Correlation of PRS with cell type composition after ILR transformation provides new insights into the relationship between immune-related diseases and PBMCs cell type proportions

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1. Motivation

Many diseases, such as Obesity, Type 1 Diabetes Mellitus, Asthma, Inflammatory Bowel Disease, show immune-related alterations. These alterations can result in an imbalanced composition of Peripheral Blood Mononuclear Cell (PBMCs) that can be measured by scRNA-seq experiments.

For most of these disorders, the involvement of specific PBMC types remains unclear.

2. Aims of the project

- Provide a **novel and robust method** to study the relationship between Polygenic Risk Scores (PRS) and cell type composition estimated from scRNA-seq experiments
- Study the influence of **genetic predisposition to inflammatory traits** on PBMCs compositions

3. Data & Methods

OneK1K cohort[1]
Blood from 982 donors with Northern European ancestry

~ 1.27 million PBMCs

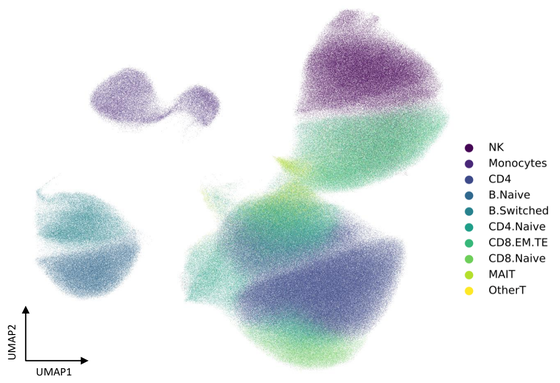
mRNA capture and sequencing

Data for PRS weights
GWAS catalog[4]
PGS catalog[5]
Neale Lab, UKBB cohort[6]

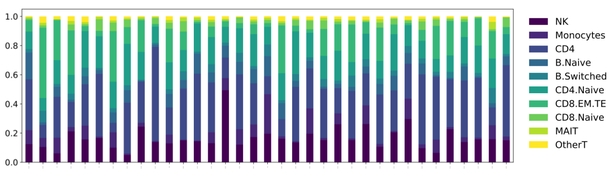
Validation traits
- Monocytes counts
- Lymphocytes count

Traits tested
- Inflammatory Bowel Disease (IBD)
- Ulcerative Colitis (UC)
- Crohn's Disease
- Asthma
- Type 1 Diabetes Mellitus
- Body Mass Index (BMI)

We applied the most recent best practices for single-cell quality control[2] and annotated cell types using **Celltypist**



Since compositional data is intrinsically biased, we applied **ILR** (isometric log-ratio)[3] transformation on cell type proportions



First, we build a dendrogram of cell types to guide comparisons between cell groups (any two branches in the tree can be compared)

* CD4 are in separate groups because they derive from different Leiden clusters
** OtherT include: γδ T, ILC, IL22

	Mono	B Naive	B Switched	NK	CD8 EM & TE	CD8 Naive	7_CD4*	CD4 Naive	OtherT**	MAIT	4_CD4*	3_CD4*	6_CD4*
D1	1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1
D2	0	1	1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1
D3	0	1	-1	0	0	0	0	0	0	0	0	0	0
D4	0	0	0	1	1	1	-1	-1	-1	-1	-1	-1	-1
D5	0	0	0	1	-1	-1	0	0	0	0	0	0	0
D6	0	0	0	0	1	-1	0	0	0	0	0	0	0
D7	0	0	0	0	0	0	1	1	1	1	-1	-1	-1
D8	0	0	0	0	0	0	1	1	-1	-1	0	0	0
D9	0	0	0	0	0	0	1	-1	0	0	0	0	0
D10	0	0	0	0	0	0	0	0	1	-1	0	0	0
D11	0	0	0	0	0	0	0	0	0	0	1	-1	-1
D12	0	0	0	0	0	0	0	0	0	0	0	1	-1

Each comparison is transformed into a ILR direction

Genotypes data and imputed genotypes

X w

$$PRS = \sum_{i=1}^{n} w_i X_i$$

PRS
Donors

Linear model fitting

$$ILR\ directions \sim age + sex + pool\_group + PRS$$

with 926 donors

ILR directions
Donors

Finally, we compute the weighted sum of proportions for each donor *i*

$D1_i = pA_i * wA1 + pB_i * wB1 + pC_i * wC1 + pD_i * wD1 + pE_i * wE1$

$D2_i = pA_i * wA2 + pB_i * wB2 + pC_i * wC2 + pD_i * wD2 + pE_i * wE2$

...

4. Results

Validation traits

$ILR\ directions \sim age + sex + pool\_group + \boldsymbol{PRS_{Lympho}}$

The PRS for **lymphocytes** count is **negatively** correlated with **D1** (p.val = 0.040, t.val = -2.05)

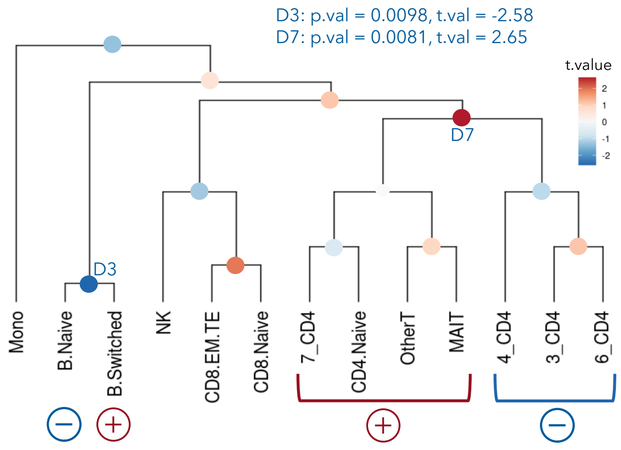
$ILR\ directions \sim age + sex + pool\_group + \boldsymbol{PRS_{Mono}}$

The PRS for **monocytes** count is **positively** correlated with the ratio monocytes/lymphocites (p.val = 0.05, t.val = 1.94)

Traits tested

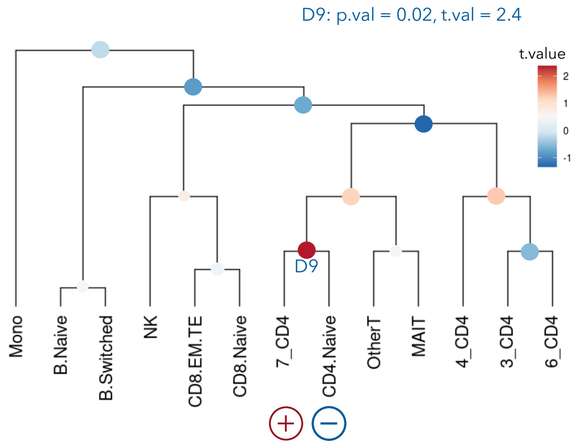
$ILR\ directions \sim age + sex + pool\_group + \boldsymbol{PRS_{BMI}}$

D3: p.val = 0.0098, t.val = -2.58
D7: p.val = 0.0081, t.val = 2.65



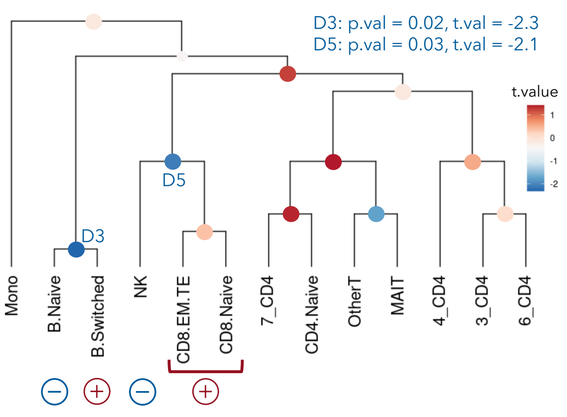
$ILR\ directions \sim age + sex + pool\_group + \boldsymbol{PRS_{IBD}}$

D9: p.val = 0.02, t.val = 2.4



$ILR\ directions \sim age + sex + pool\_group + \boldsymbol{PRS_{T1DM}}$

D3: p.val = 0.02, t.val = -2.3
D5: p.val = 0.03, t.val = -2.1



How to read the plots

Each dot (**node**) on the dendrogram represents a **contrast or direction** between two groups of cells. The colors represent the **t value** of the association between that ILR Direction and the PRS for the trait of interest, with red for positive and blue for negative. If there is a **positive relationship** (red dot), then you know that the cell type on the left of that node increase (respect to the one on the right) together with the increase in PRS for the trait tested.

5. Conclusions and future perspectives

In summary, our approach provides a novel and robust method to correlate the genetic risk for a phenotype of interest and cell-type composition.
Most of our results are in concordance with existing literature about obesity, T1DM, IBD and immune cell types involvement in those diseases.
In addition, our findings highlight for example the possible consequences of **obesity** on the immune system showing a shift towards an increase in less common T cell types, including **MAIT** and other T (**γδ T**, ILC, IL22).
Nonetheless, these associations should be further validated studying the phenotypes directly measured. In the future we would like to test our method on a bigger dataset and extend the analysis to other traits.

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6. https://www.nealelab.is/uk-biobank, phenotype 21001