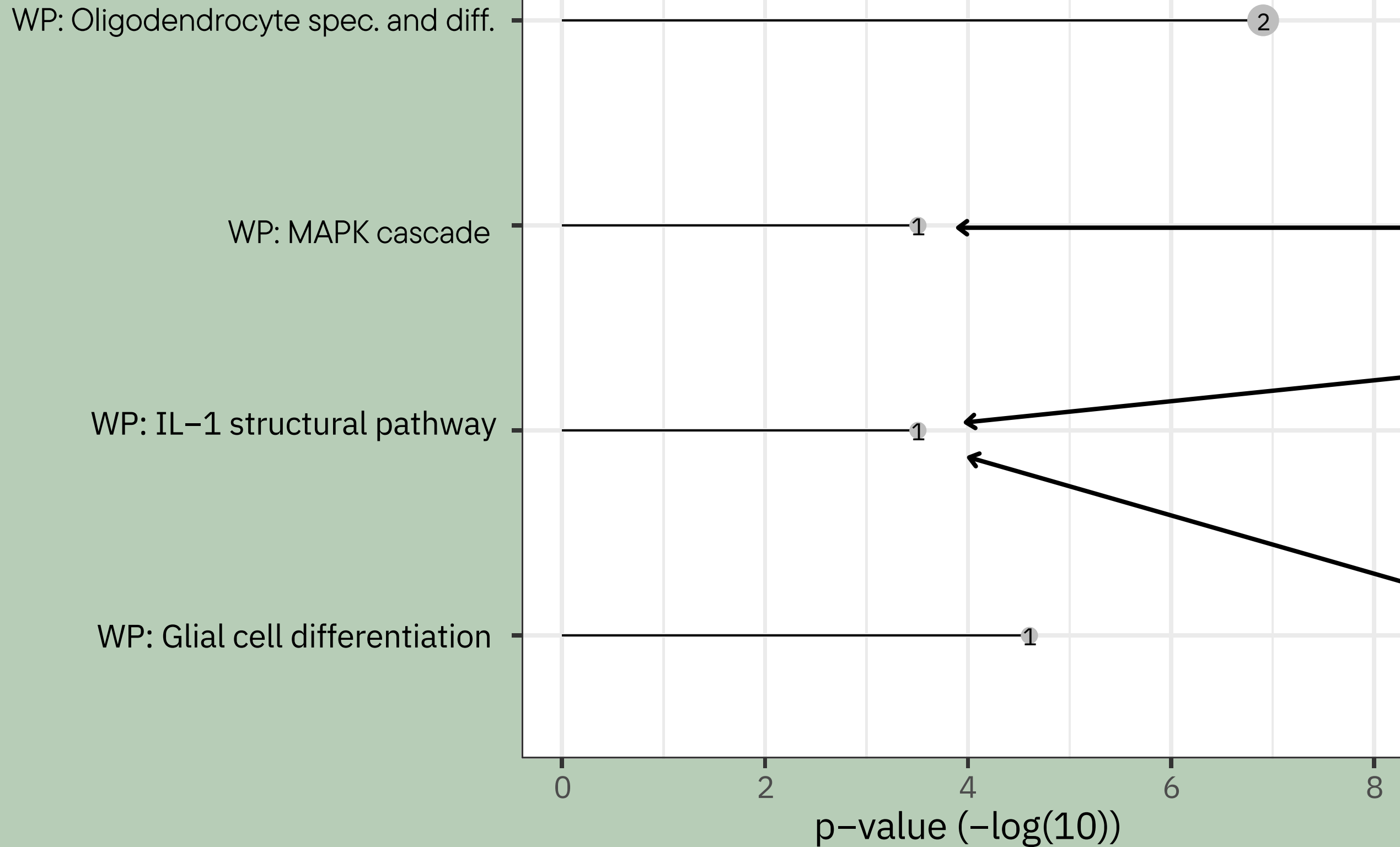
- tool for detection of differentially methylated regions (developed by the bioinf leipzig group).
- cut off: DMR methylation difference > 0.1

Sign. enriched pathways (selection)

III/ Results

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pathway



female vs. male : lesion Methylation

Promotes cell survival and inhibits apoptosis.

involved in the regulation of oligodendrocyte differentiation and remyelination

might also participate in reparative mechanisms.

Multiple Sclerosis

DataSet and Pipeline

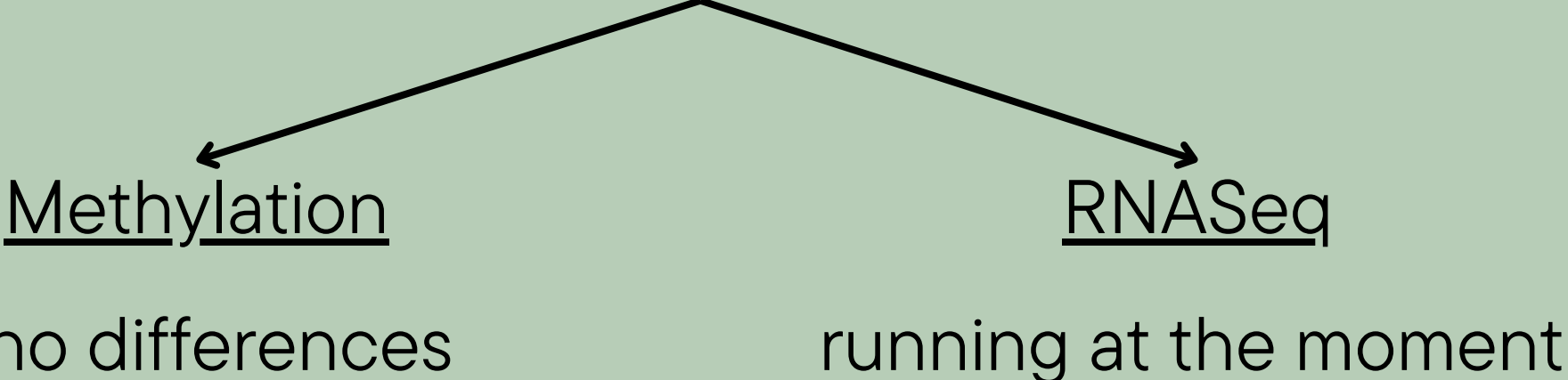
Results

**female vs. male - lesion
RNAseq**



4 genes differentially expressed:
IGKC, SEMA3B, LDB3, TYMSOS

**female vs. male - non
lesion**

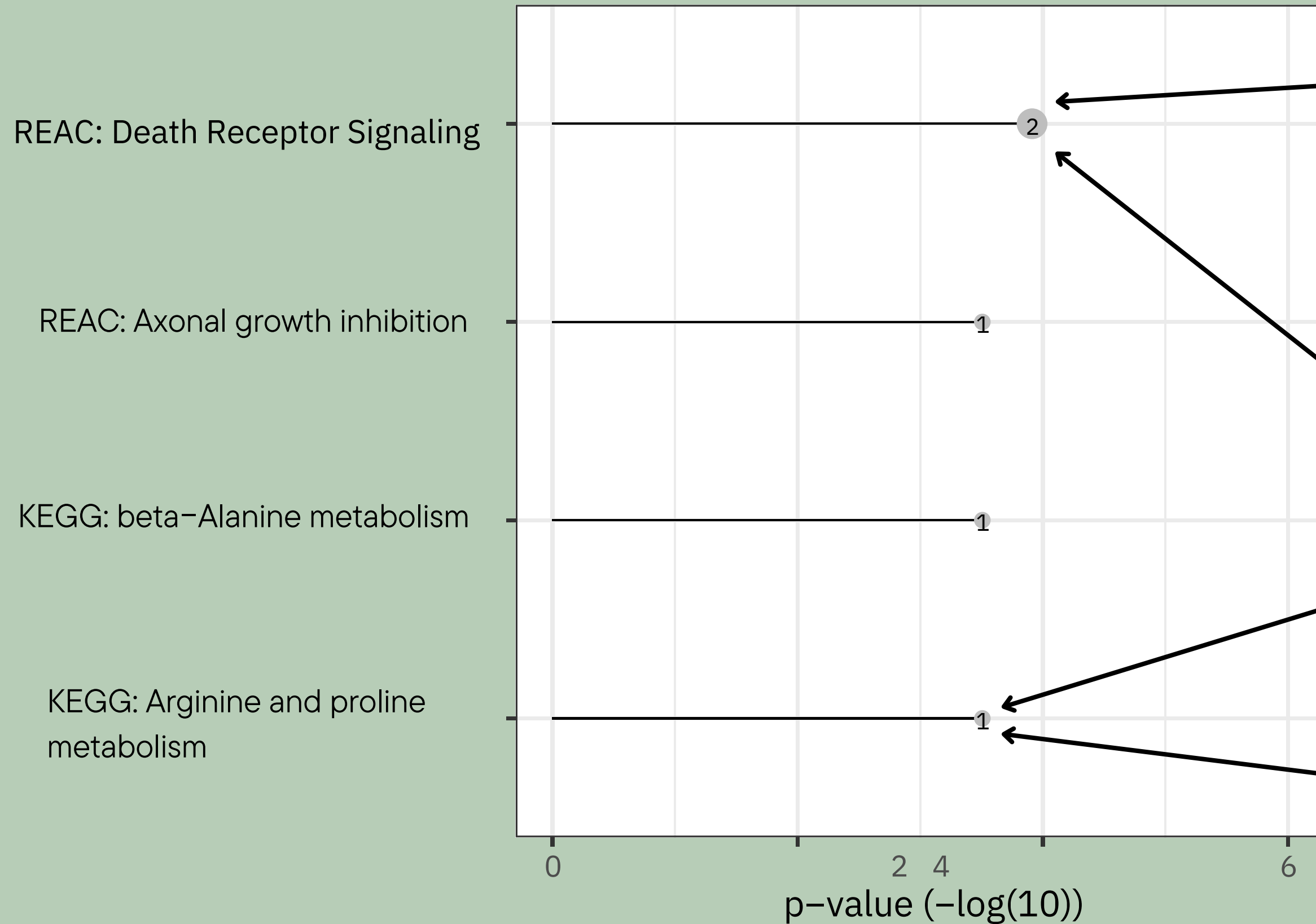


female lesion vs. non-lesion-Methylation

RNASeq -> No differences

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pathway



Activation leads to progressive damage to myelin and neurons in the central nervous system, contributing to MS progression.

Sex hormones such as estrogen have been shown to modulate TNF(tumor necrosis factor) signaling, influencing disease outcomes in a sex-specific manner.

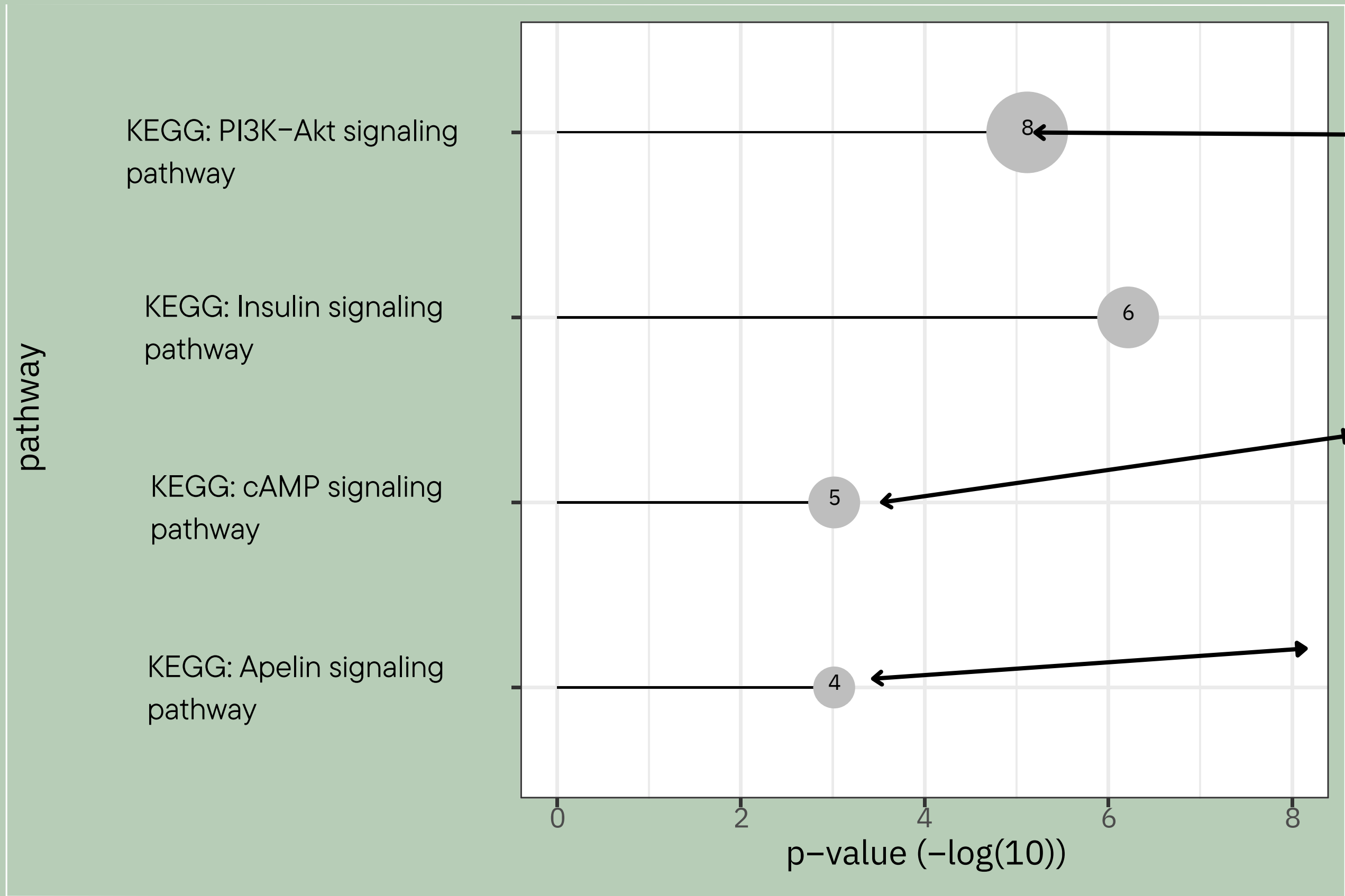
Dysregulation of arginine metabolism is linked to immune dysfunction and oxidative stress in MS.

Changes in proline levels are associated with neuroinflammation and oxidative stress.

Multiple Sclerosis

DataSet and Pipeline

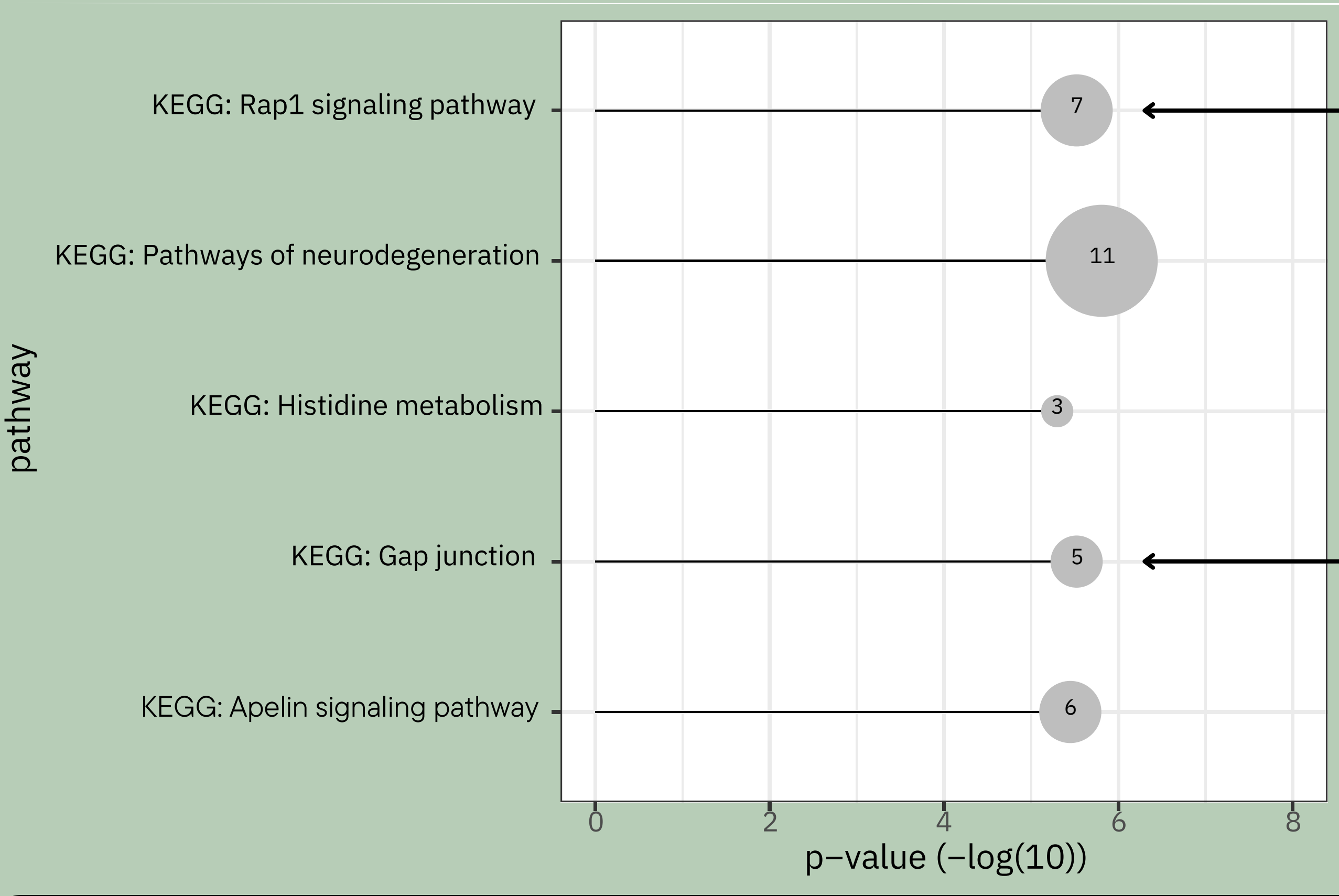
Results



Is positively regulated in active myelination and remyelination followed by neuronal damage.

High cAMP levels cause immunosuppression.

a peptide hormone most active form - Apelin-13(which can be used as a biomarker of oxidative stress)



protects the brain by keeping the blood-brain barrier strong

- stops immune cells from entering the central nervous system (CNS) and making neuroinflammation worse.

Dysfunction of gap junctions between oligodendrocytes impairs myelin repair mechanisms.

Summary

- 1/ Surprisingly only small differences in males vs. females.
- 2/ Mainly methylation and expression differences in males (lesion vs. non lesion).
- 3/ Could explain worse outcome of males with MS (and autoimmune diseases in general).

Acknowledgements



Stephan H. Bernhart
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Peter F. Stadler



Thank you for your attention!



III/ Significance of Including Sex as a Variable

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Scientists have often used only one sex (generally male) for experiments and applied the findings to both sexes, without solid grounds.

-> Leading to a lack of understanding of potential sex-based differences in disease susceptibility, progression, and treatment response.

-> development of more precise and personalized approaches to diagnosis, treatment, and prevention of diseases, ultimately improving healthcare outcomes for both sexes.

Multiple Sclerosis

DataSet and Pipeline

Results



- limited access to gender data in datasets → focus on sex disparities
- case number of intersex persons in most studies very low or exclusion
→ focus on females and males at the moment