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Polygenic Scores for Type 2 Diabetes and High Blood pressure comorbidity prediction

Полігенні шкали для прогнозування коморбідності діабету 2 типу та високого кров'яного тиску

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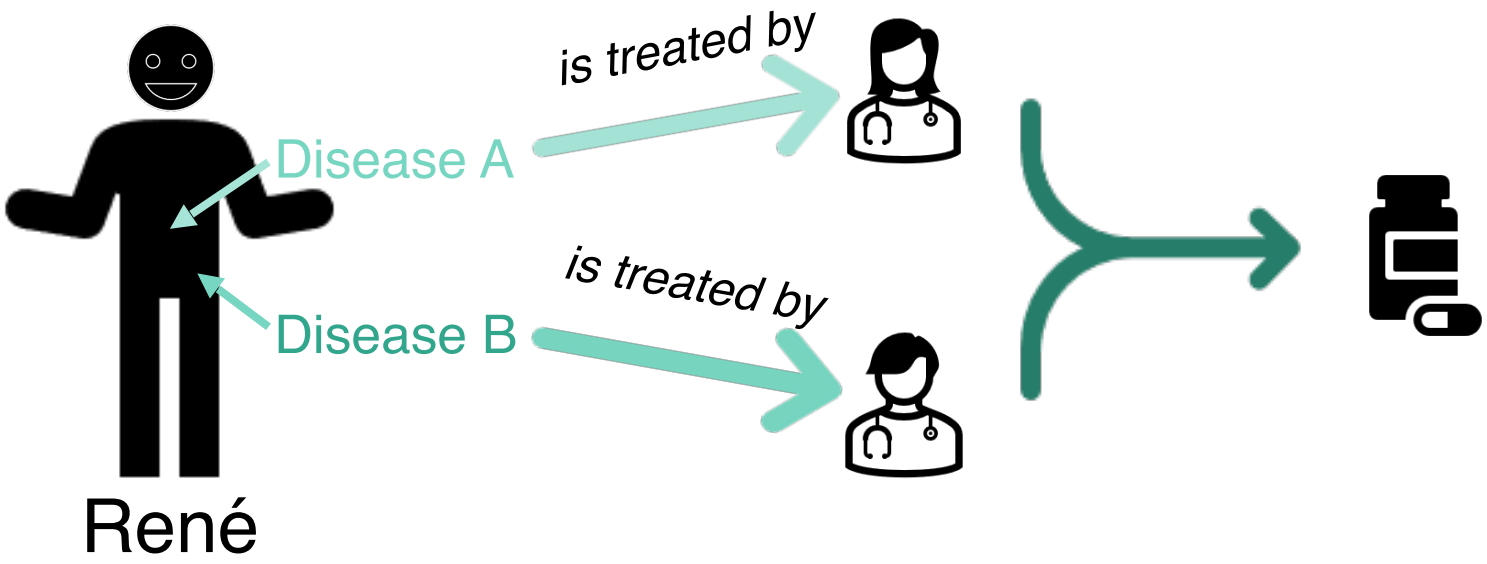
Marzieiev Readings, 23-24 October, 2025, Kyiv

Precision medicine as a solution

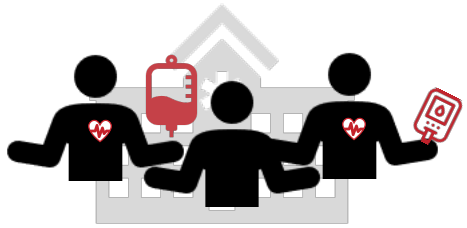


Precision medicine

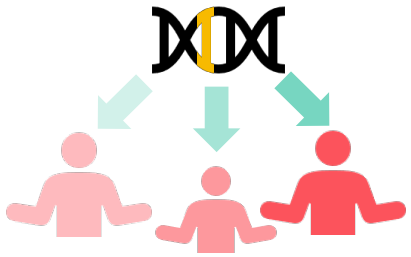
+ better understanding of the biological mechanisms

Genetics as an additional data to apply precision medicine

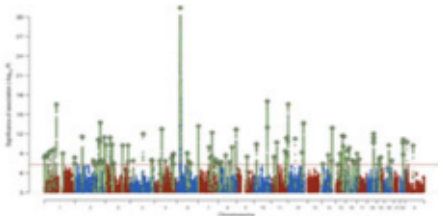
Problem statement



Comorbidity and complication are **major threats** on our healthcare systems



Using data available to do **stratification of risks and tailored treatment** can improve it, and **genetic data** offers additional and novel information



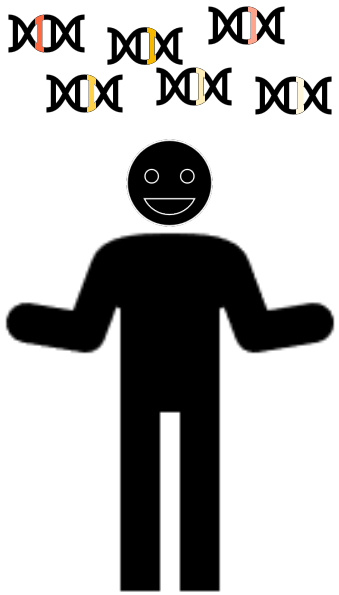
Genome-wide investigation can illuminate underlying **biological mechanisms of complex conditions**

Polygenic score (PGS), or genetic information as the additive sum of all genetic variants

$$PGS_{René} = \sum \beta_{ij} \times SNV_i$$

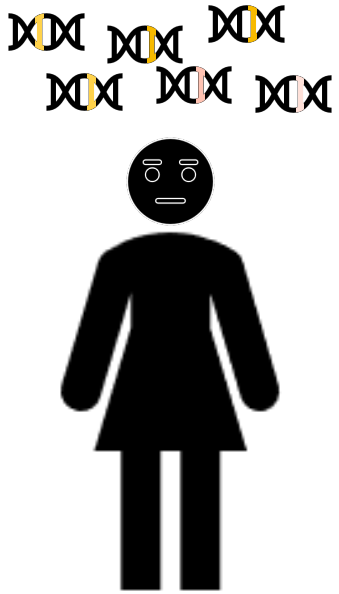
PGS: sum of **all known (common) variants**, usually Single Nucleotide Variants (SNVs) to calculate a **genetic risk of getting a particular disease, j**

Calculating PGS within a population…



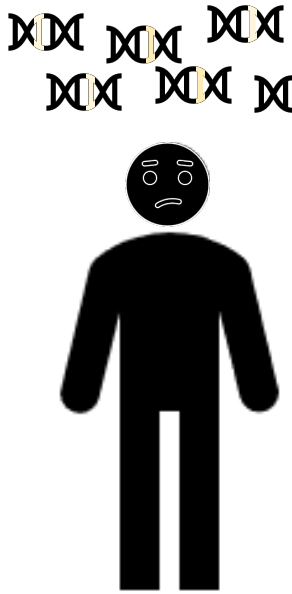
René

$$PGS_{René,\,j} = \sum_{i \in René} \beta_{ij} \times SNV_i$$



Françoise

$$PGS_{Françoise,\,j} = \sum_{i \in Françoise} \beta_{ij} \times SNV_i$$

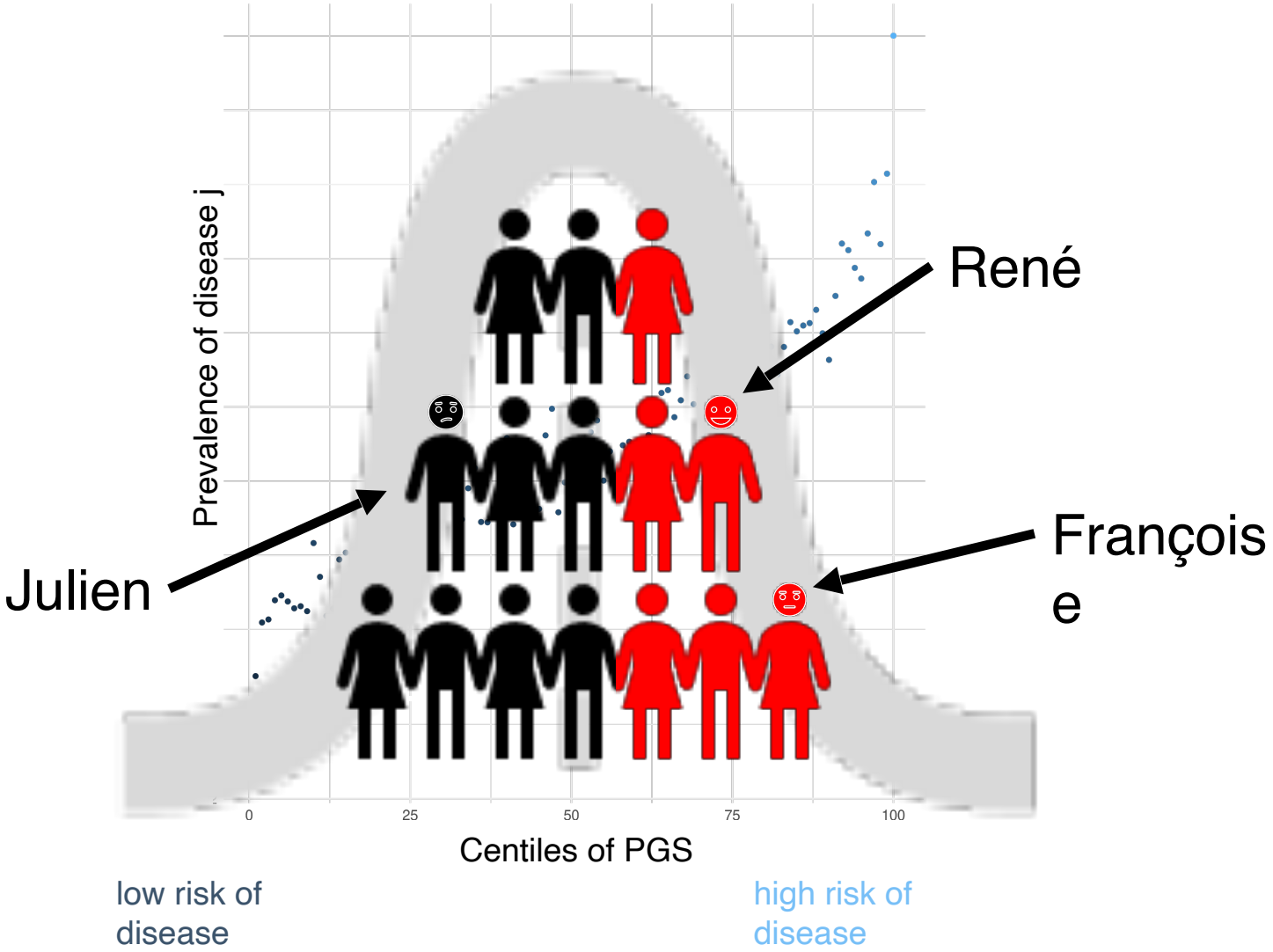


Julien

$$PGS_{Julien,\,j} = \sum_{i \in Julien} \beta_{ij} \times SNV_i$$

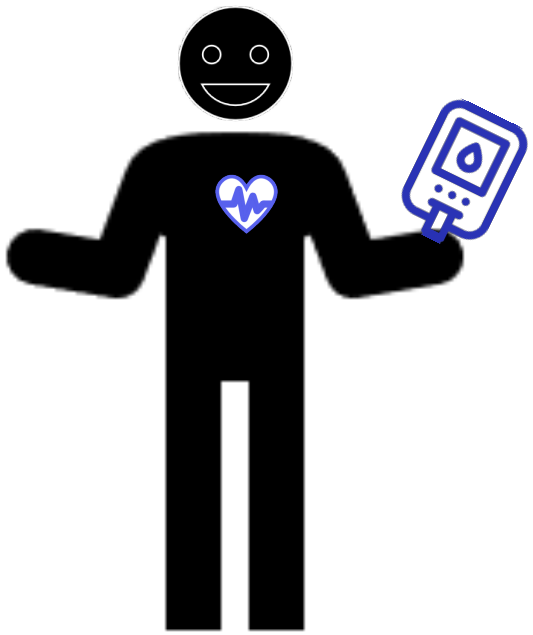
PGS is a relative number that needs to be compared within a **genetically closed population**

… allows to identify individuals at risk



The PGS distribution helps to identify **individuals** at **higher risk** of a **particular disease j**

The T2D – high BP project aims with René



René

René has **T2D and hypertension**

Like others in his situation, he is **struggling to reach optimal levels of glucose and BP**

Could we have **predicted René's comorbidity problem**, and **tailored a medical monitoring + treatment**?

What are the shared pathogenetic mechanisms between T2D and high BP?

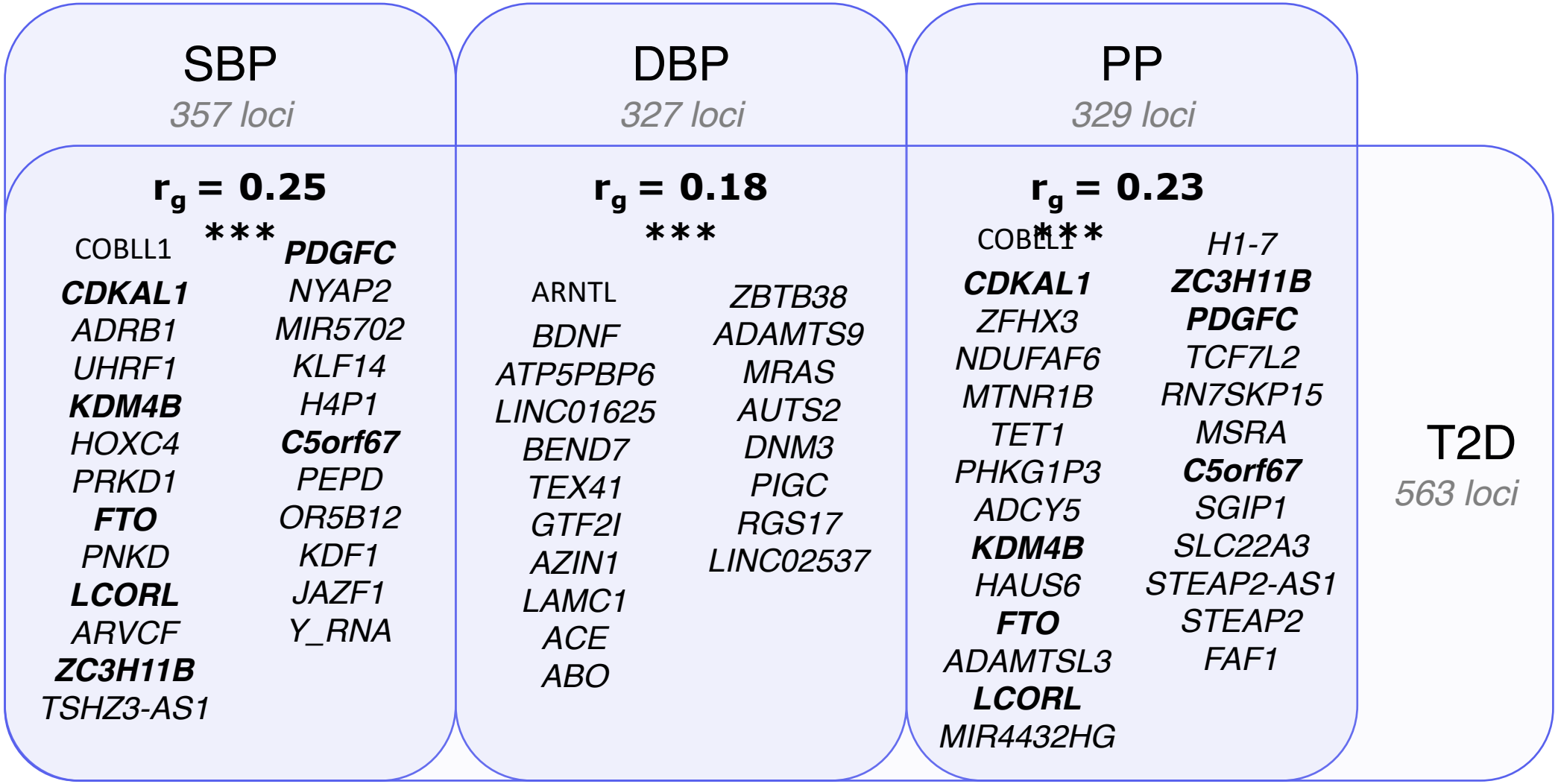
Material and methods

- A large-scale multiomic cohort of 460,000 individuals, the biobank uk

- GWAS of
  - T2D
  - High BP: SBP, DBP, PP

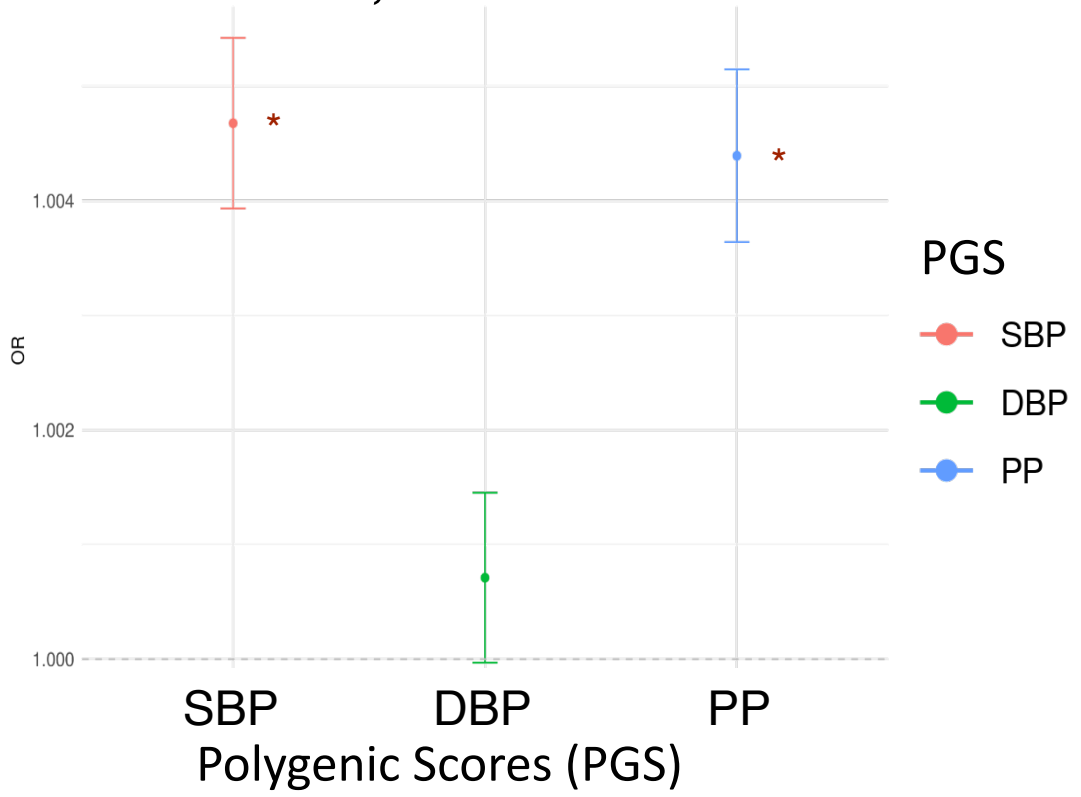
- Latest tools for genomic investigation
  - PGS, via *comorbidPGS*
  - Mendelian Randomization (MR)
  - Colocalisation
  - single-cell ATAC sequencing (scATAC-seq)

Results: High T2D-BP genetic correlation and overlap

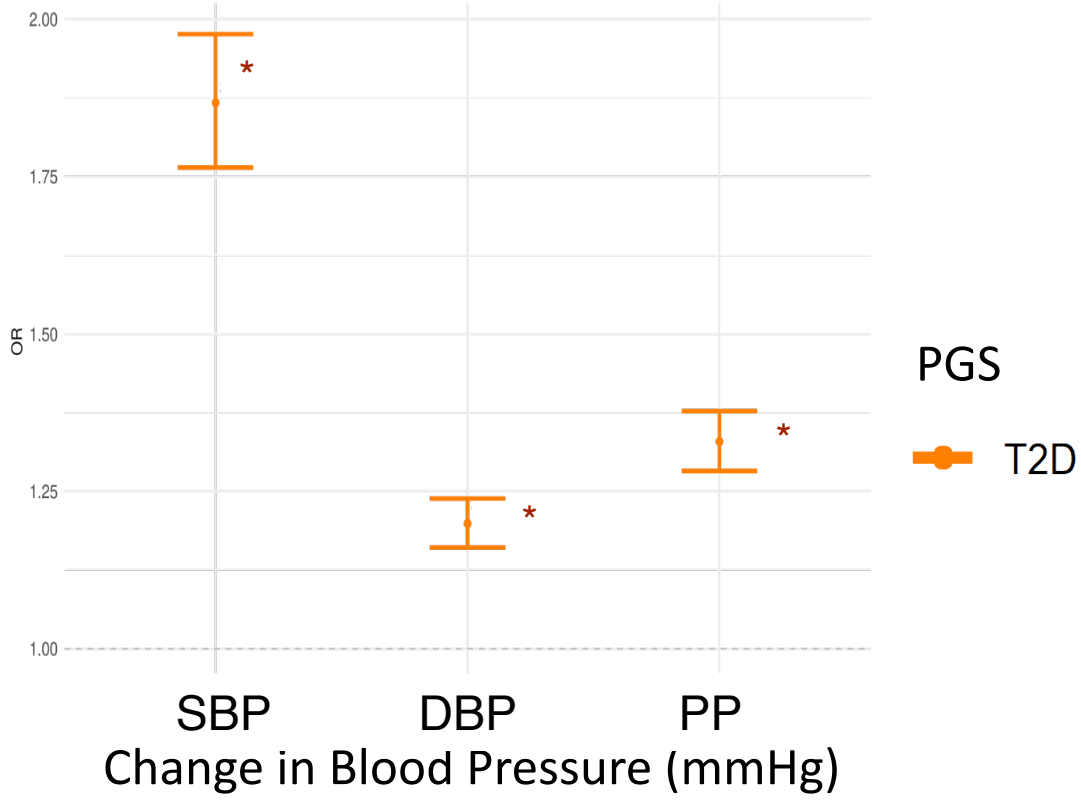


Results: Reciprocal T2D-BP risk prediction using polygenic scores

a. *Association between high BP PGS and risk of T2D, 95% CI*



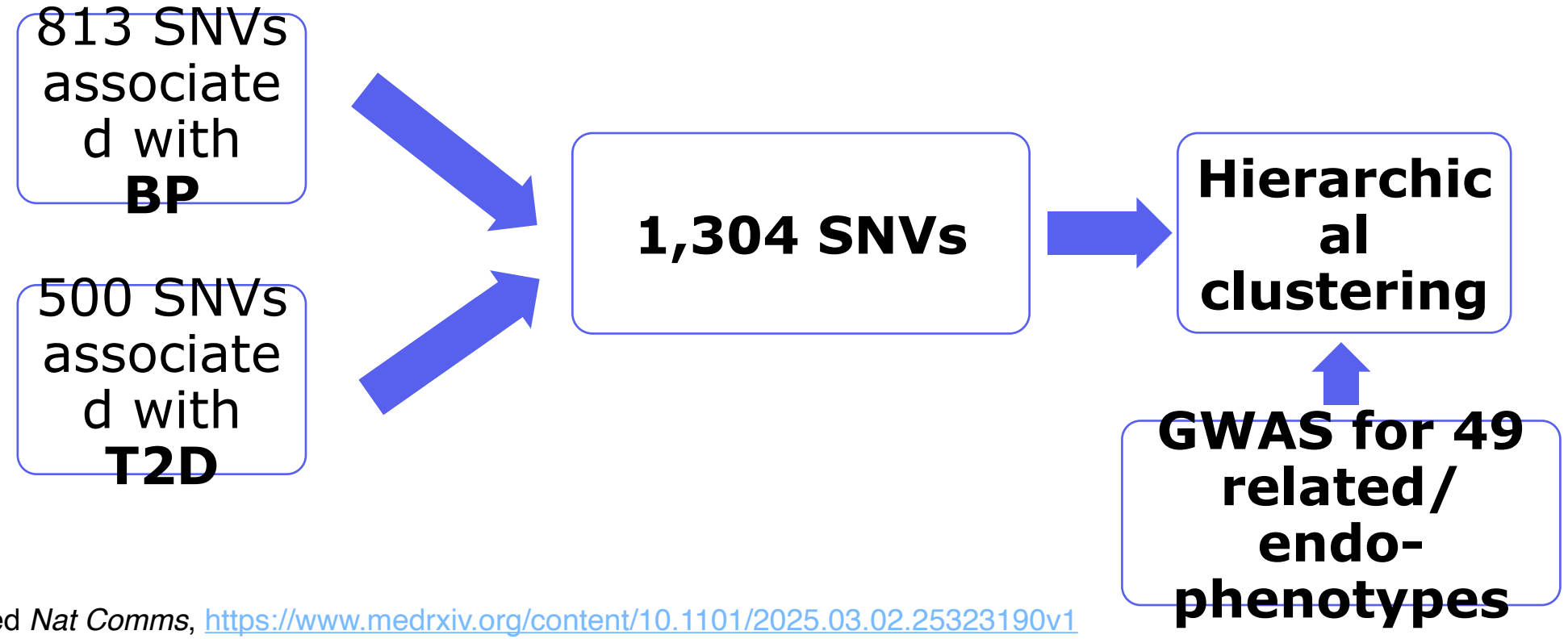
b. *Association between T2D PGS and high BP, 95% CI*



Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

Clustering of T2D-BP SNVs into groups of different pathogenetic processes

We grouped **1,304 SNVs of T2D and high BP** using **49 endophenotype GWAS traits**



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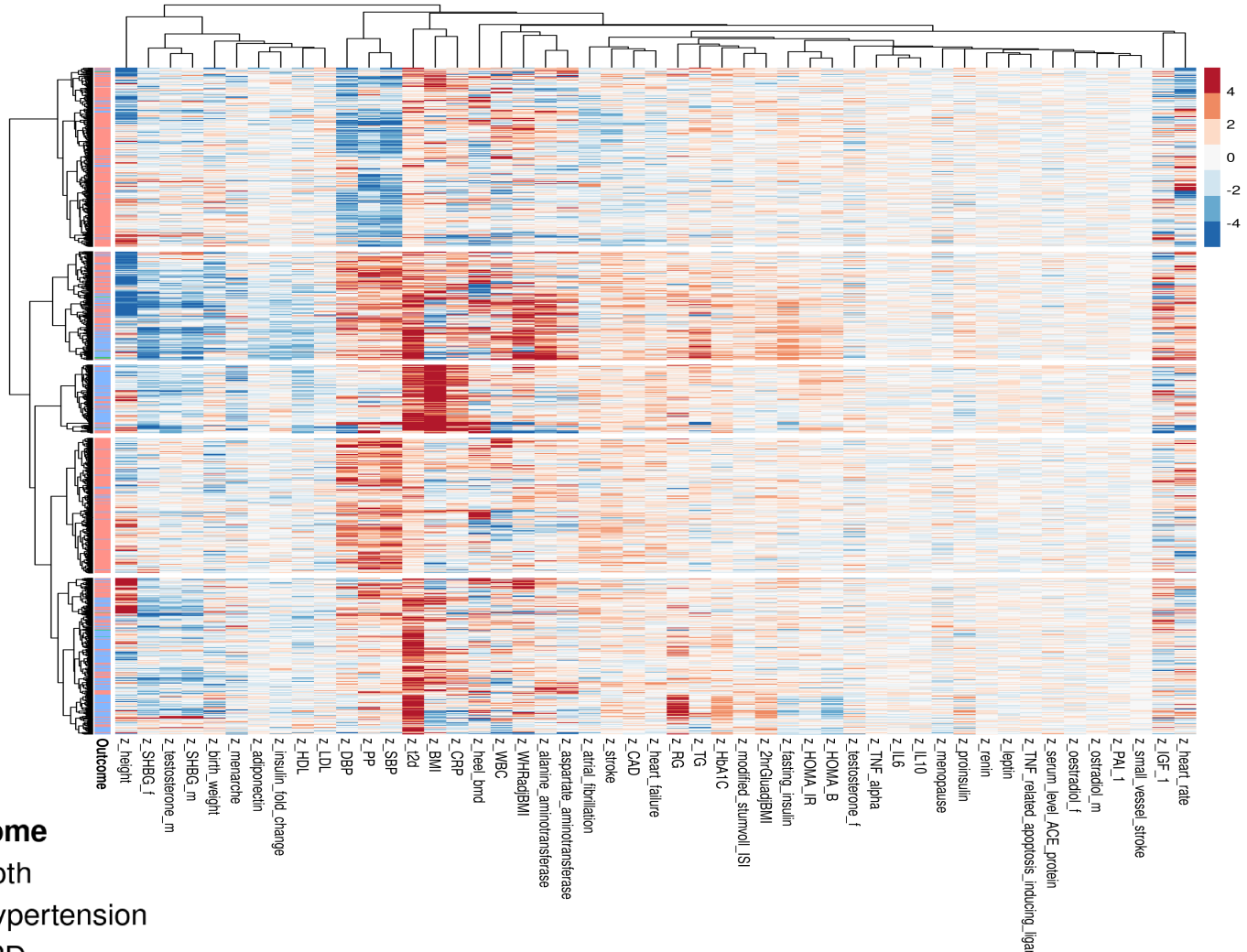
More details on the T2D-BP clustering of SNVs



*Cluster*1 – **Inverse T2D-BP risk**

*Cluster*2 - **Metabolic Syndrome (WHR, IR, shorter stature)**

*Cluster*3 – High adiposity

*Group*4 – Vascular dysfunction

*Group*5 – Reduced beta-cell function

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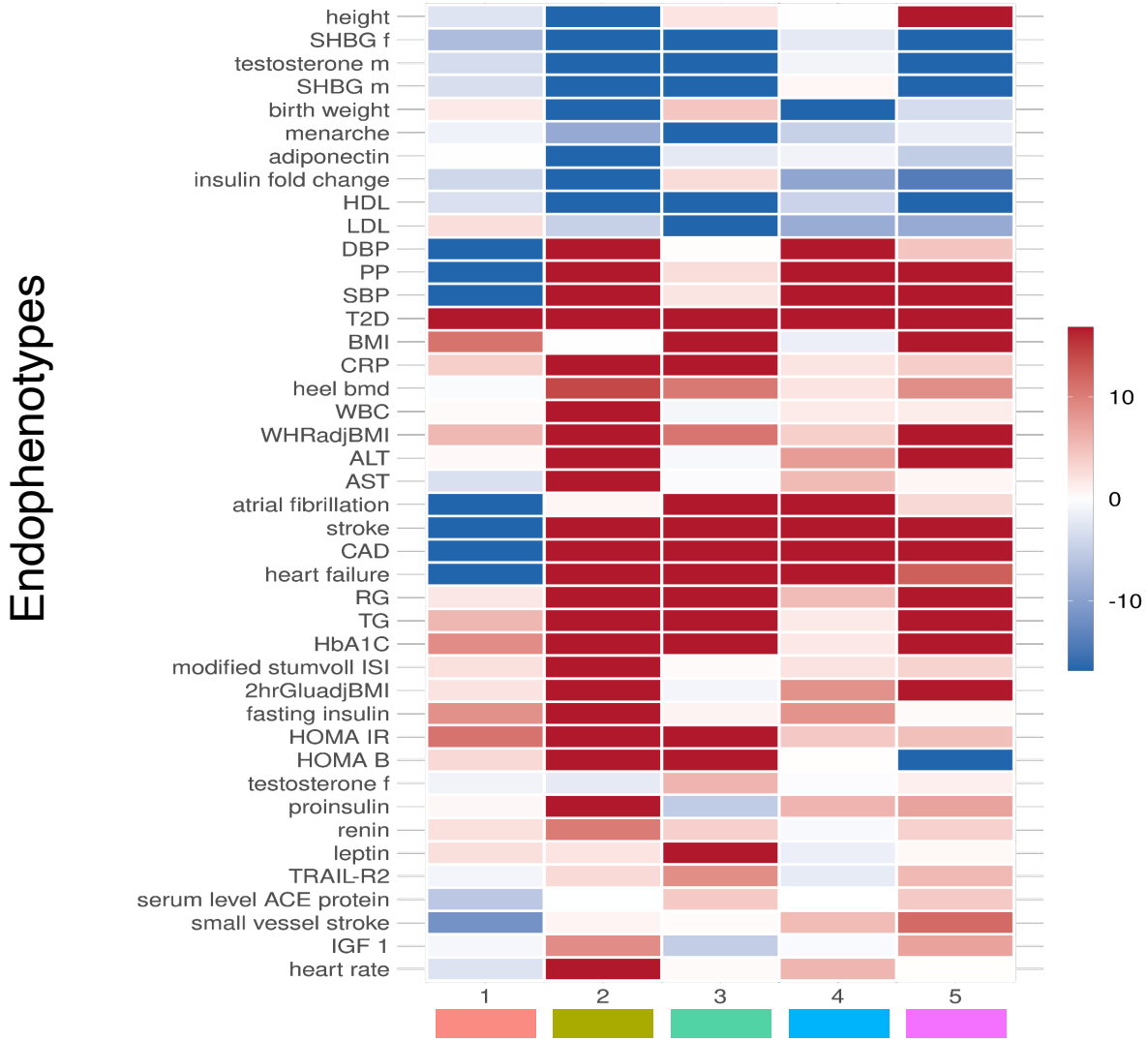
Results: Clustering of T2D-BP SNVs into groups of different pathogenetic processes

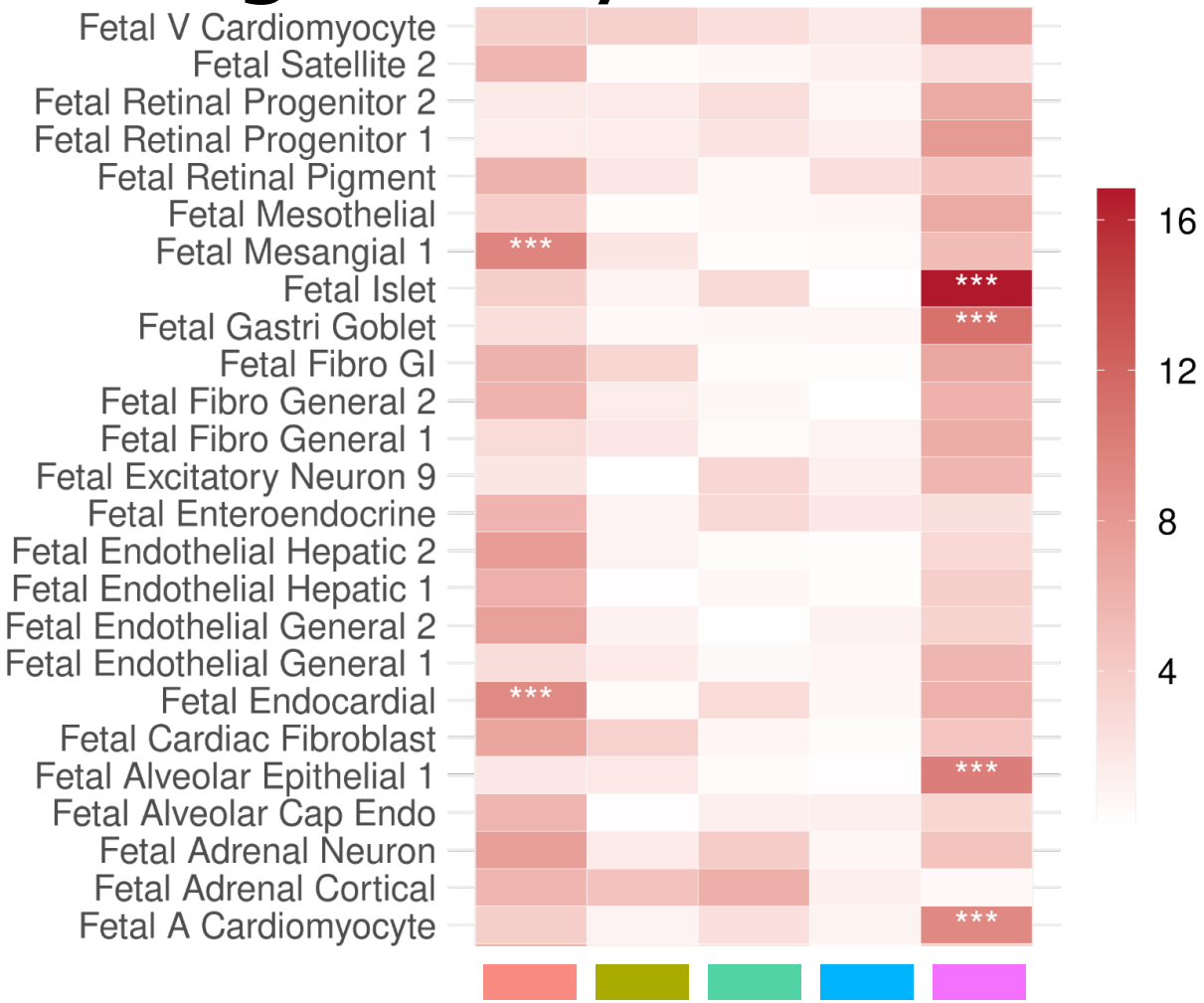


[More details]

Comparison with published clusterings

Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

Results: Cluster characterization: regulatory elements using scATAC-seq atlas



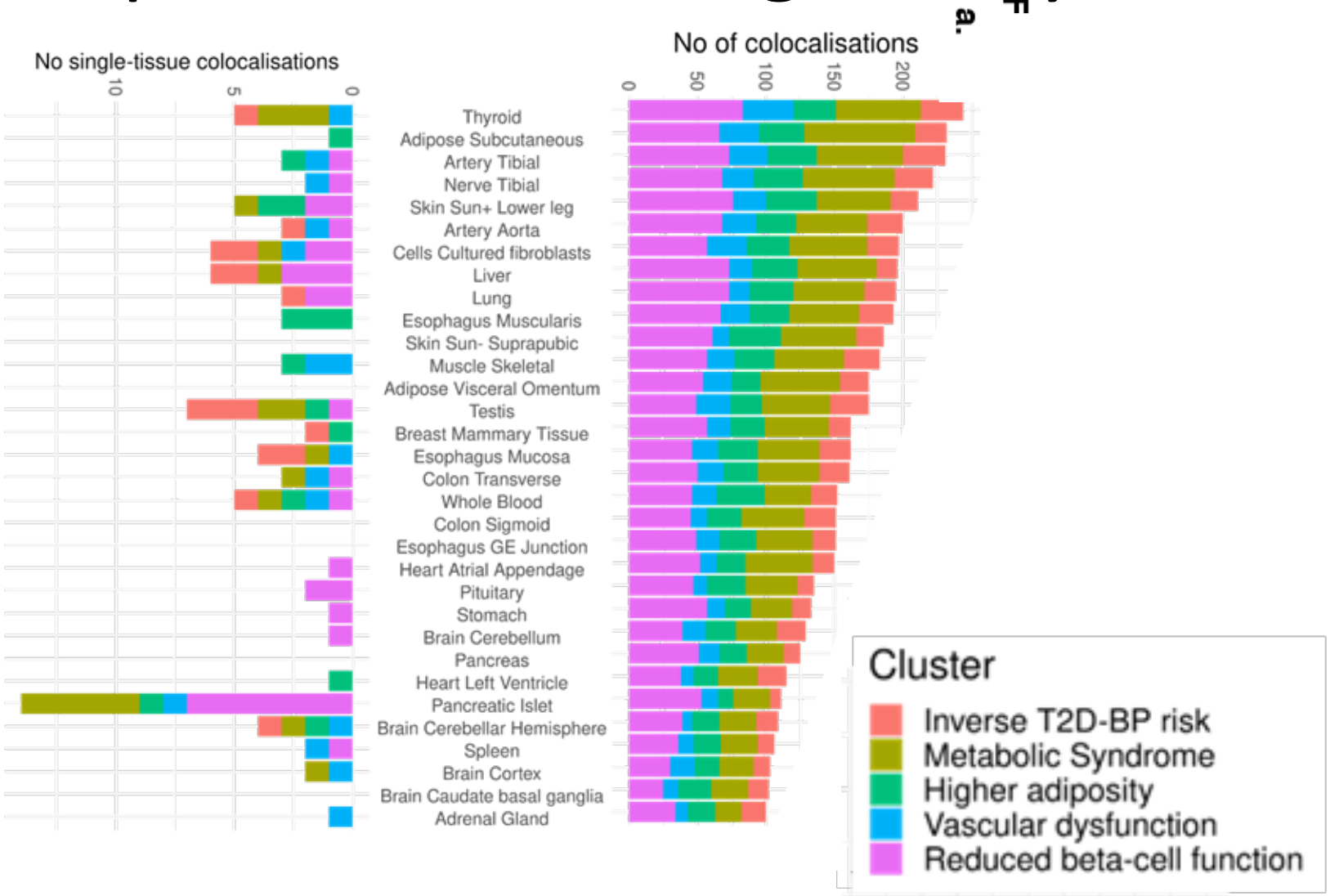
Atlases of single cell of open chromatin region (**CATLAS**) in 222 cell types derived from 30 adult tissues and 15 fetal tissues

Enrichment between the clusters and the open chromatin regions of **the fetal cells**

Methods

Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

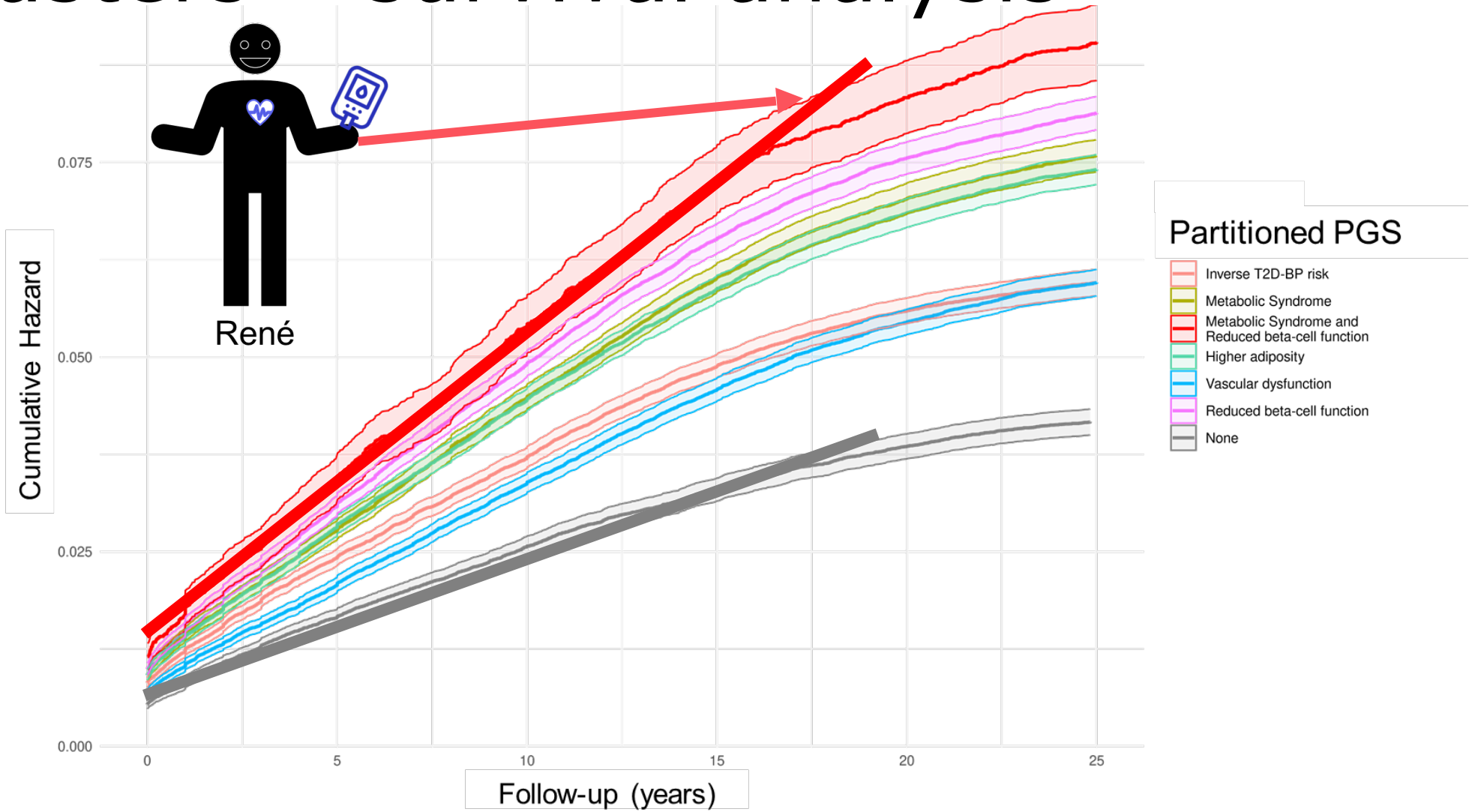
Results: Cluster characterisation by gene expressions and regulatory mechanisms



Distribution of colocalised loci across clusters in 50 human adult tissues.
Bars – number of colocalised signals per tissue
Colours – contribution from the five clusters

Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

Results: Partitioned PGS based on clusters – survival analysis



Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

Results: Partitioned PGS based on clusters: how can we predict the risk of T2D-BP clustering?

Individuals in the top 10% of the PGS distribution based on…	**Relative risk of comorbidity (T2D and hypertension)**
cluster	1.04
cluster	1.14
cluster	1.36
cluster	1.44
cluster	1.55
clusters	2.13

PGS distribution

Pascat et al, accepted *Nat Comms*, https://www.medrxiv.org/content/10.1101/2025.03.02.25323190v1

Discussion

- T2D and BP regulation genetics are **highly intertwined**

- We identified **five clusters of pathogenetic processes** underlying the T2D-BP relationship, including an **inverse T2D-BP risk cluster**

- We bring forward a property of **partitioned PGS to identify high-risk individuals for complex phenotype** (and complications) at a **very young age**

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