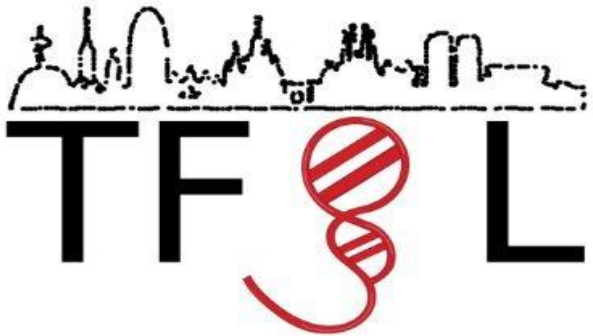
The landscape of expression and alternative splicing variation across human traits

Raquel Garcia-Perez
Juan de la Cierva postdoctoral researcher
Transcriptomics and functional genomics lab
Barcelona Supercomputing Center

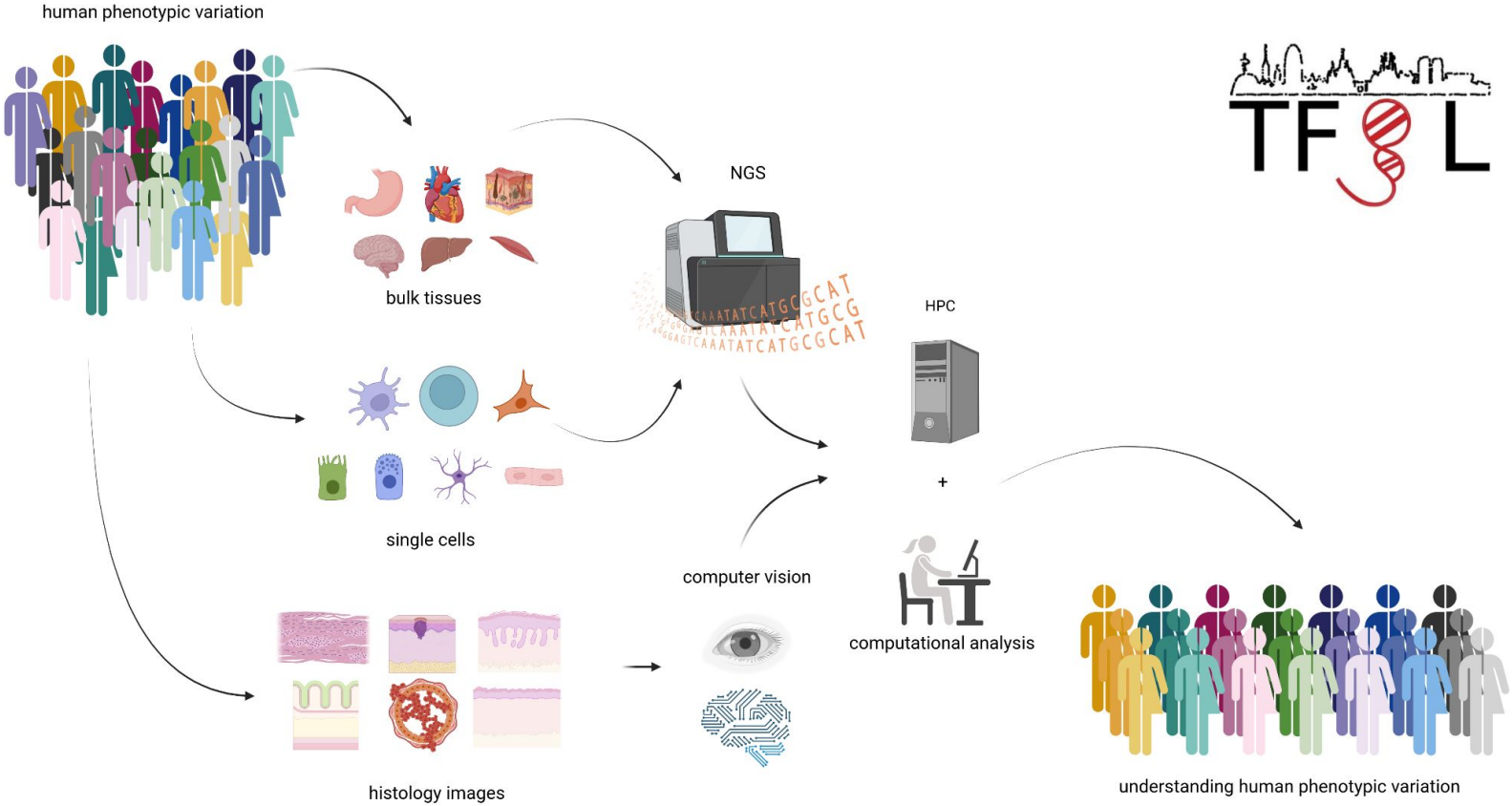


human phenotypic variation

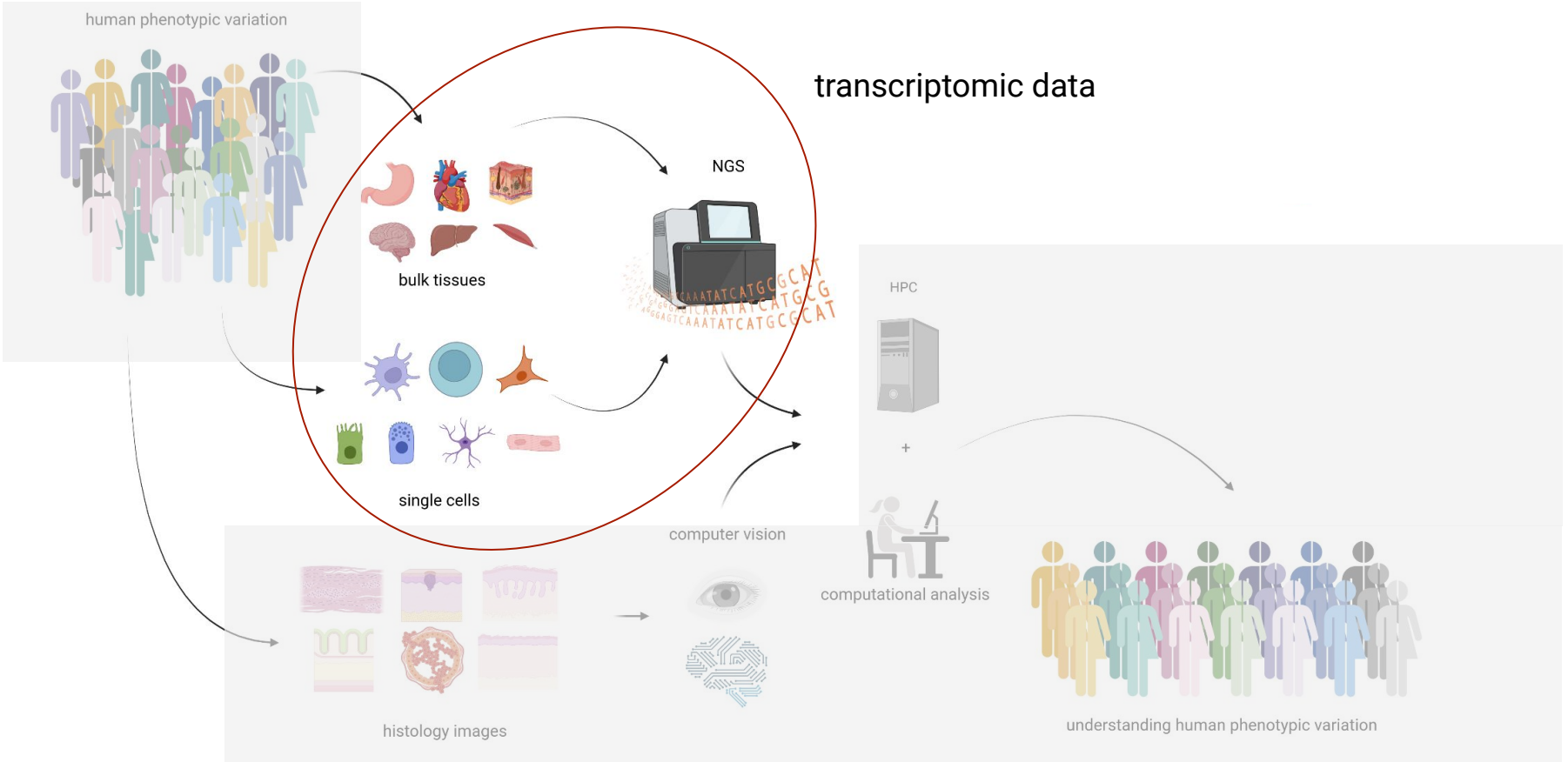
?

understanding human phenotypic variation

Created with BioRender.com

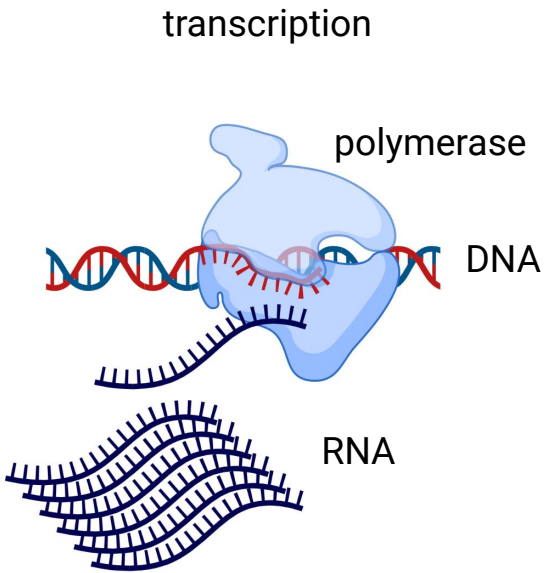


Created with BioRender.com



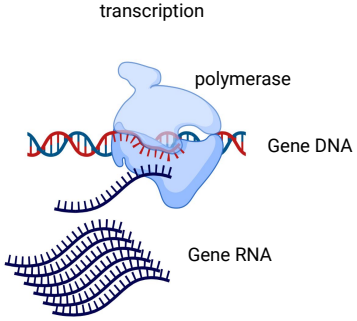
Created with BioRender.com

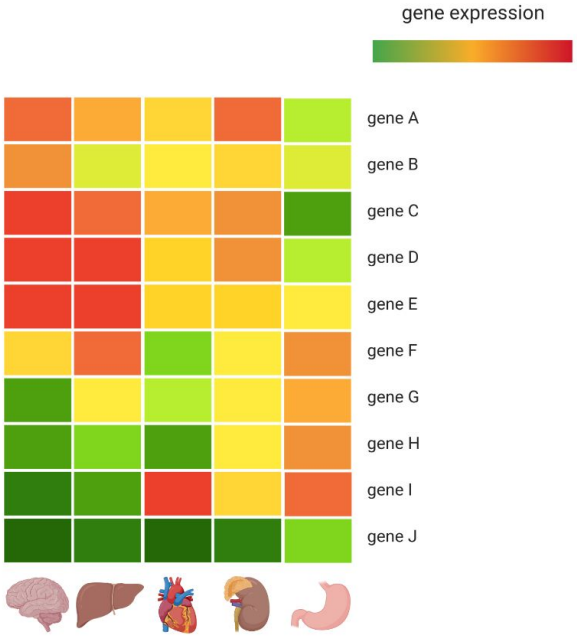
From **gene expression** to human phenotypes



Created with BioRender.com

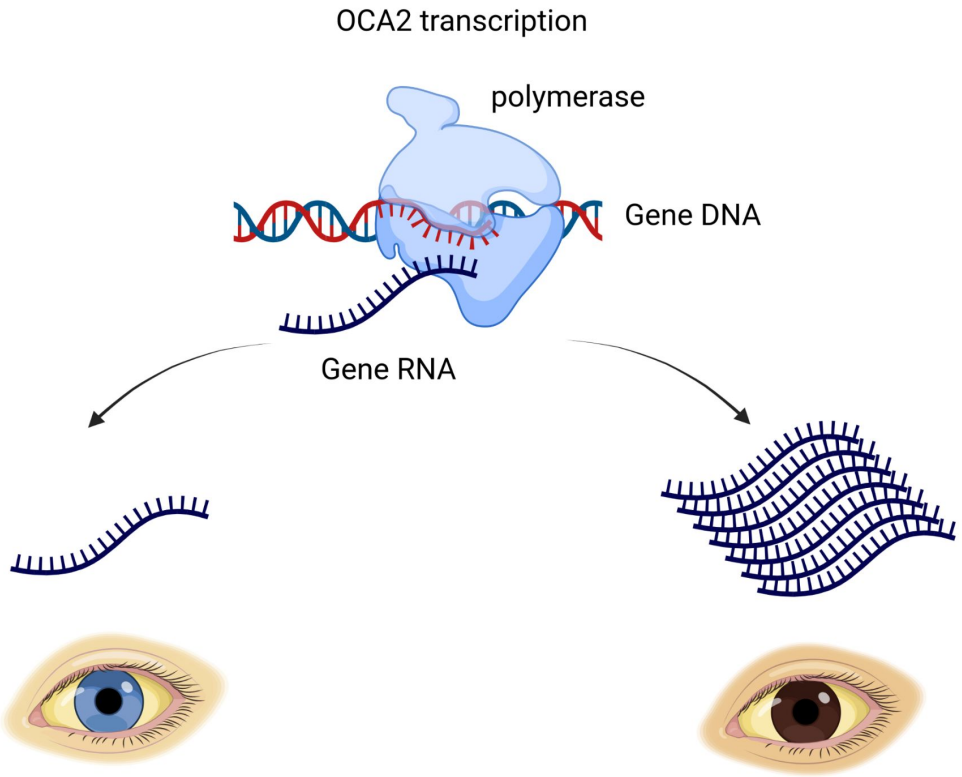
From **gene expression** to human phenotypes





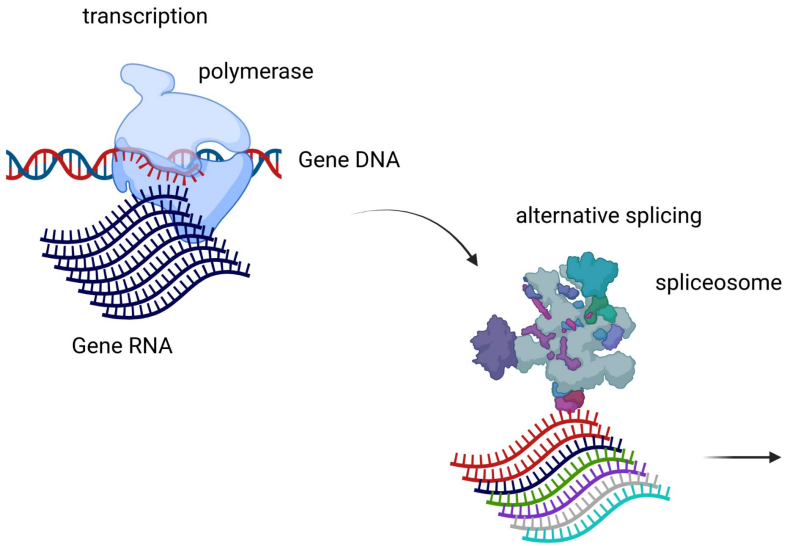
Created with BioRender.com

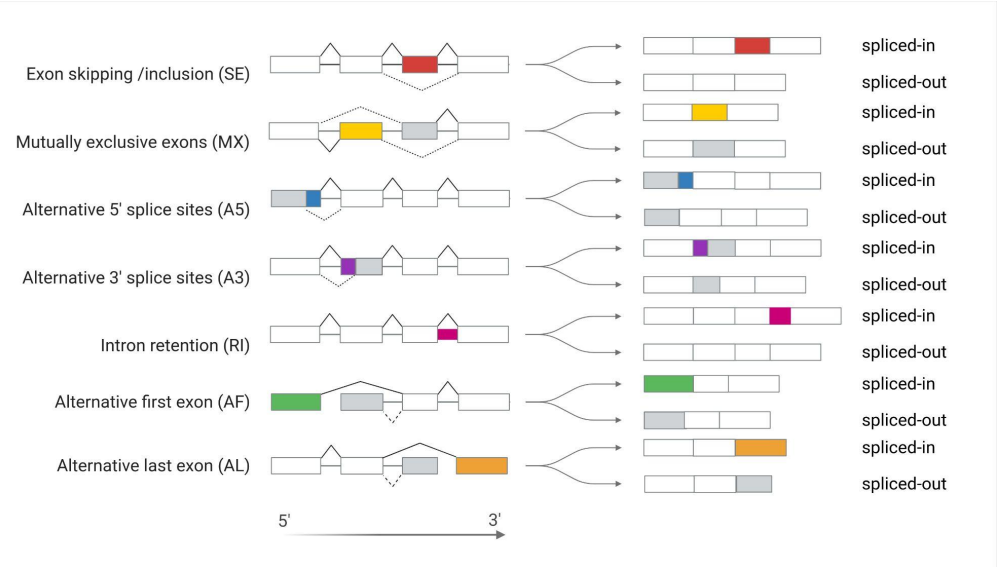
From **gene expression** to human phenotypes



Created with BioRender.com

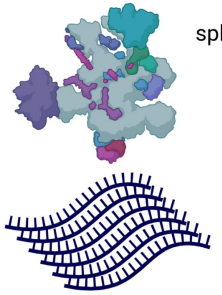
From **alternative splicing** to human phenotypes

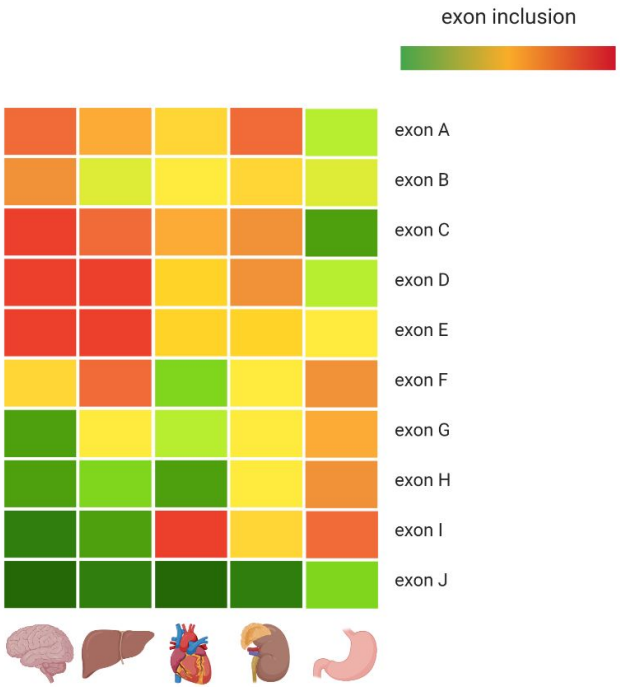




Created with BioRender.com

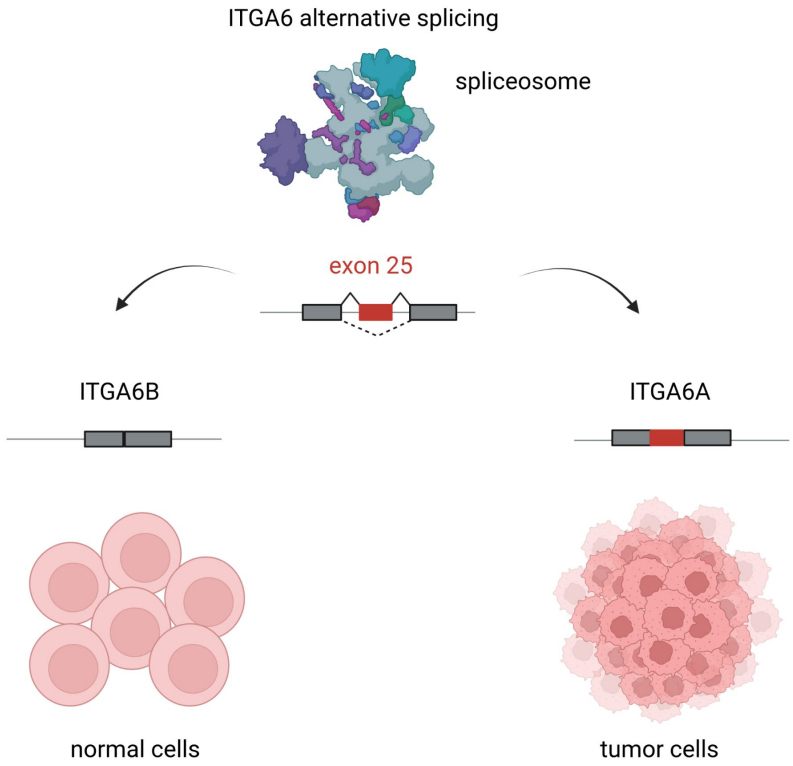
From **alternative splicing** to human phenotypes



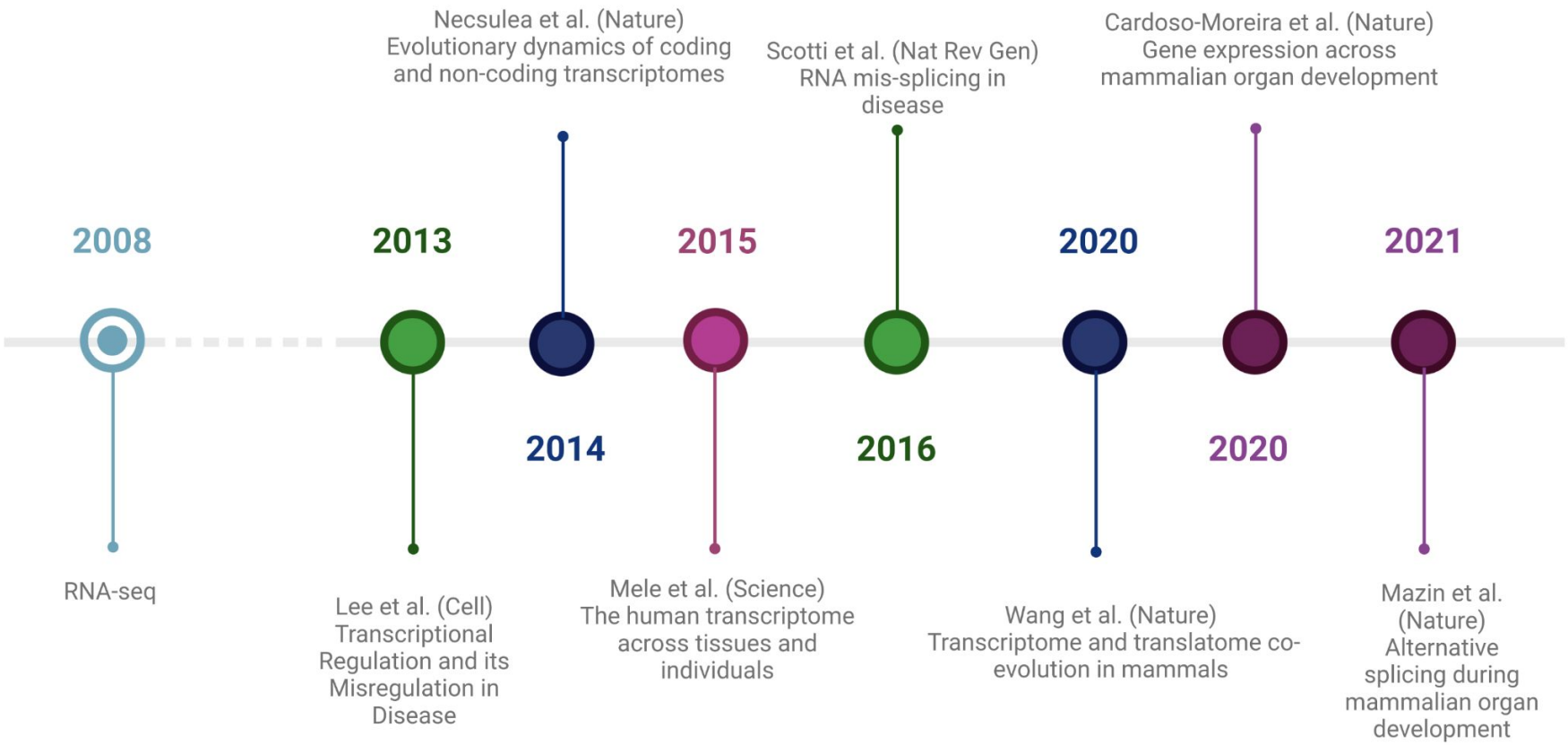


Created with BioRender.com

From **alternative splicing** to human phenotypes



Created with BioRender.com



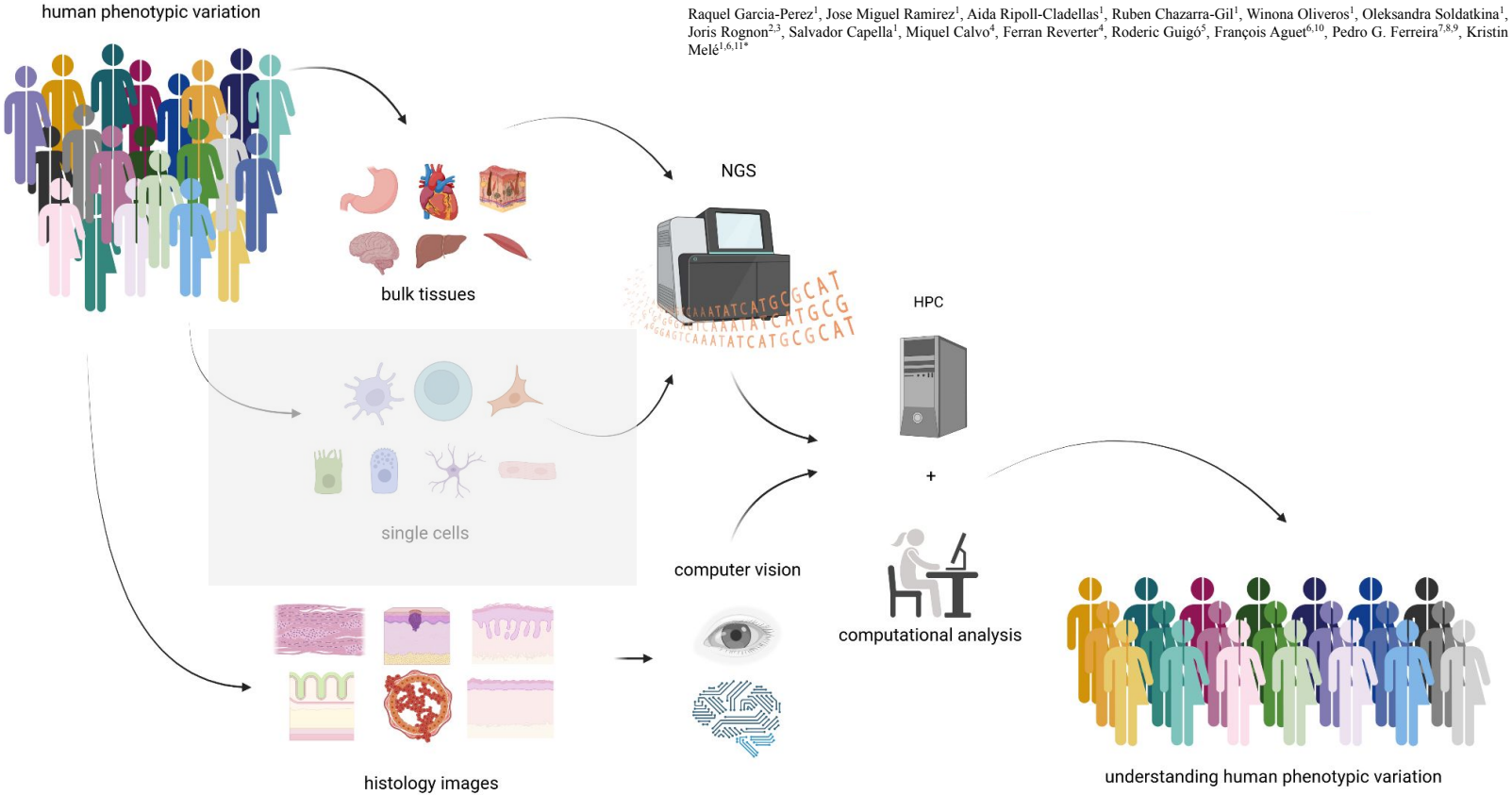
Created with BioRender.com

Lack of **multi-tissue** and **multi-trait** transcriptomic studies

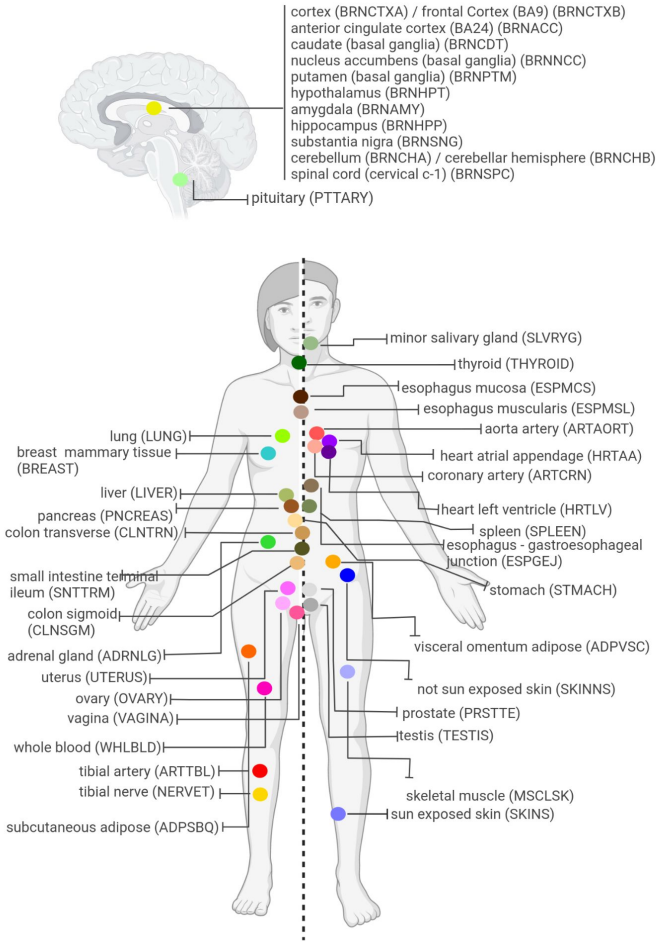
- Transcriptomic studies limited to one or few tissues
- Transcriptomic studies limited to a single trait
- Transcriptomic studies limited to gene expression or alternative splicing

The landscape of expression and alternative splicing variation across human traits (under review)

Raquel Garcia-Perez[1], Jose Miguel Ramirez[1], Aida Ripoll-Cladellas[1], Ruben Chazarra-Gil[1], Winona Oliveros[1], Oleksandra Soldatkina[1], Mattia Bosio[1], Paul Joris Rognon[2,3], Salvador Capella[1], Miquel Calvo[4], Ferran Reverter[4], Roderic Guigó[5], François Aguet[6,10], Pedro G. Ferreira[7,8,9], Kristin G. Ardlie[6] & Marta Melé[1,6,11*]



Created with BioRender.com



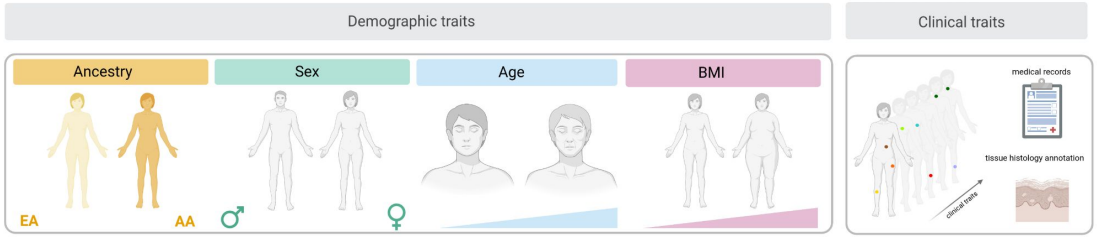
Created with BioRender.com

The landscape of expression and alternative splicing variation across human traits (under review)

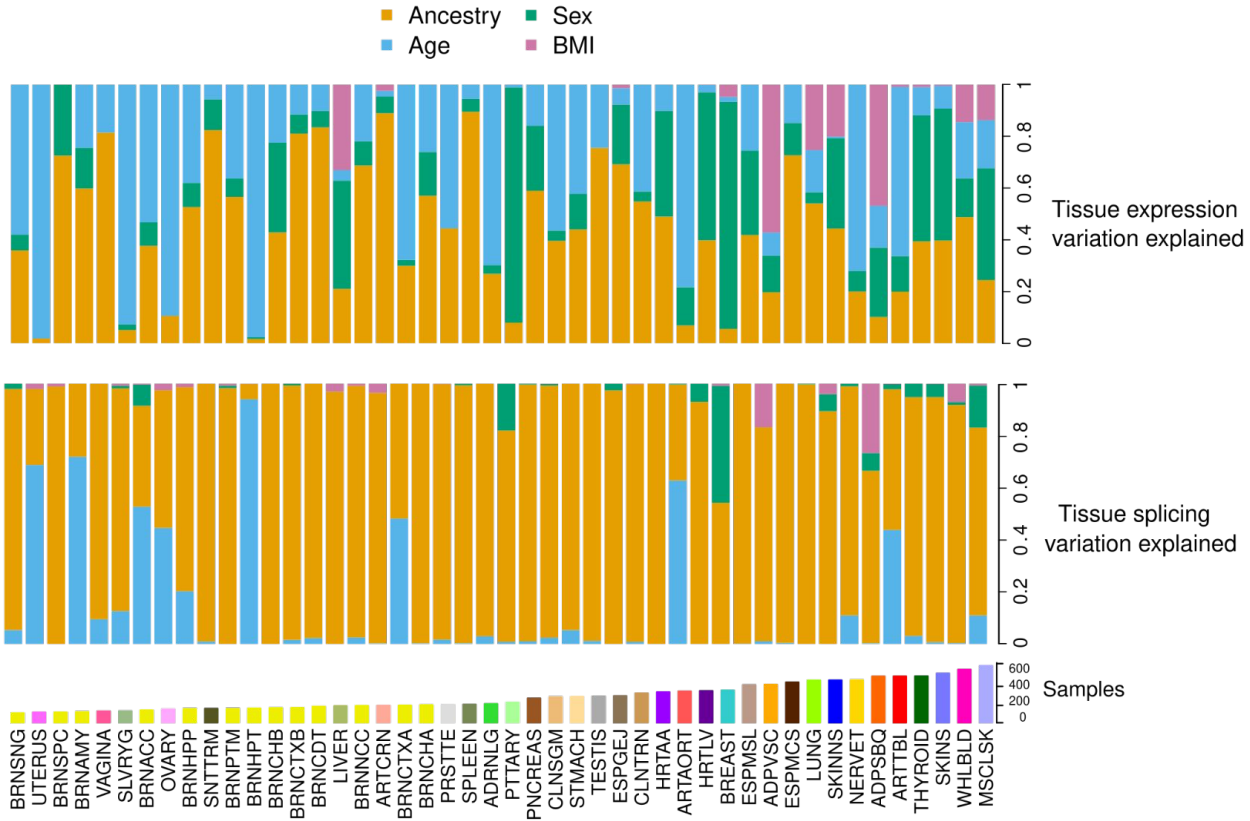
Raquel Garcia-Perez[1], Jose Miguel Ramirez[1], Aida Ripoll-Cladellas[1], Ruben Chazarra-Gil[1], Winona Oliveros[1], Oleksandra Soldatkina[1], Mattia Bosio[1], Paul Joris Rognon[2,3], Salvador Capella[1], Miquel Calvo[4], Ferran Reverter[4], Roderic Guigó[5], François Aguet[6,10], Pedro G. Ferreira[7,8,9], Kristin G. Ardlie[6] & Marta Melé[1,6,11*]

GTEx v8 data

RNA-seq, WGS and histology images	46 tissues 781 individuals	22,967 genes 62,269 splicing events

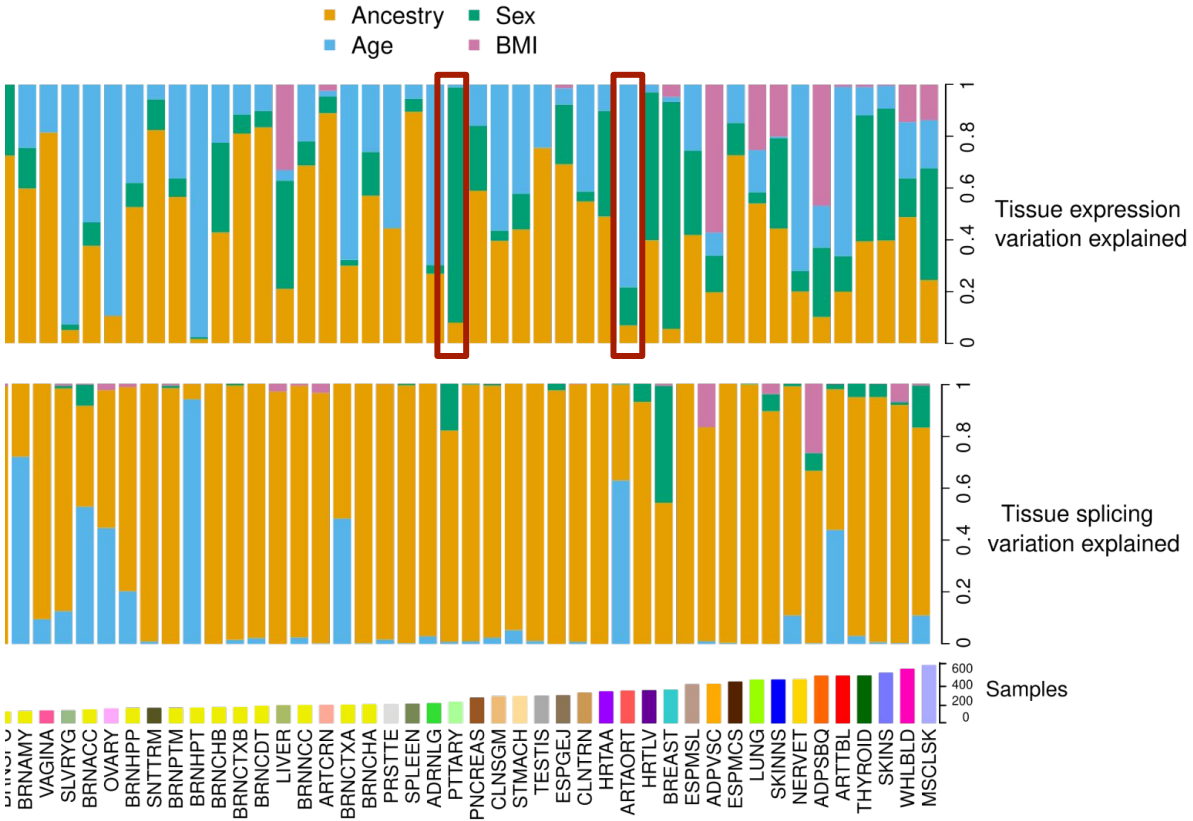


Tissue-specific contribution of human traits to gene expression variation



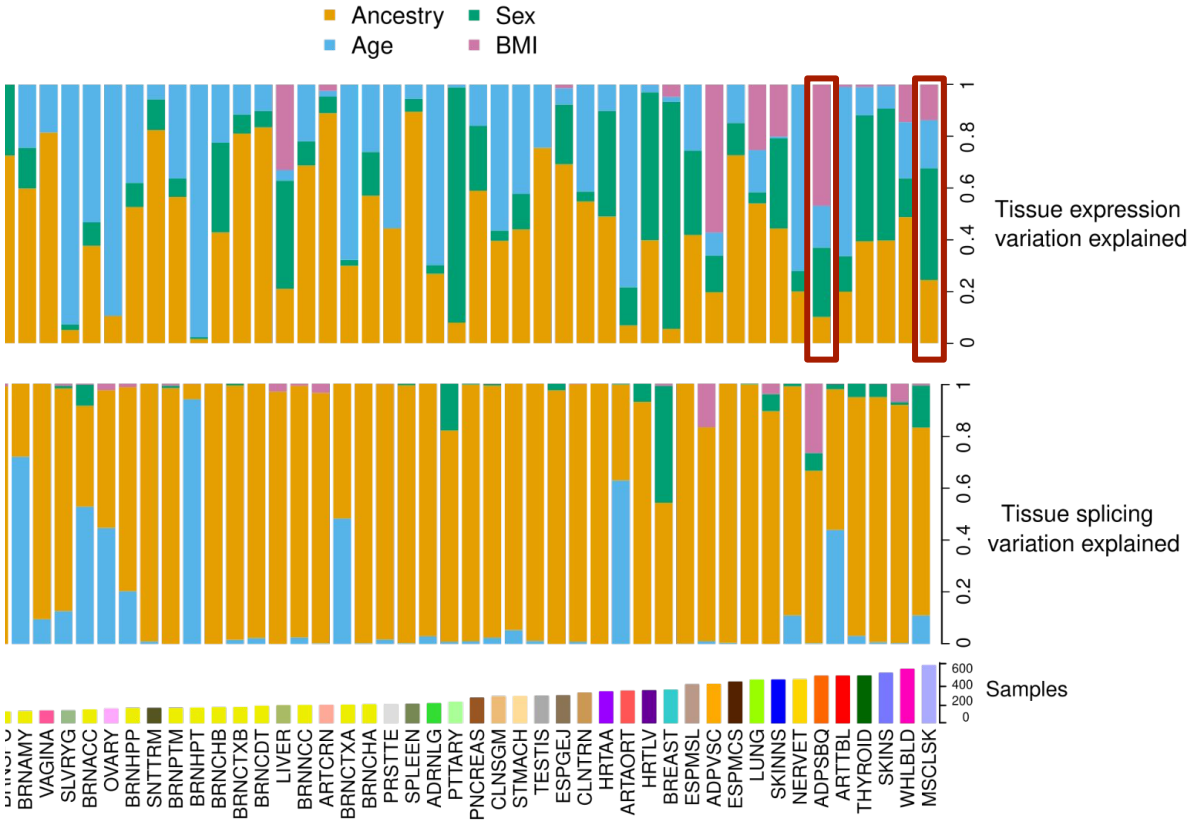
Garcia-Perez et al.

Tissue-specific contribution of human traits to gene expression variation



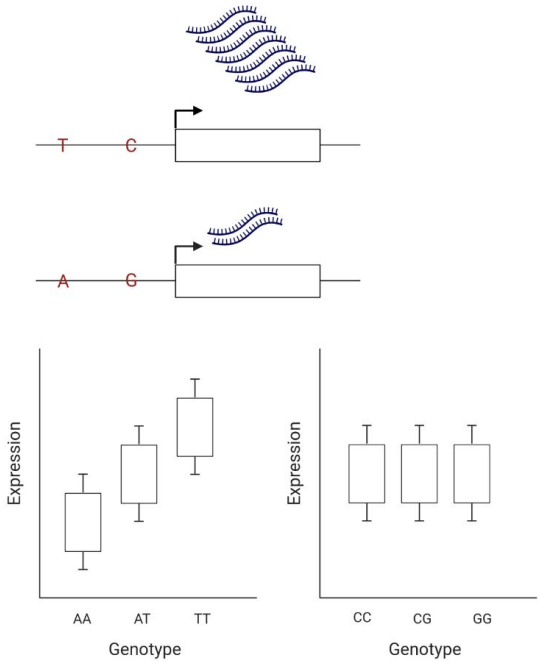
Garcia-Perez et al.

Tissue-specific contribution of human traits to gene expression variation

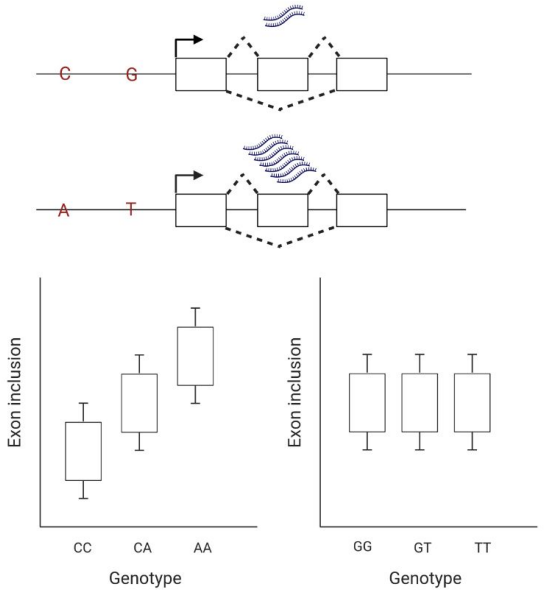


Garcia-Perez et al.

Gene expression and alternative splicing differences between human populations are under **genetic control**



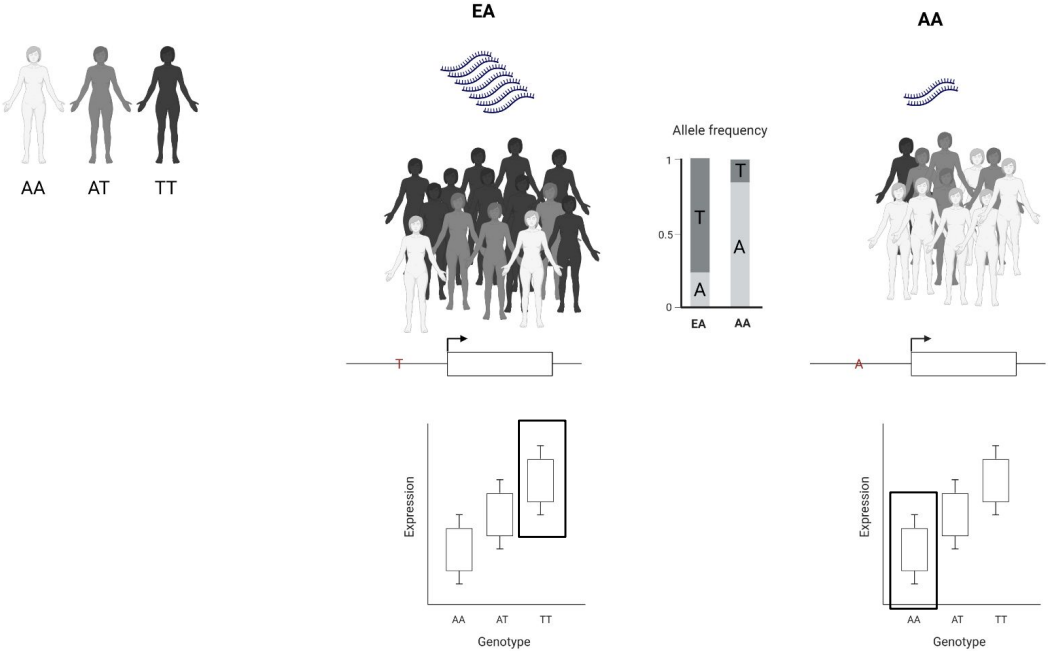
regulatory variation is measured as expression quantitative trait loci (eQTL)



regulatory variation is measured as splicing quantitative trait loci (sQTL)

Created with BioRender.com

Gene expression and alternative splicing differences between human populations are under **genetic control**



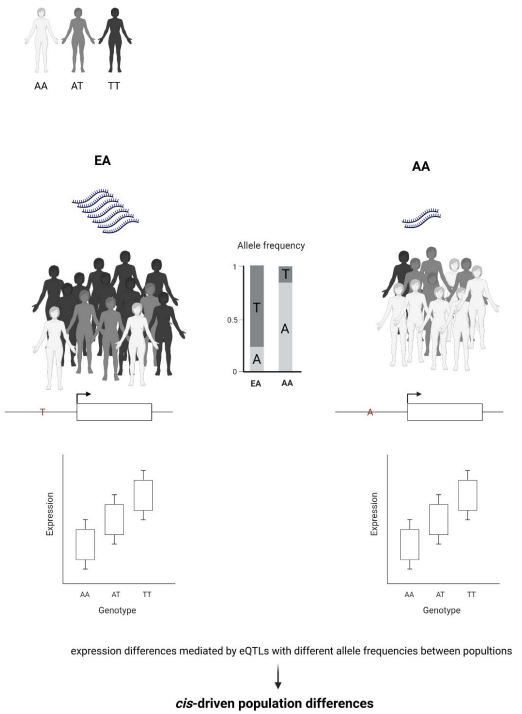
expression differences mediated by eQTLs with different allele frequencies between popultions

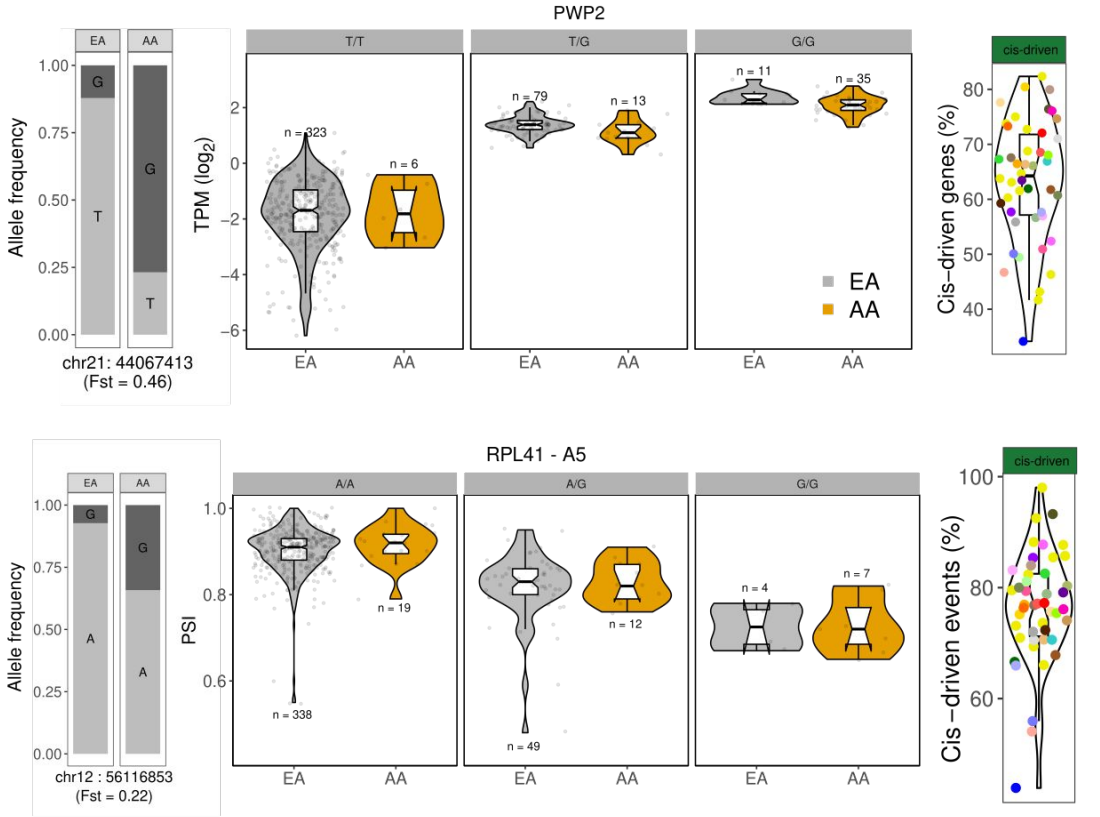
↓

***cis*-driven population differences**

Created with BioRender.com

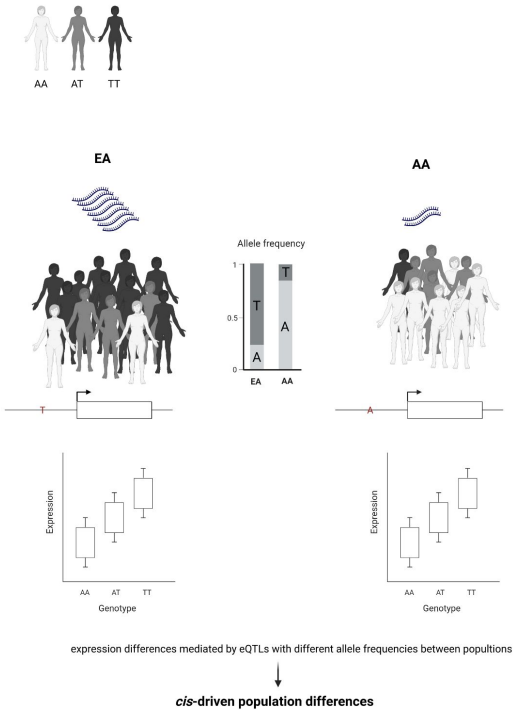
Gene expression and alternative splicing differences between human populations are under **genetic control**

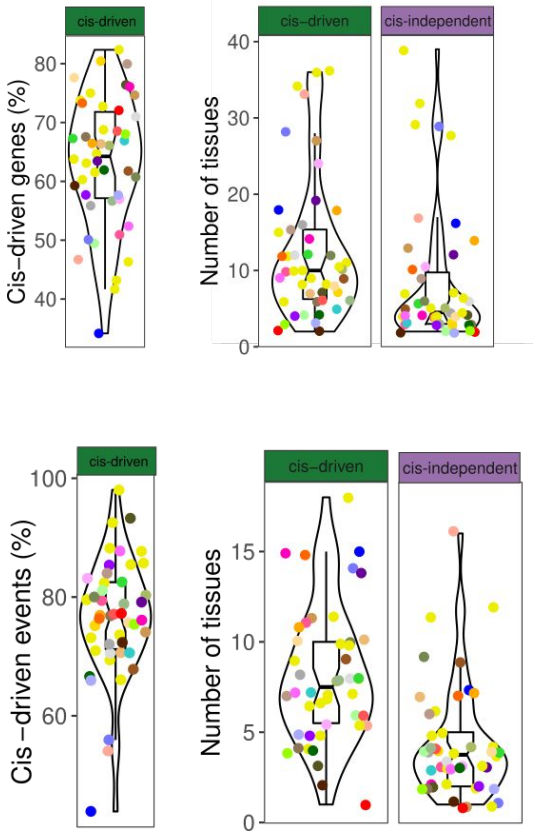




Garcia-Perez et al.

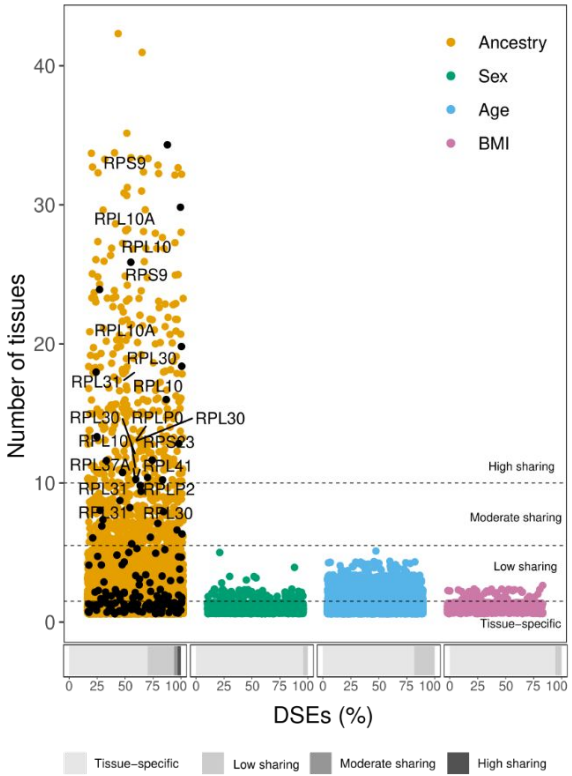
Gene expression and alternative splicing differences between human populations are under **genetic control**





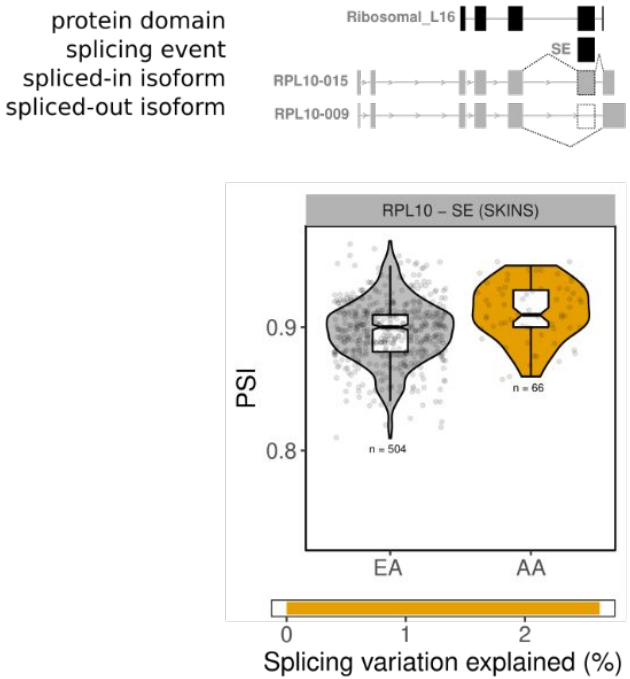
Garcia-Perez et al.

Ribosomal proteins are differentially spliced between populations across tissues



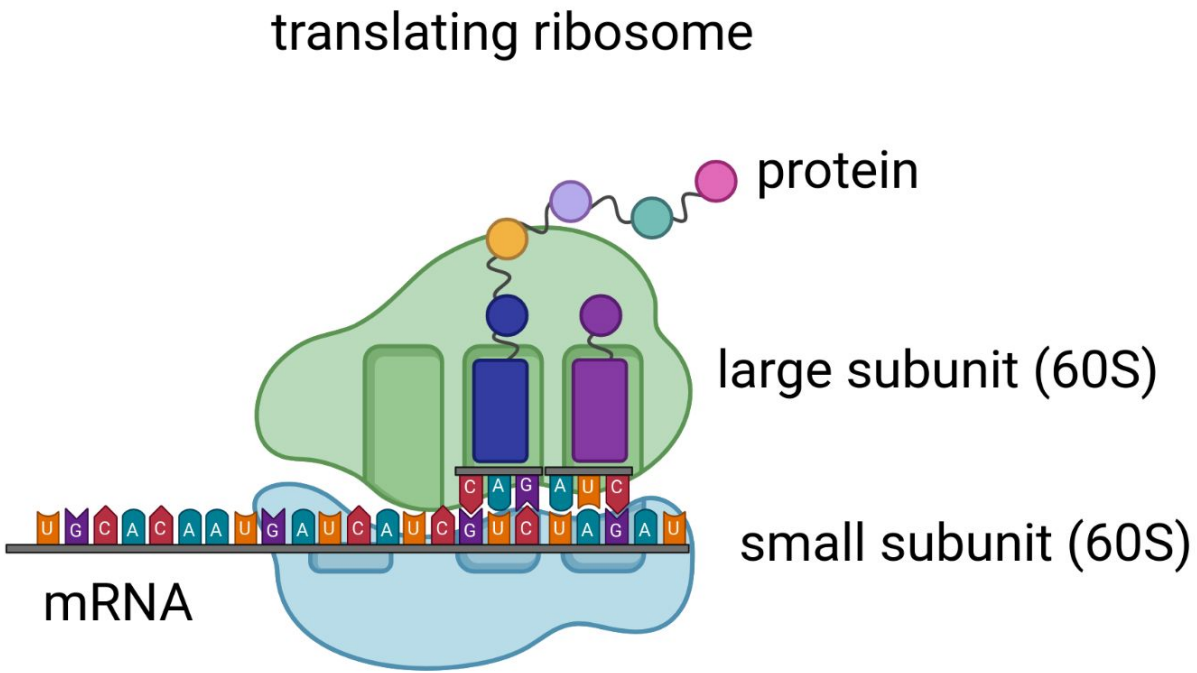
Garcia-Perez et al.

Ribosomal proteins are differentially spliced between populations across tissues



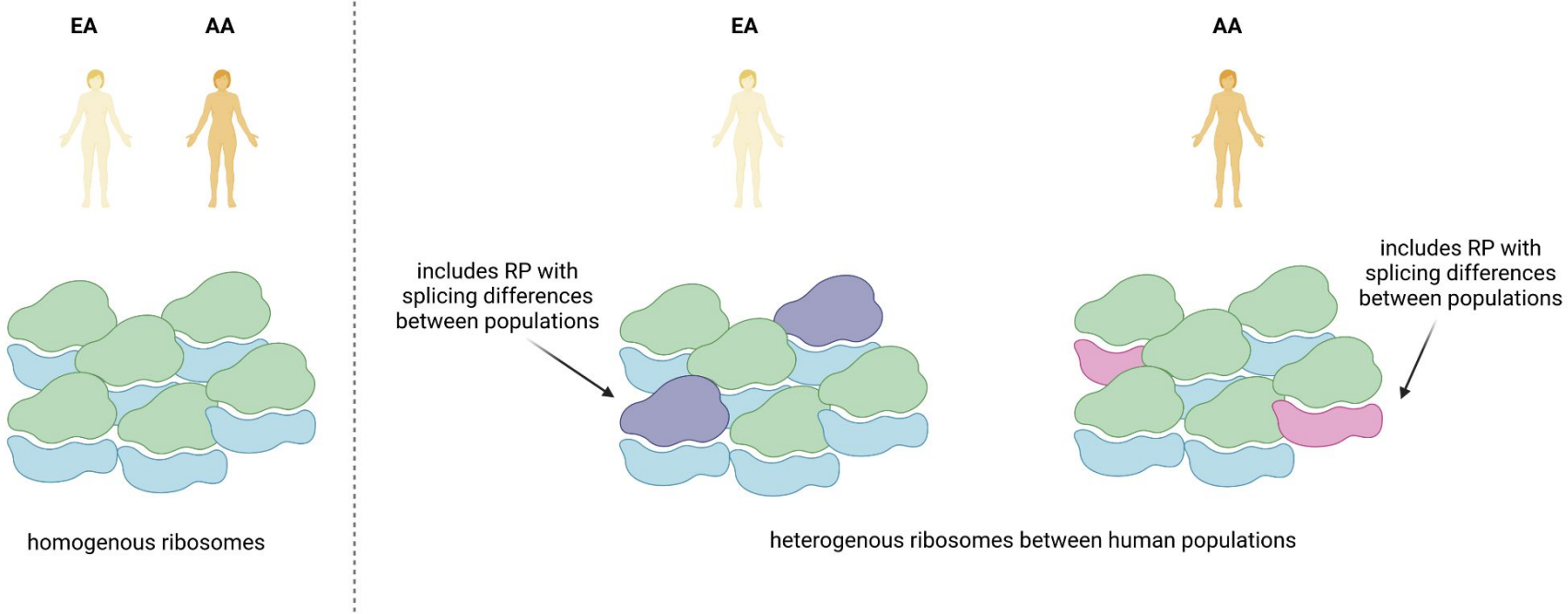
Garcia-Perez et al.

Ribosomal proteins are differentially spliced between populations across tissues



Created with BioRender.com

Ribosomal proteins are differentially spliced between populations across tissues

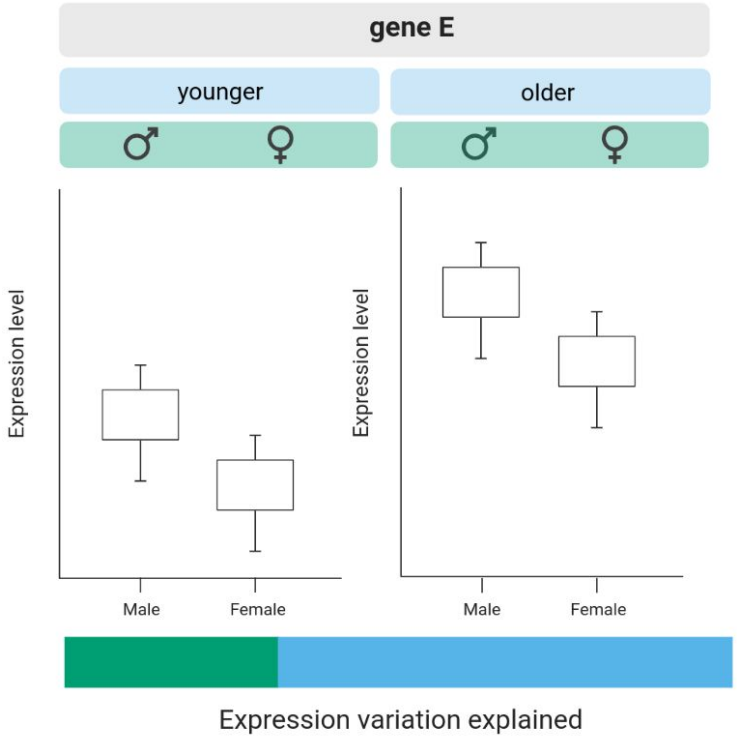


Created with BioRender.com

Lack of **multi-tissue** and **multi-trait** transcriptomic studies

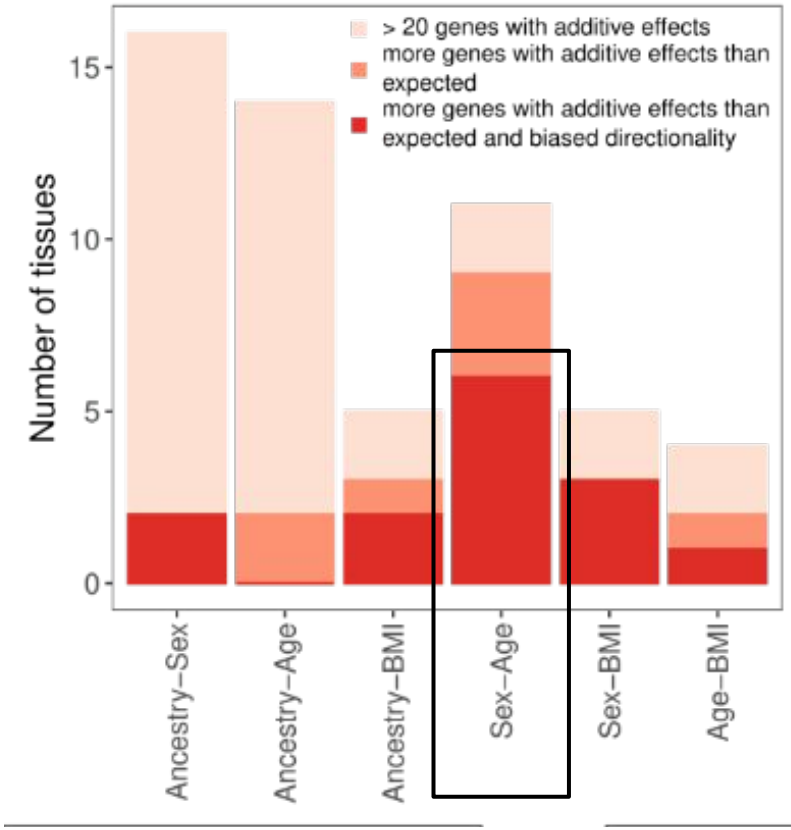
- Transcriptomic studies limited to one or few tissues
- Transcriptomic studies limited to a **single trait**
- Transcriptomic studies limited to gene expression or alternative splicing

Multiple traits have **additive effects** on gene expression levels



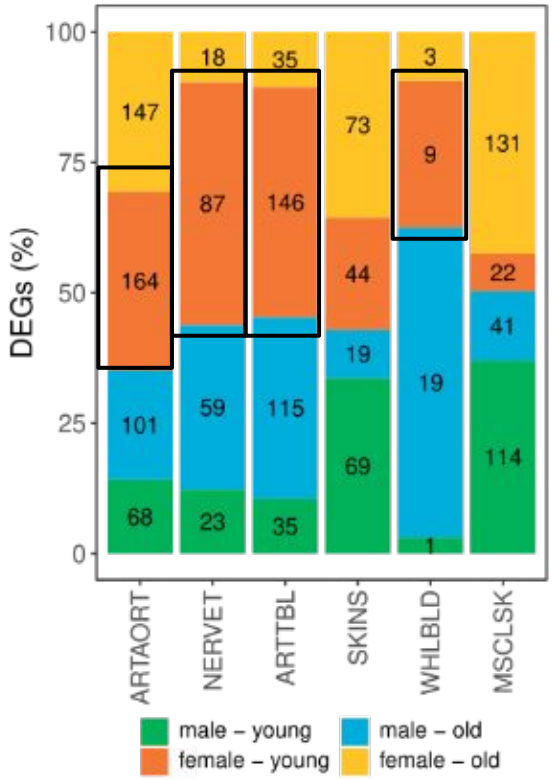
Created with BioRender.com

Multiple traits have **additive effects** on gene expression levels



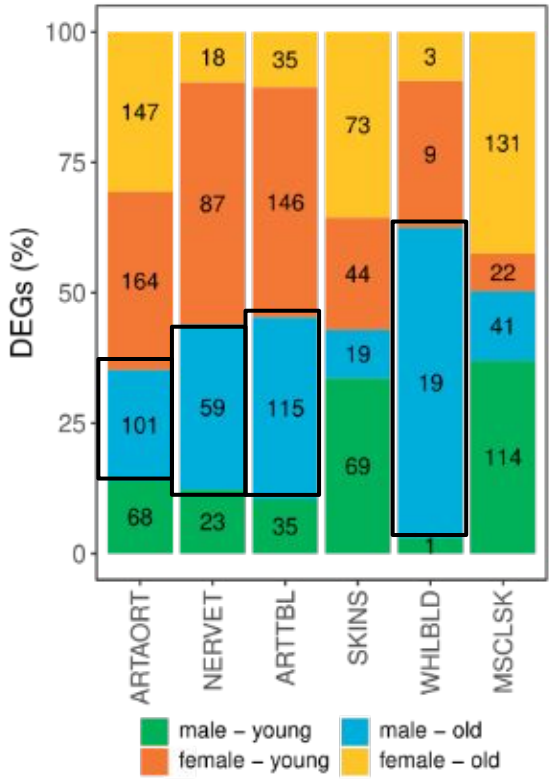
Garcia-Perez et al.

Additive effects have biased directionalities



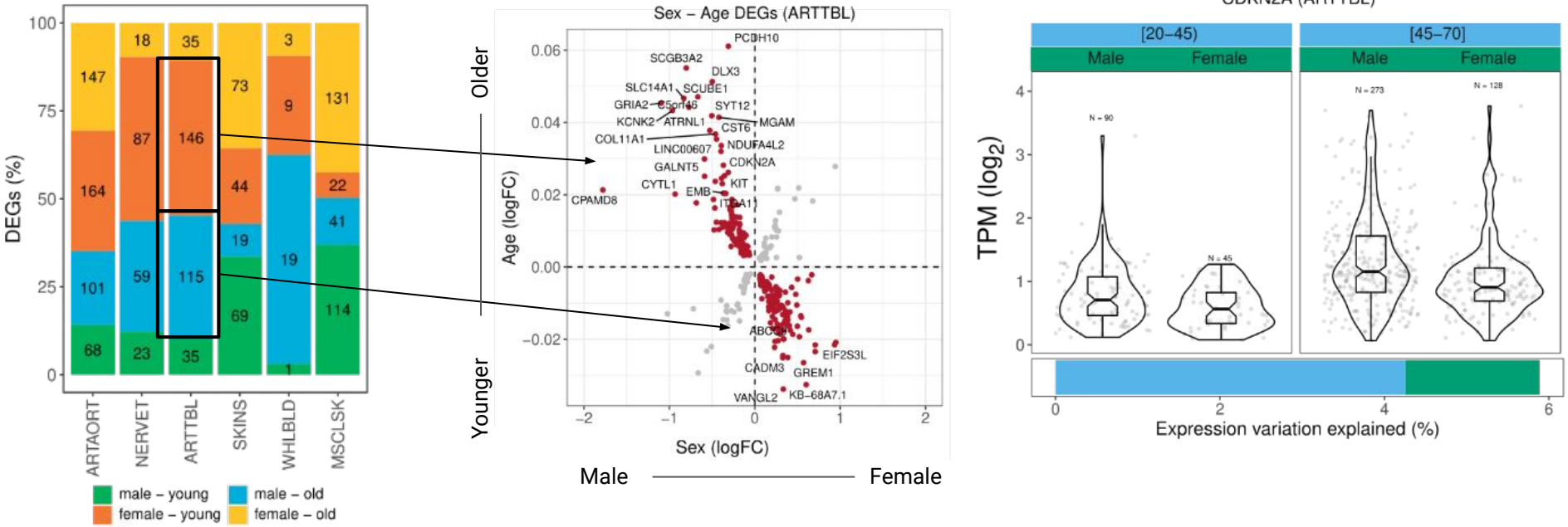
Garcia-Perez et al.

Additive effects have biased directionalities



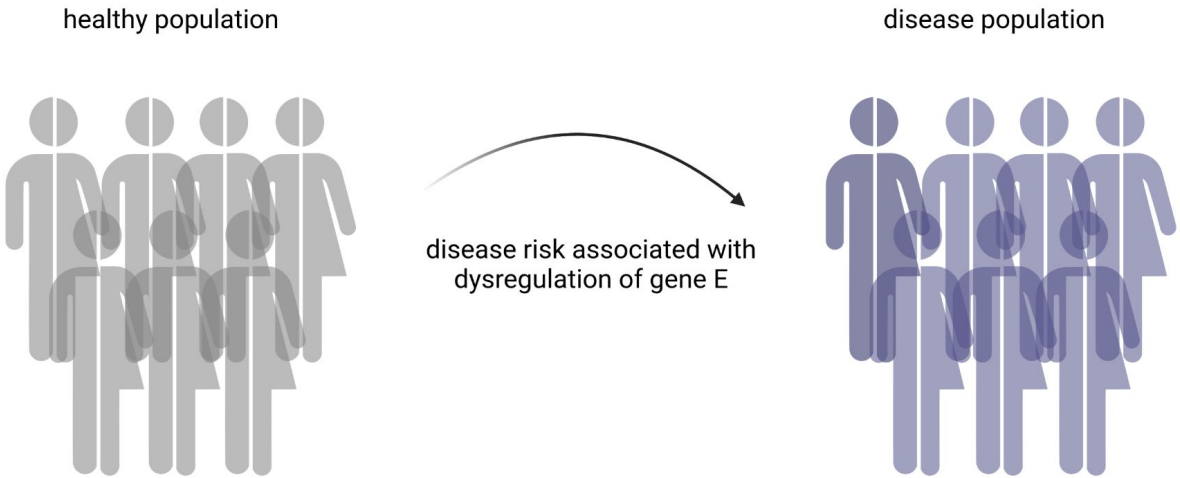
Garcia-Perez et al.

Additive effects have biased directionalities

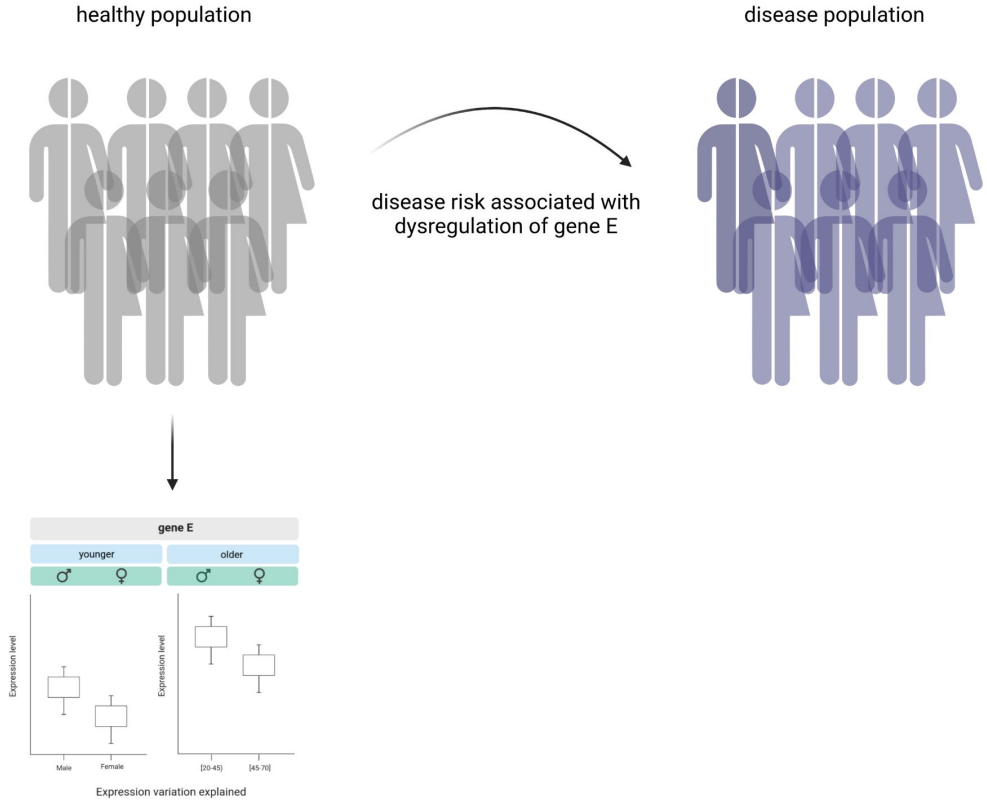


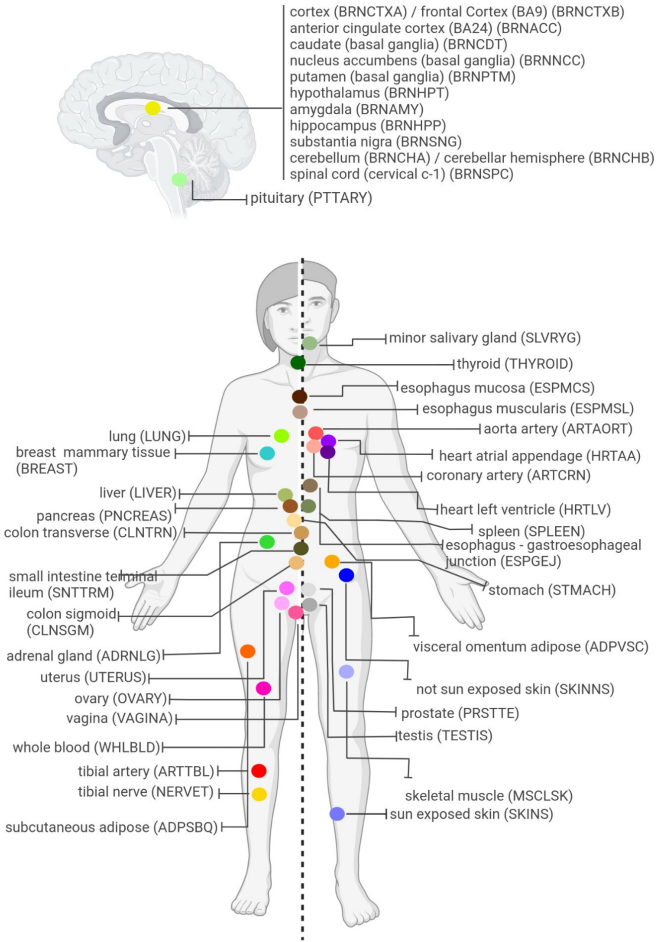
Garcia-Perez et al.

Additive effects and precision medicine



Additive effects and precision medicine





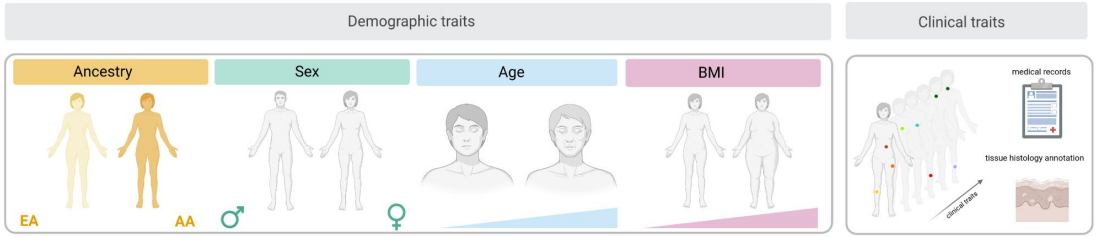
Created with BioRender.com

The landscape of expression and alternative splicing variation across human traits (under review)

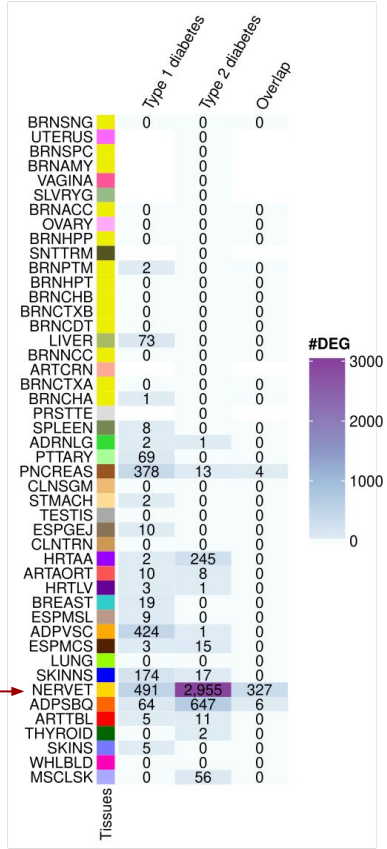
Raquel Garcia-Perez[1], Jose Miguel Ramirez[1], Aida Ripoll-Cladellas[1], Ruben Chazarra-Gil[1], Winona Oliveros[1], Oleksandra Soldatkina[1], Mattia Bosio[1], Paul Joris Rognon[2,3], Salvador Capella[1], Miquel Calvo[4], Ferran Reverter[4], Roderic Guigó[5], François Aguet[6,10], Pedro G. Ferreira[7,8,9], Kristin G. Ardlie[6] & Marta Melé[1,6,11*]

GTEx v8 data

RNA-seq, WGS and histology images	46 tissues 781 individuals	22,967 genes 62,269 splicing events

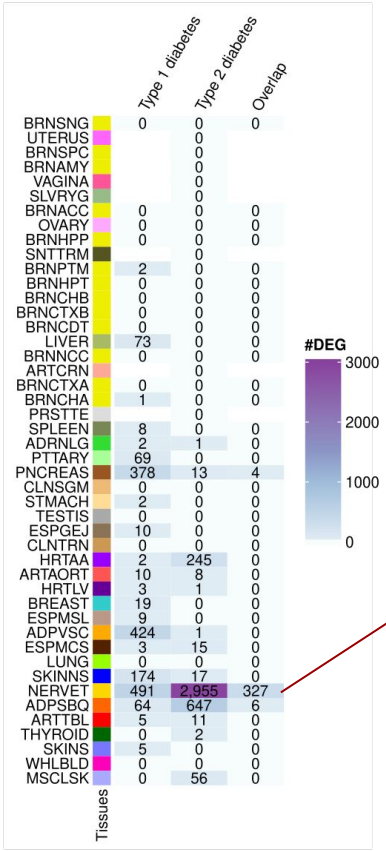


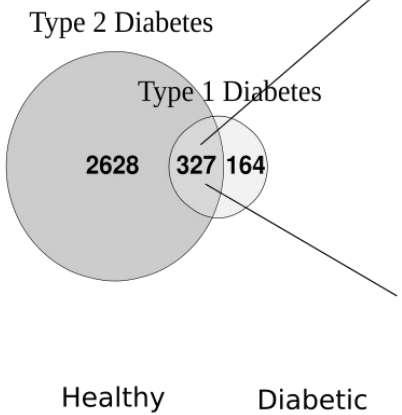
The **tibial nerve** is the tissue most affected by type 1 and 2 **diabetes**

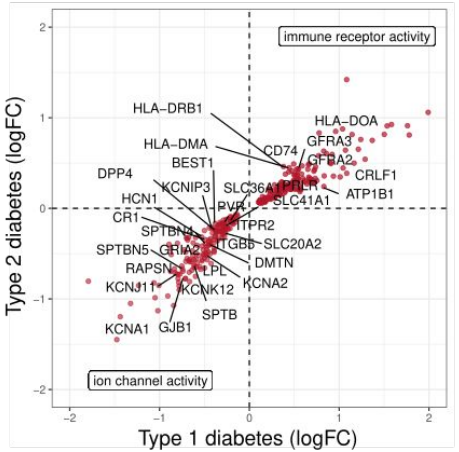


Garcia-Perez et al.

The **tibial nerve** is the tissue most affected by type 1 and 2 **diabetes**

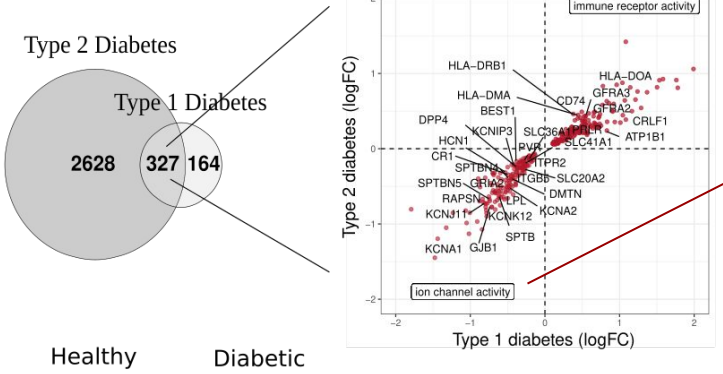


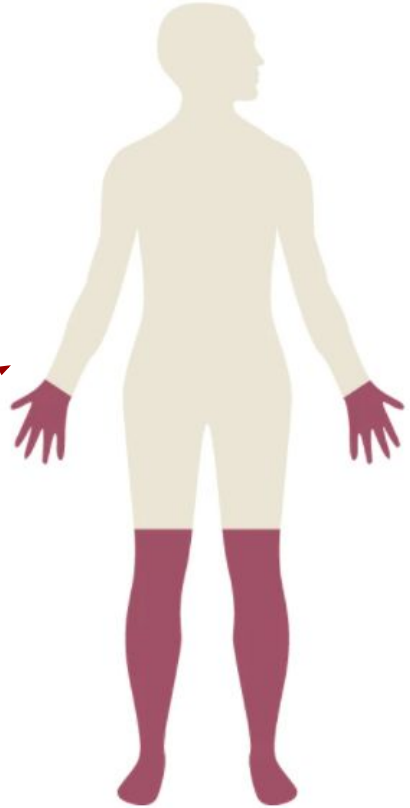




Garcia-Perez et al.

The **tibial nerve** is the tissue most affected by type 1 and 2 **diabetes**





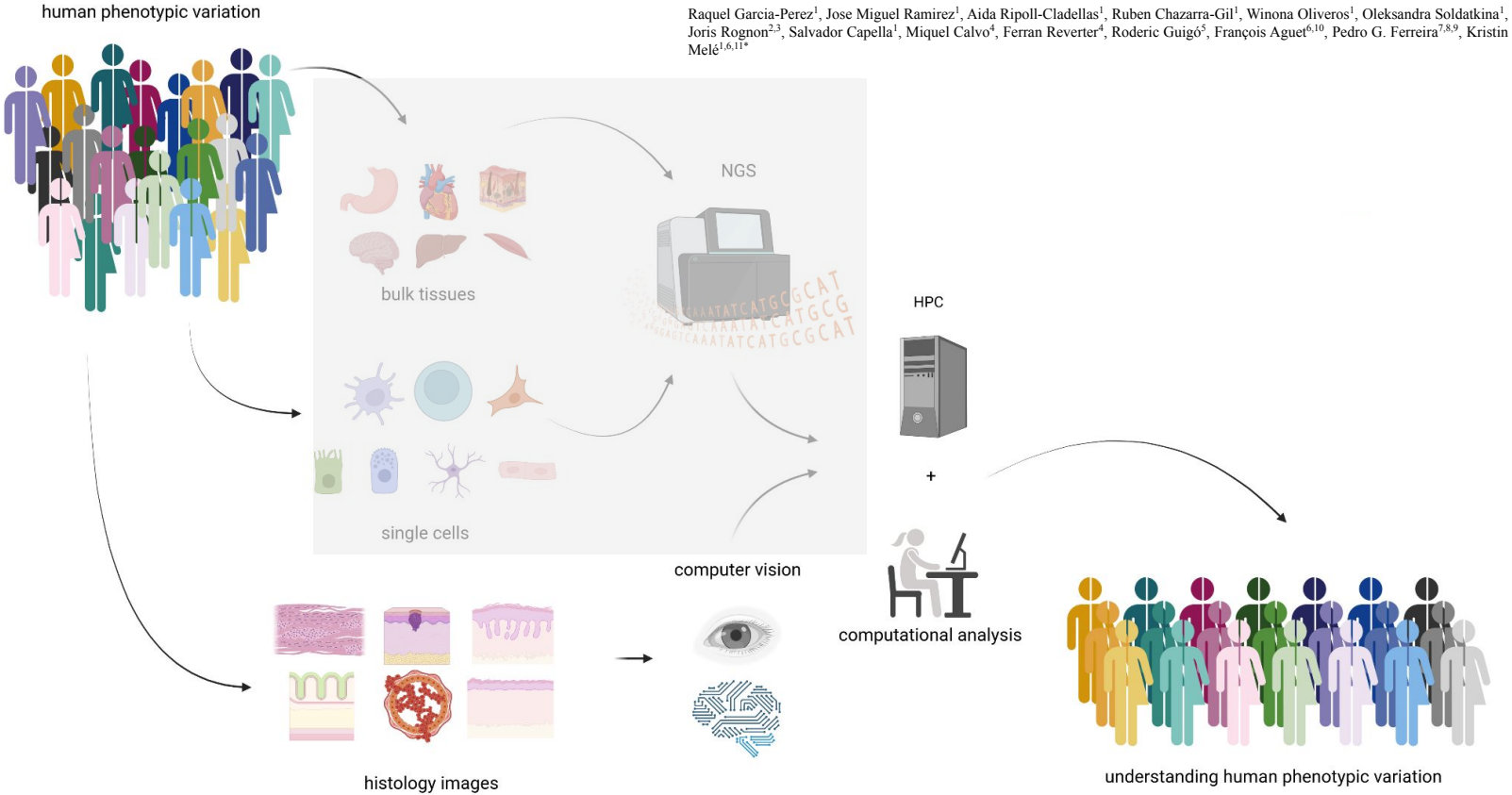
Diabetic neuropathy

- numbness or reduced ability to feel pain or temperature changes
- tingling or burning feeling
- sharp pains or cramps
- muscle weakness
- extreme sensitivity to touch
- serious foot problems, such as ulcers, infections, and bone and joint damage

Garcia-Perez et al.

The landscape of expression and alternative splicing variation across human traits (under review)

Raquel Garcia-Perez[1], Jose Miguel Ramirez[1], Aida Ripoll-Cladellas[1], Ruben Chazarra-Gil[1], Winona Oliveros[1], Oleksandra Soldatkina[1], Mattia Bosio[1], Paul Joris Rognon[2,3], Salvador Capella[1], Miquel Calvo[4], Ferran Reverter[4], Roderic Guigó[5], François Aguet[6,10], Pedro G. Ferreira[7,8,9], Kristin G. Ardlie[6] & Marta Melé[1,6,11*]

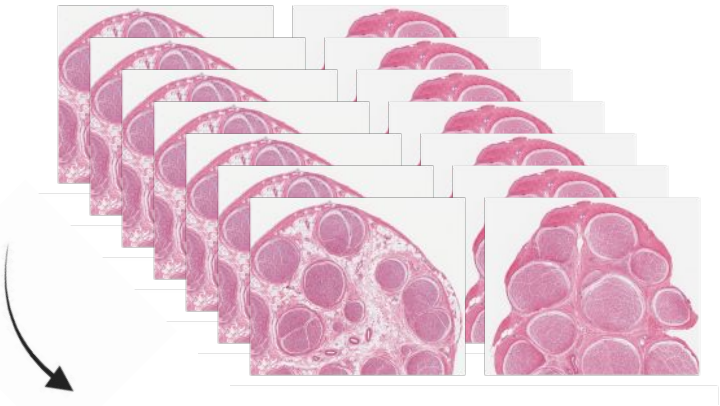


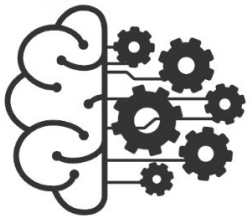
Created with BioRender.com

Computer vision techniques allow us to **predict diabetic status**

Histology images

non-diabetic diabetic





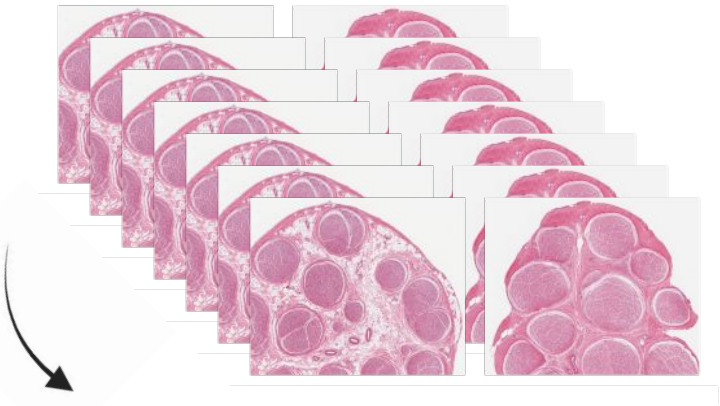
Support vector machine
- training set (75% of the data)
- test set (25% of the data)
- 100 permutations

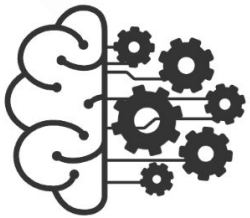
Garcia-Perez et al.

Computer vision techniques allow us to **predict diabetic status**

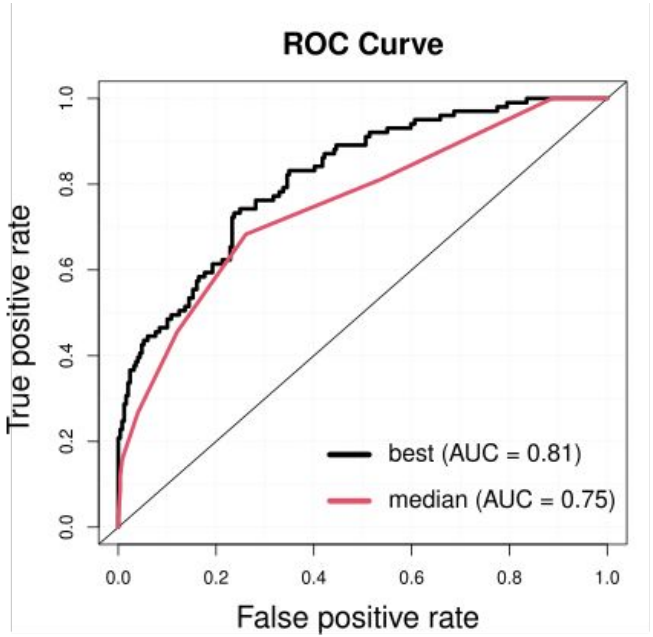
Histology images

non-diabetic diabetic



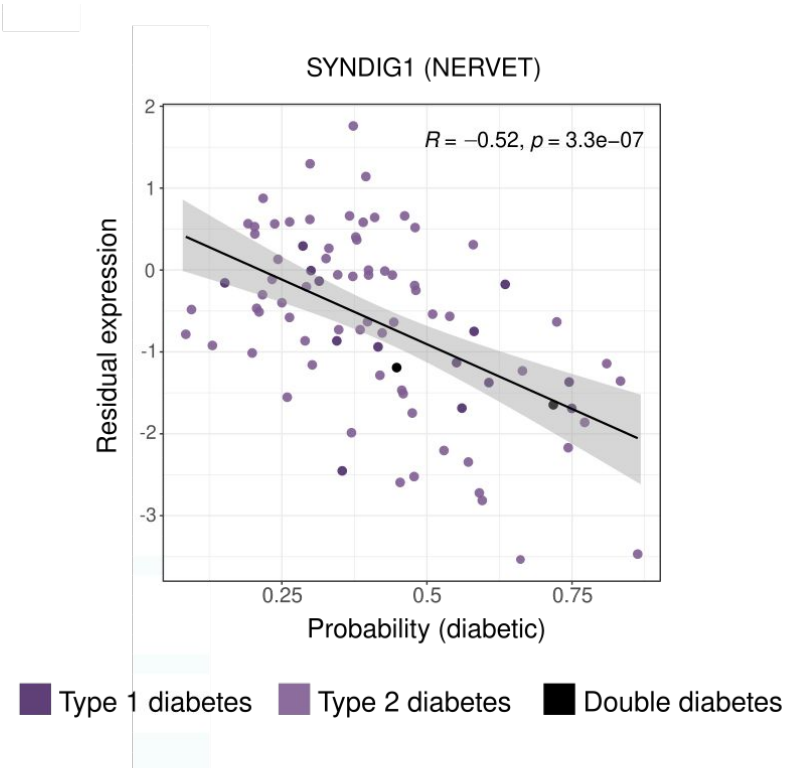


Support vector machine
- training set (75% of the data)
- test set (25% of the data)
- 100 permutations



Garcia-Perez et al.

We identify genes associated with **diabetic neuropathy**



Garcia-Perez et al.

Take home messages

- Ancestry, sex, age and BMI simultaneously influence gene expression variation but their relative importance is tissue-specific.
- Alternative splicing variation is mostly driven by differences between populations.
- Transcriptome differences between human populations are mostly *cis*-driven.
- Ribosomal proteins are differentially spliced between human populations.
- Additive effects are widespread and tissue-specific
- The tissue most affected by type 1 and 2 diabetes is the tibial nerve.
- Machine learning analysis of tibial nerve histology images allows us to predict the diabetic status and to find genes associated with diabetic neuropathy.

Acknowledgements

Marta Mele
Jose Miguel Ramirez
Oleksandra Soldatkina
Aida Ripoll-Cladellas
Ruben Chazarra-Gil
Winona Oliveros
Paul Rognon

Mattia Bosio
Salvador Capella

Miquel Calvo
Ferran Reverter

Universitat de Barcelona
Facultat de Biologia

Pedro G. Ferreira
Roderic Guigó
François Aguet
Kristin G. Ardlie

U.PORTO Universidade do Porto
CRG Centre for Genomic Regulation
BROAD INSTITUTE

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Ministerio de Ciencia e Innovación
Agencia Estatal de Investigación