The distribution, transcriptome, and TCR profiles of peripheral γδ T cells in psoriasis vulgaris

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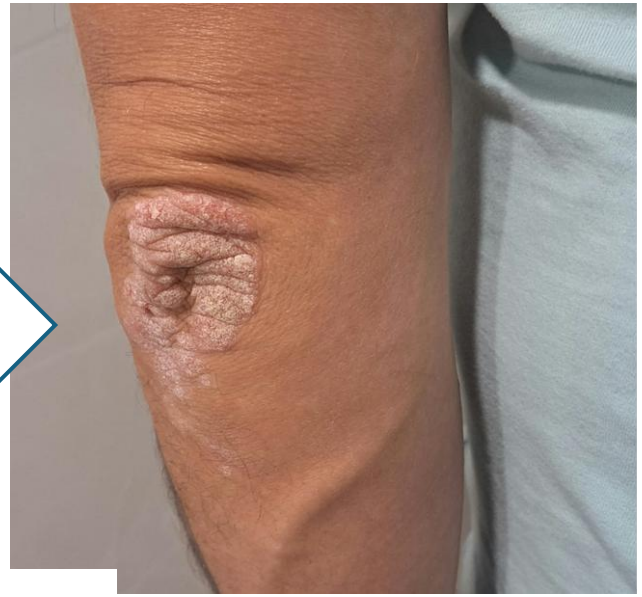
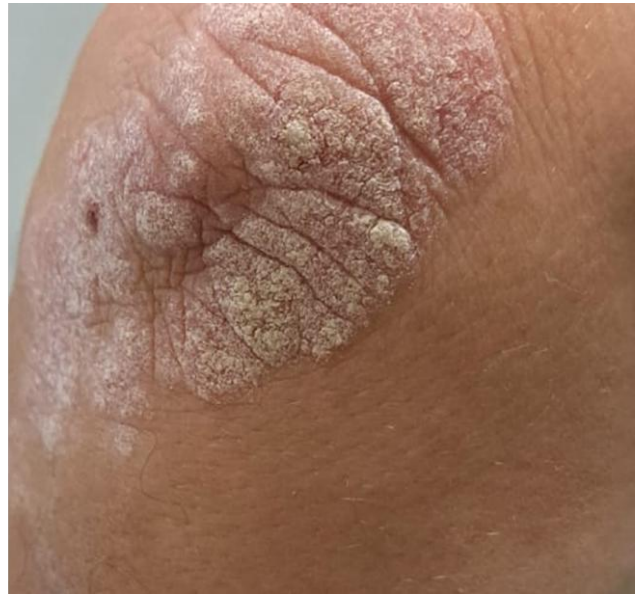
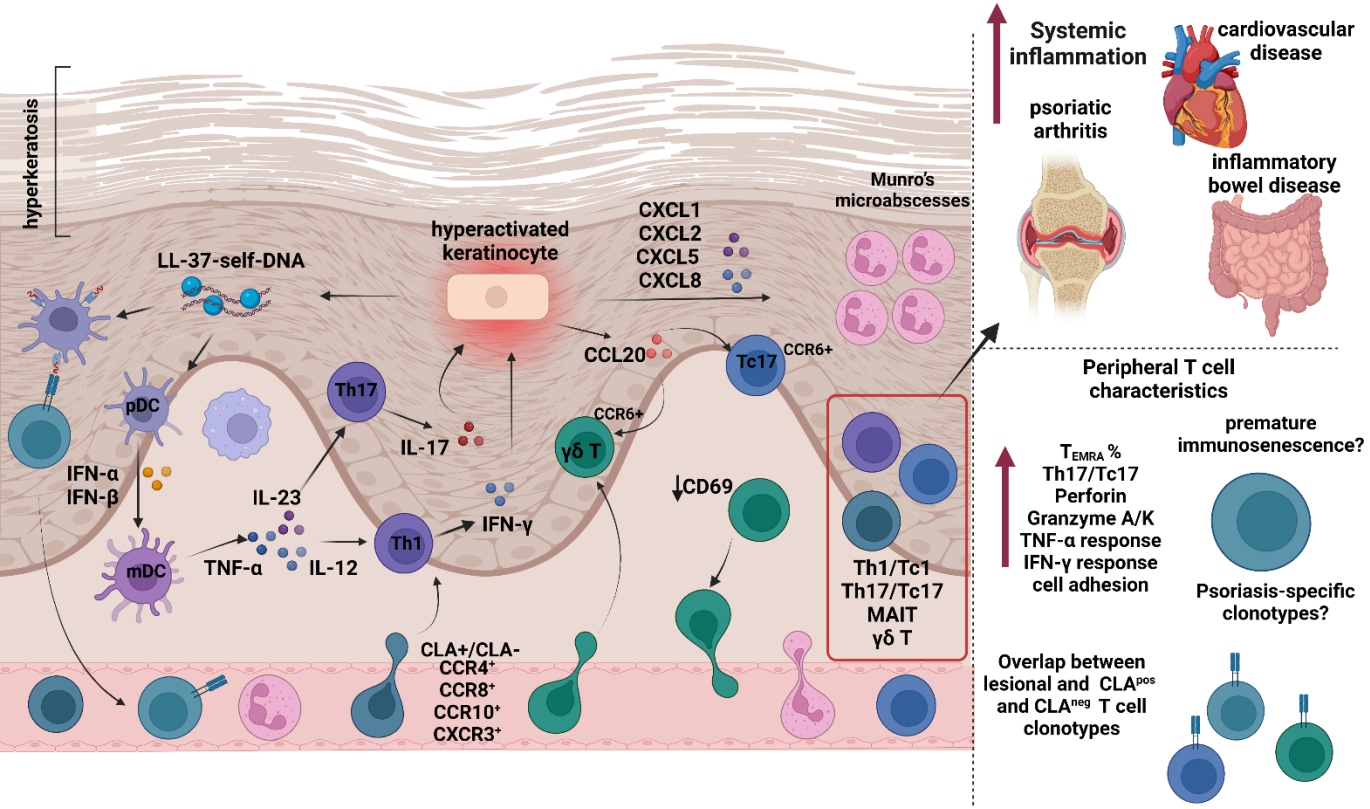
Psoriasis vulgaris

- chronic autoinflammatory skin disease
- well-defined, erythematous plaques covered with silvery-white scales





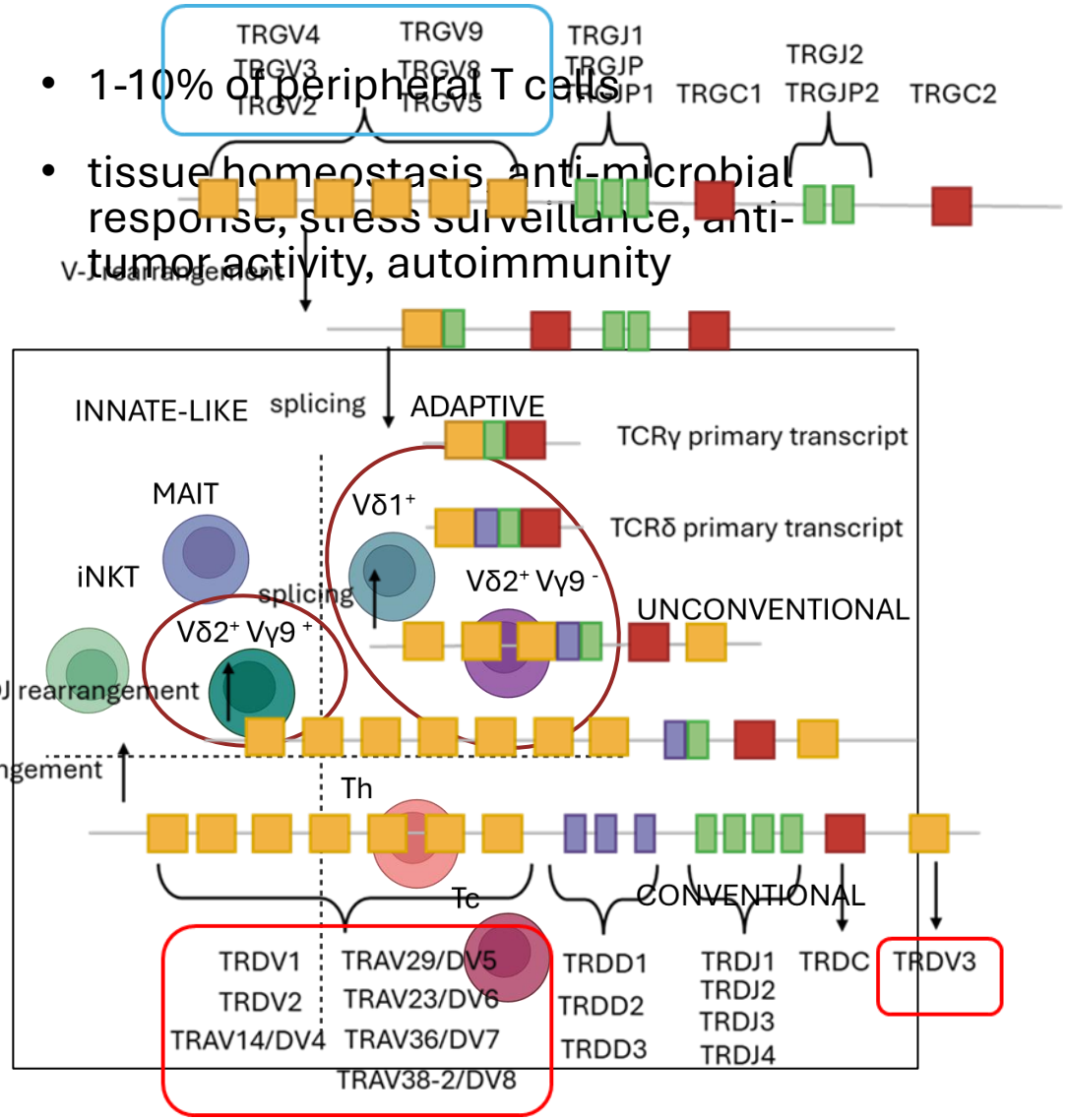


- T cell-mediated pathology
- complex network of interactions between resident and infiltrating cells
- (re)circulating T cells contribute to spreading inflammation beyond the skin
- associated comorbidities and signs of systemic inflammation

What is the role of γδ T cells in psoriasis vulgaris?

γδT cells

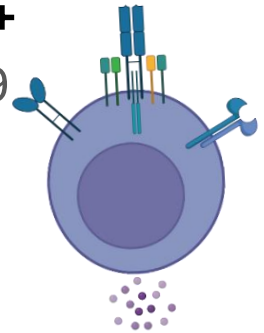
- 1-10% of peripheral T cells
- tissue homeostasis, anti-microbial response, stress surveillance, anti-tumor activity, autoimmunity



Human γδ T cells can be distinguished by δ chain usage:

Vδ2+

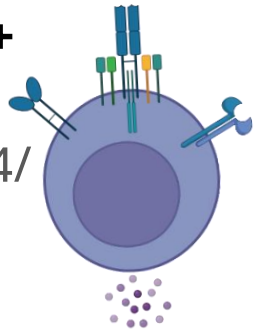
Vγ9



- 50%–90% of the peripheral γδ T
- Vγ9+Vδ2+ → innate-like effectors
- Vγ9-Vδ2 + → adaptive-like

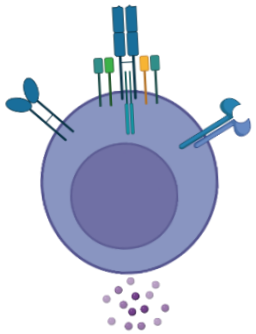
Vδ1+

Vγ2/3/4/5/8/9

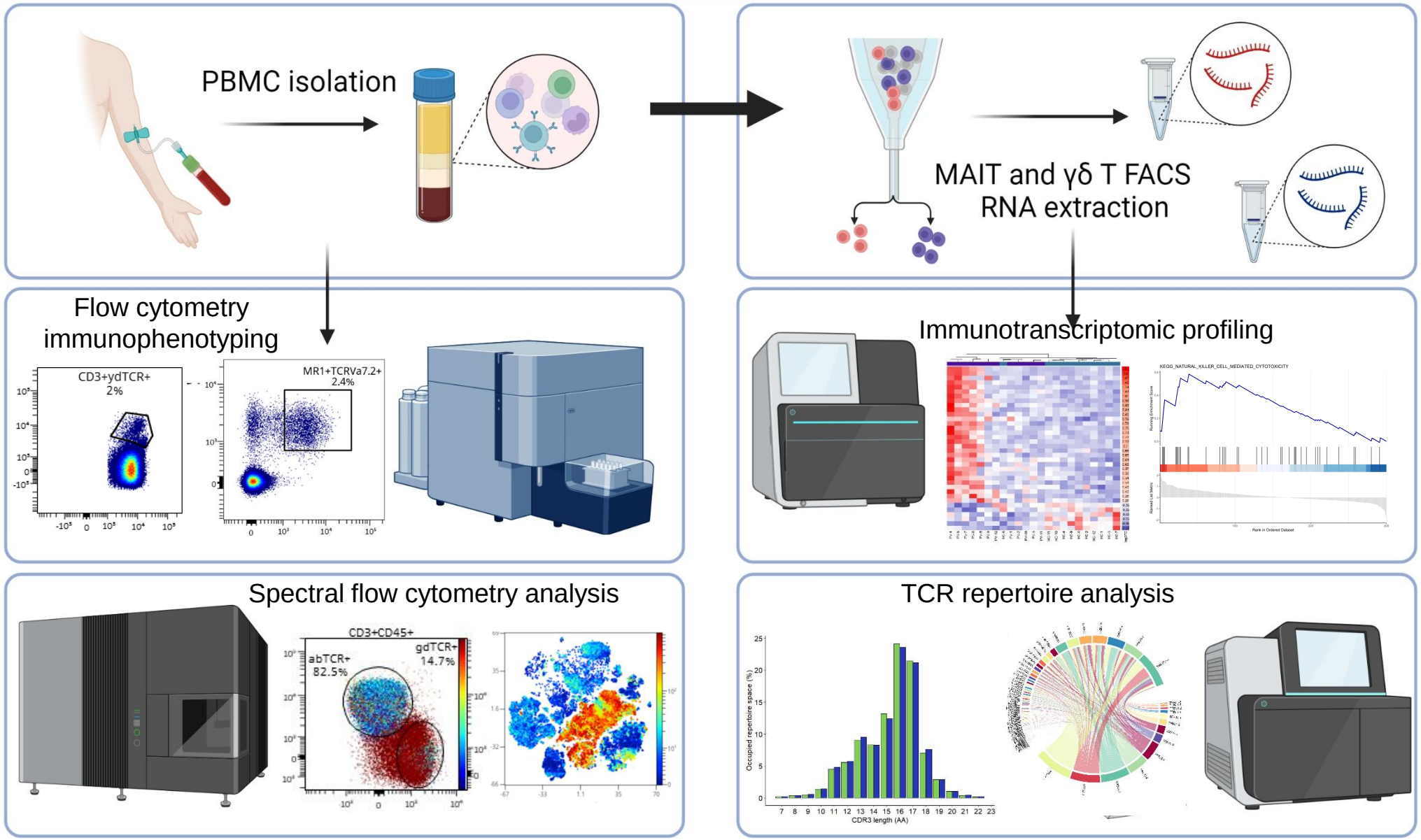


- up to ~ 30% of peripheral γδ T
- epithelial and mucosal sites → gut, skin, spleen, and liver
- adaptive immunobiology

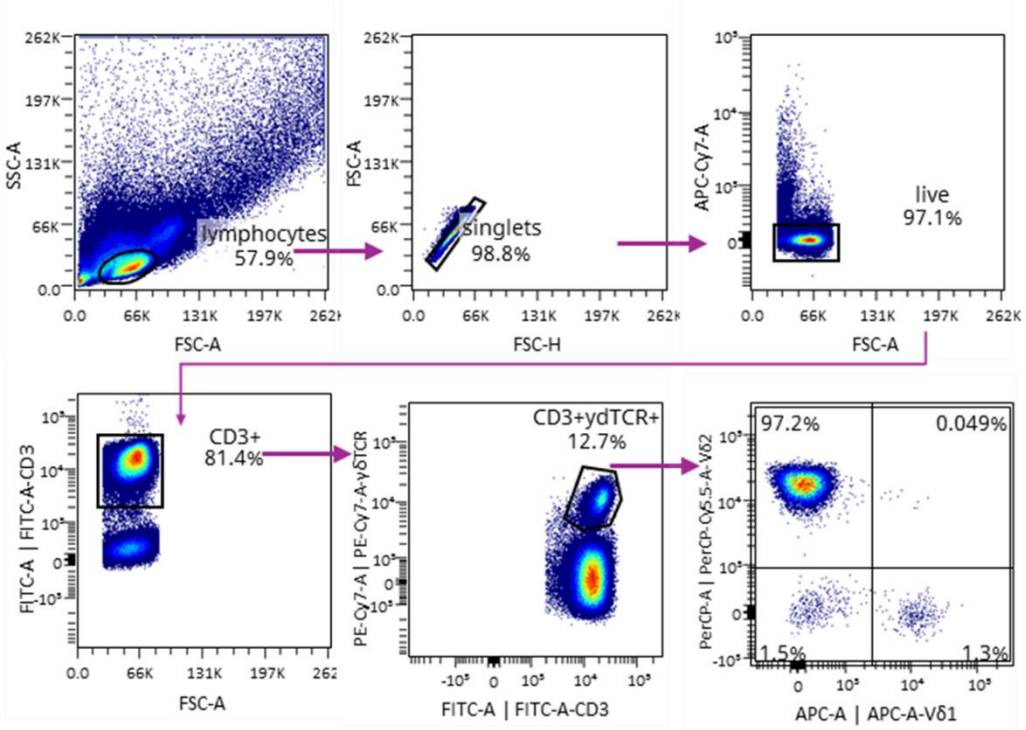
Vδ3+



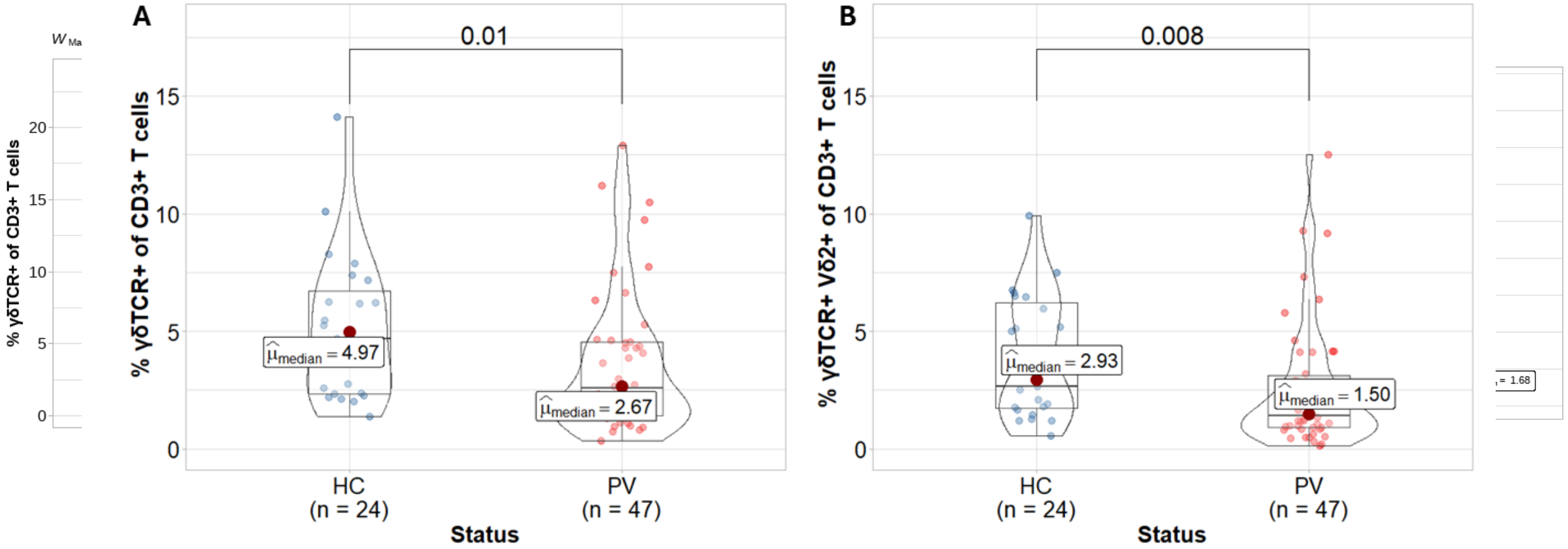
- <1% peripheral γδ T
- enriched in the liver and gut
- anti-microbial immunity
- ??


PBMC isolation
MAIT and γδ T FACS
RNA extraction
Flow cytometry
immunophenotyping
CD3+ydTCR+
2%
MR1+TCRVa7.2+
2.4%
Immunotranscriptomic profiling
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY
Spectral flow cytometry analysis
CD3+CD45+
abTCR+
82.5%
gdTCR+
14.7%
TCR repertoire analysis
Occupied repertoire space (%)
CDR3 length (AA)

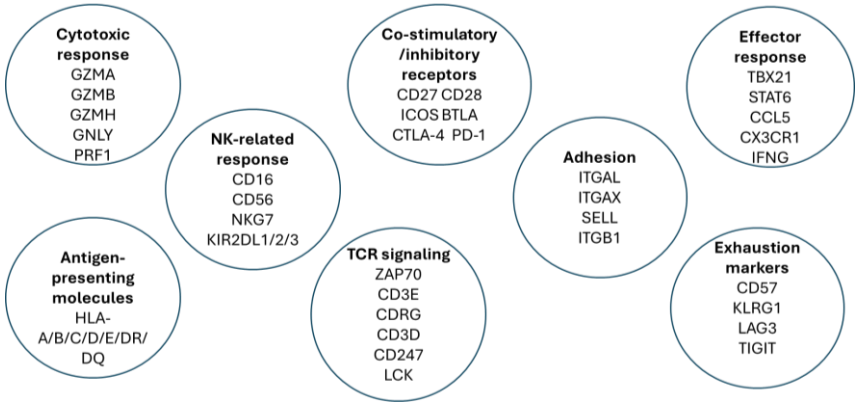
Immunophenotyping

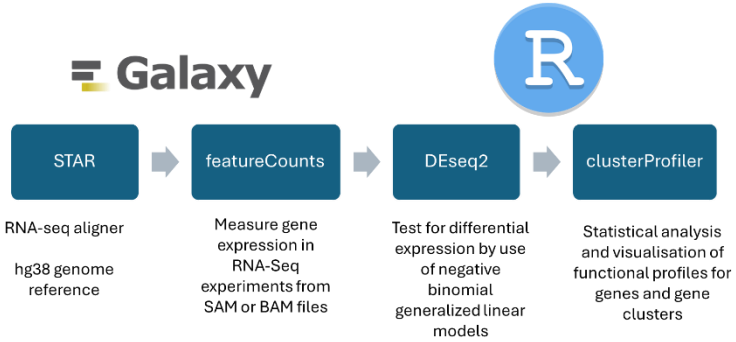


➢ A significant **reduction in γδTCR+ and γδTCR+Vδ2+** cells within the CD3+ T cell population in **male PV patients**



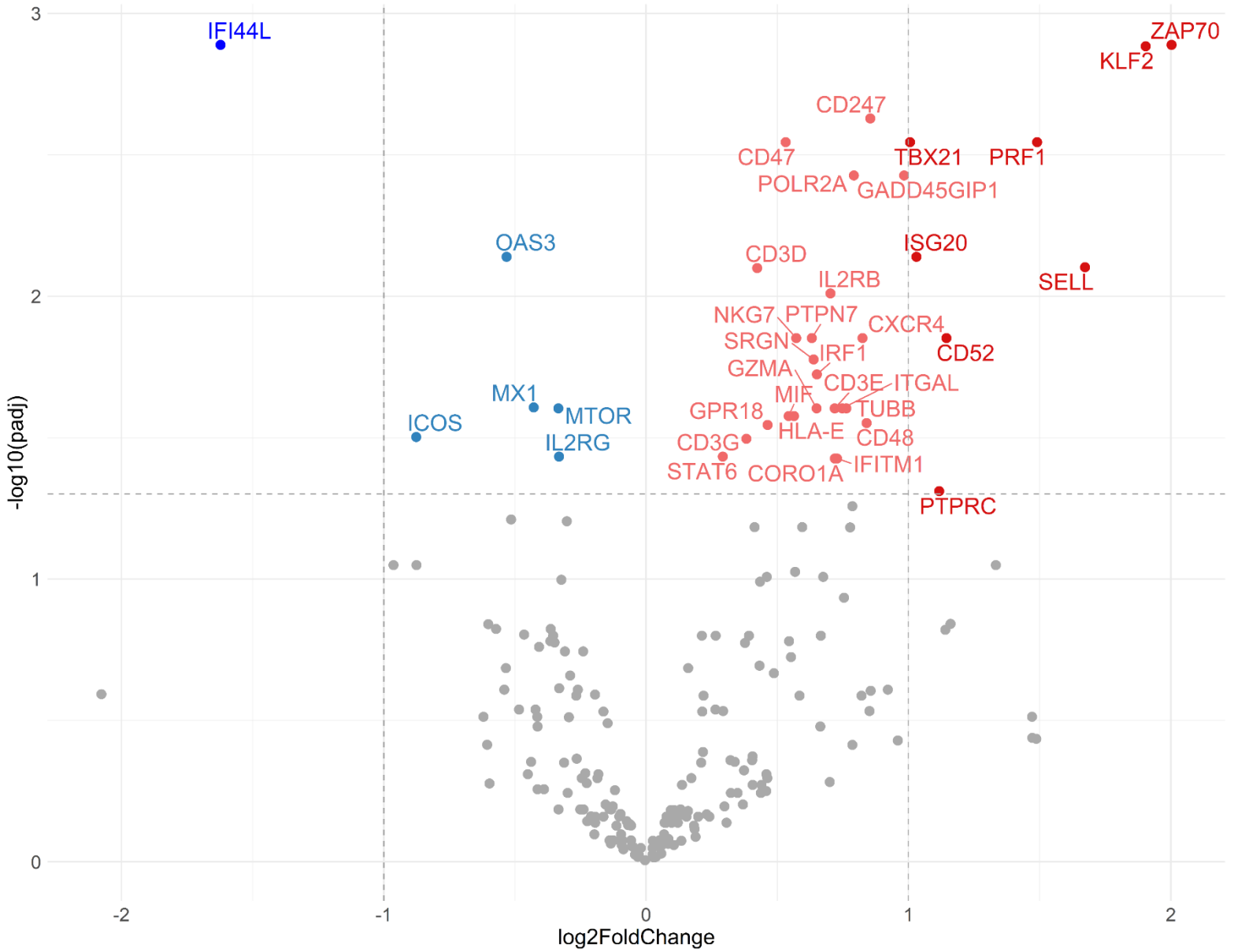
Immunotranscriptomic profiling of γδ T cells by bulk RNA sequencing





- Immune Response Panel (Illumina)
- 395 immunologically relevant genes

➢ 36 differentially expressed genes



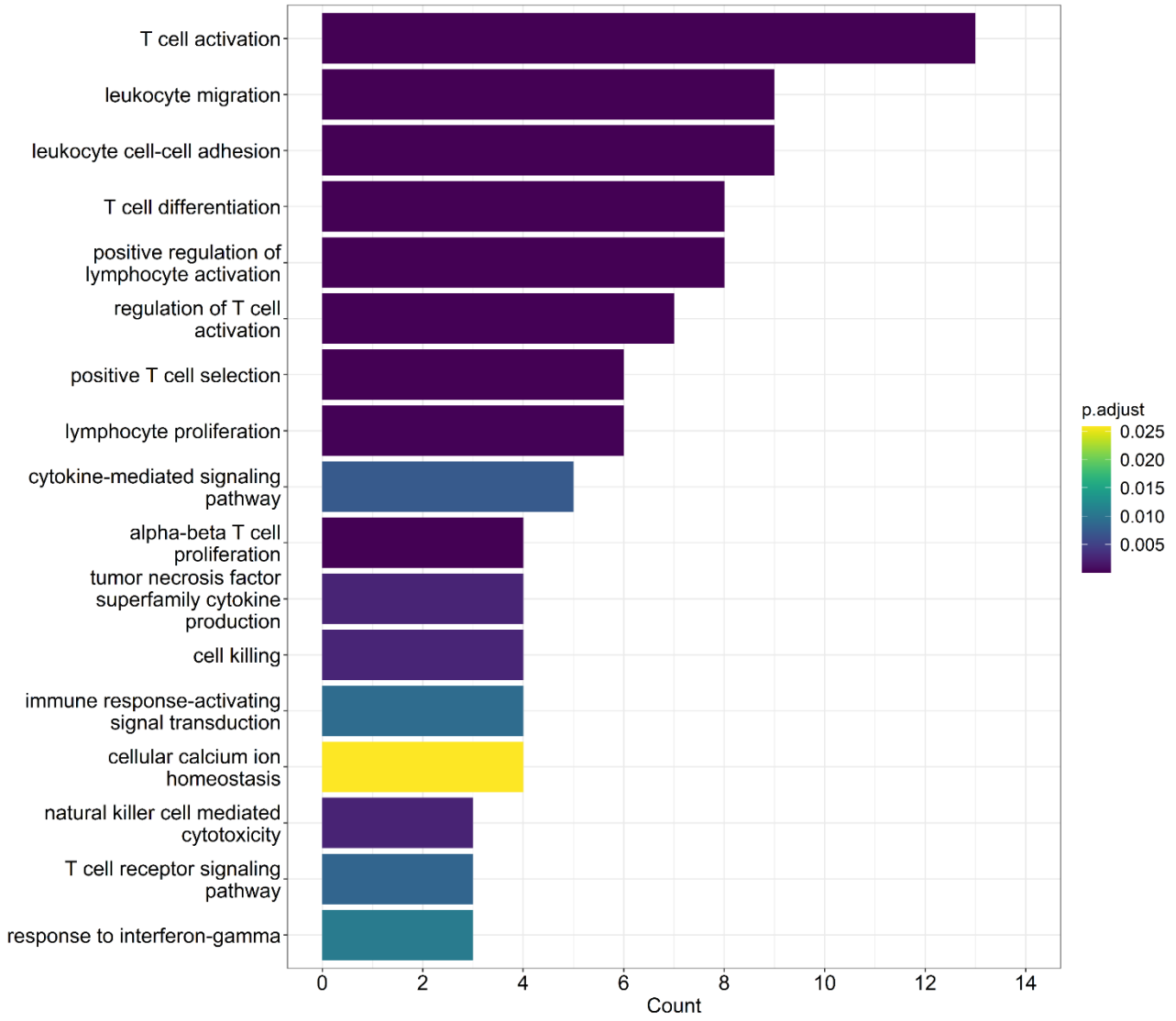
IFN-γ production and response:
TBX21, IRF1, IL2RB,
IFITM1, ISG20, GADD45G

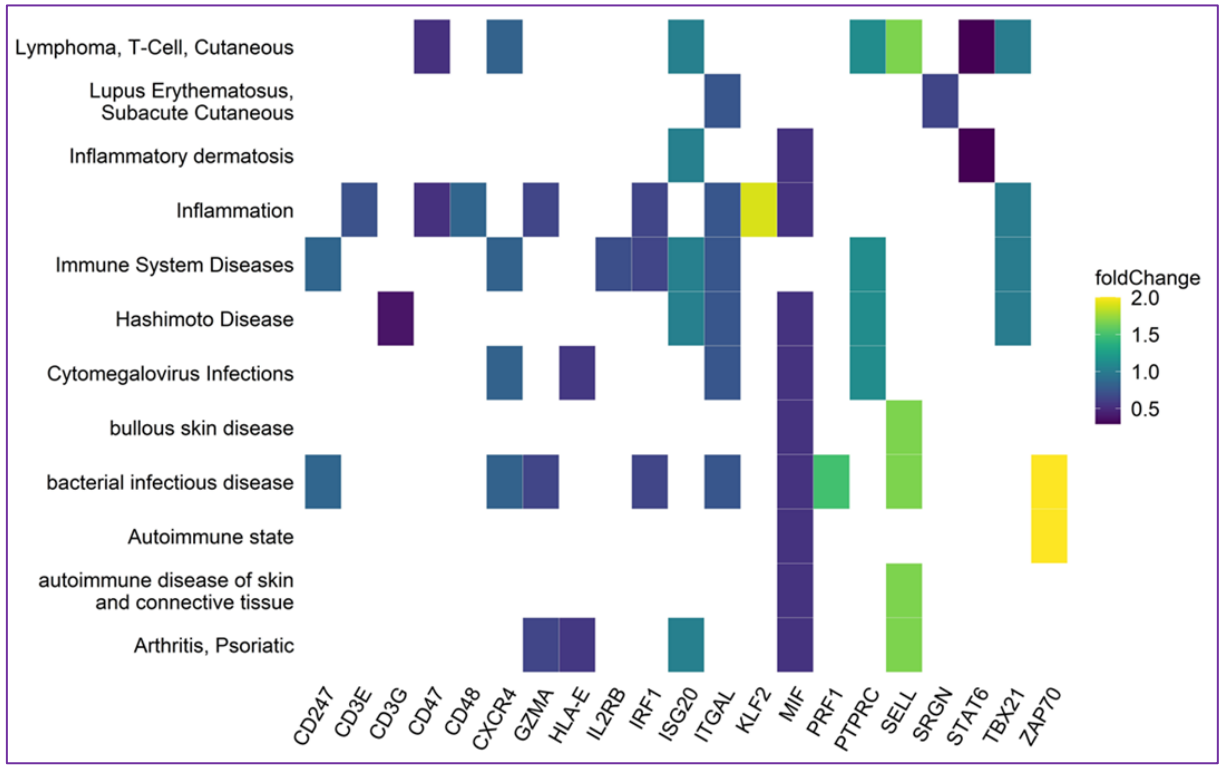
TCR signalling:
ZAP70, CD247, CDRD/E/G

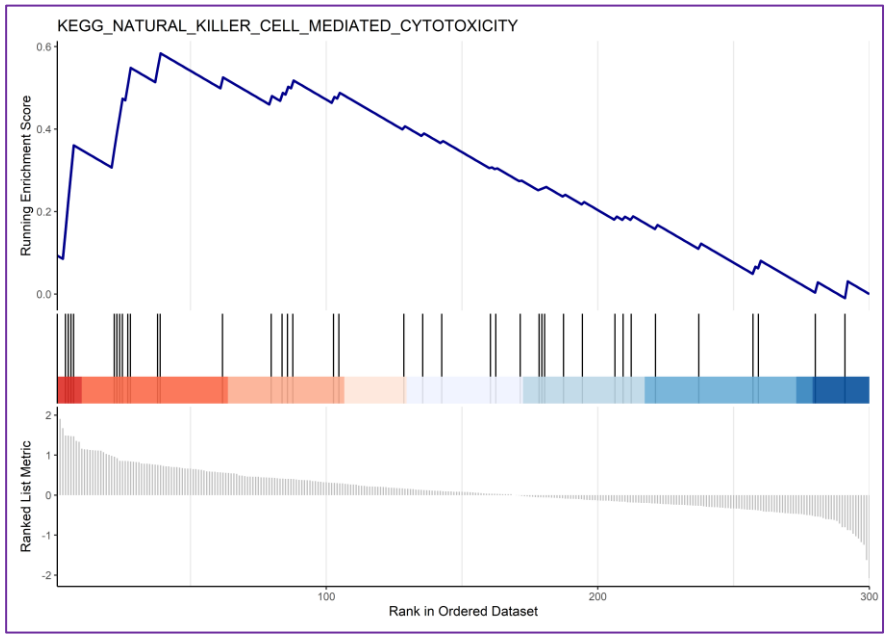
Cytotoxicity:
PRF1, GZMA, SRGN, NKG7, POLR2A

Trafficking/recirculation:
KLF2, SELL, CXCR4

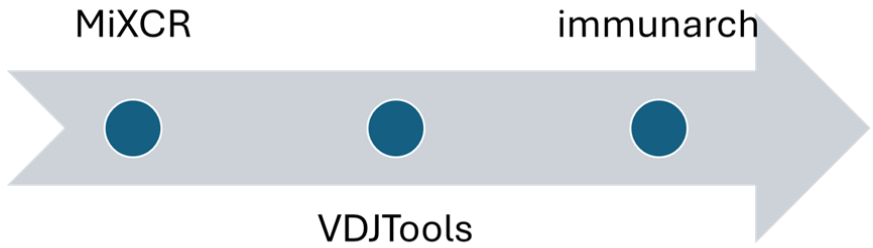
Survival:
CD47, CORO1A, HLA-E


T cell activation
leukocyte migration
leukocyte cell-cell adhesion
T cell differentiation
positive regulation of lymphocyte activation
regulation of T cell activation
positive T cell selection
lymphocyte proliferation
cytokine-mediated signaling pathway
alpha-beta T cell proliferation
tumor necrosis factor superfamily cytokine production
cell killing
immune response-activating signal transduction
cellular calcium ion homeostasis
natural killer cell mediated cytotoxicity
T cell receptor signaling pathway
response to interferon-gamma
0
2
4
6
8
10
12
14
Count
p.adjust
0.025
0.020
0.015
0.010
0.005


Lymphoma, T-Cell, Cutaneous
Lupus Erythematosus, Subacute Cutaneous
Inflammatory dermatosis
Inflammation
Immune System Diseases
Hashimoto Disease
Cytomegalovirus Infections
bullous skin disease
bacterial infectious disease
Autoimmune state
autoimmune disease of skin and connective tissue
Arthritis, Psoriatic
CD247
CD3E
CD3G
CD47
CD48
CXCR4
GZMA
HLA-E
IL2RB
IRF1
ISG20
ITGAL
KLF2
MIF
PRF1
PTPRC
SELL
SRGN
STAT6
TBX21
ZAP70
foldChange
2.0
1.5
1.0
0.5

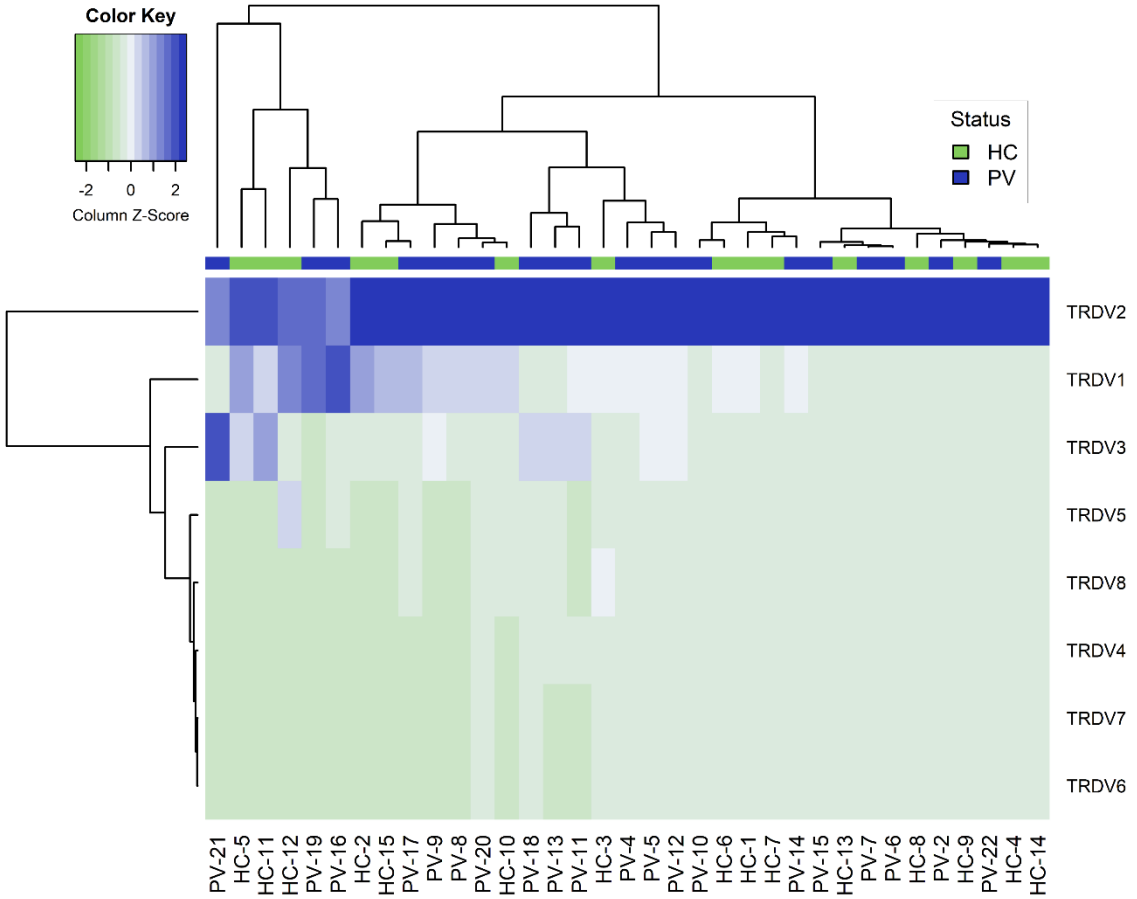

KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY
Running Enrichment Score
0.6
0.4
0.2
0.0
Ranked List Metric
2
1
0
-1
-2
100
200
300
Rank in Ordered Dataset

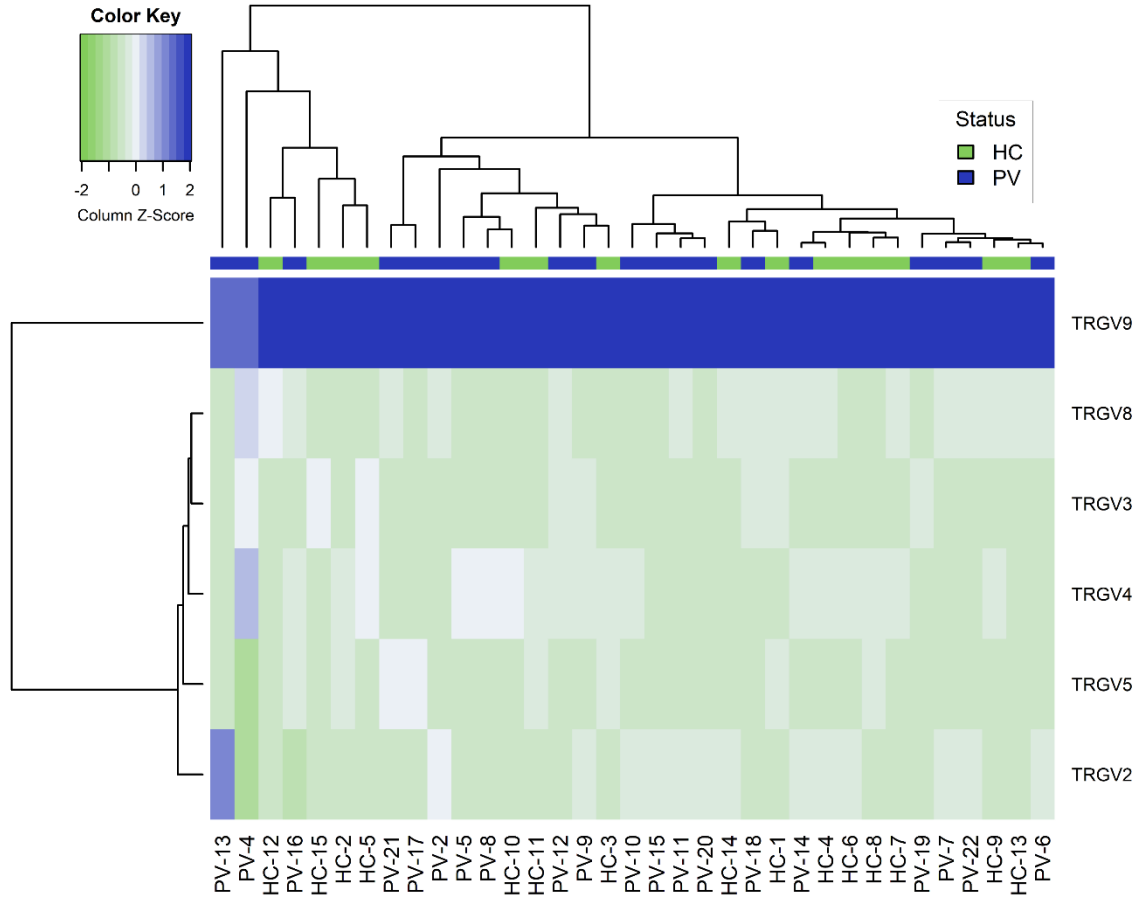
The analysis of T-cell receptor repertoires (TCR-Seq)



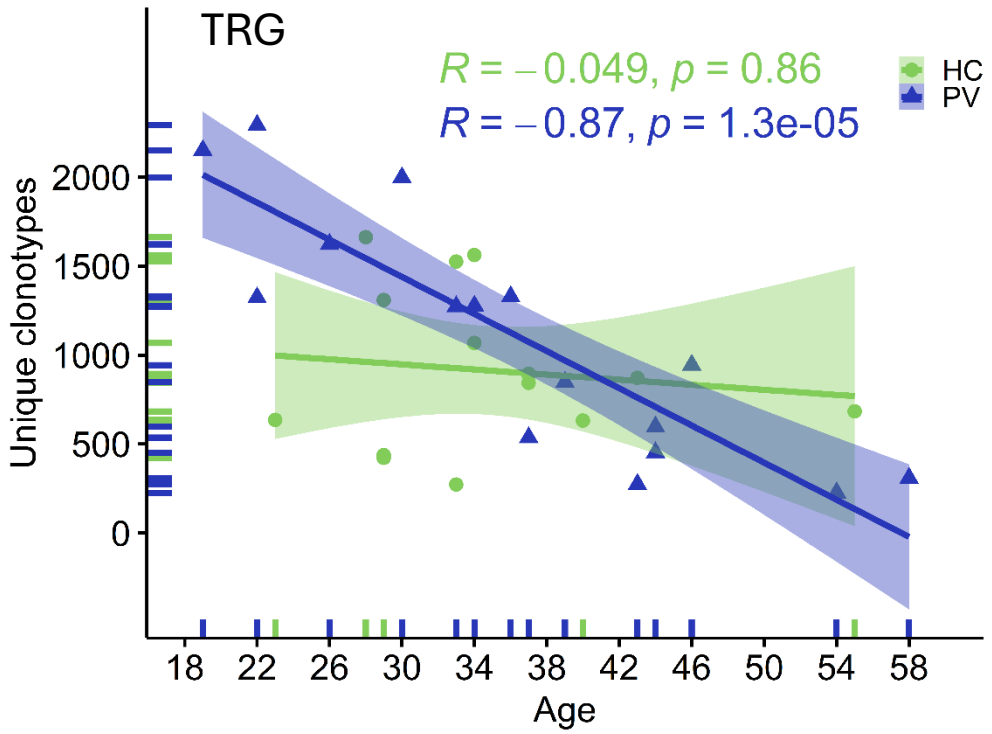
- Archer® Immunoverse™-HS TCR kit
  - Simultaneous sequencing of α, β, γ, and δ CDR3 regions

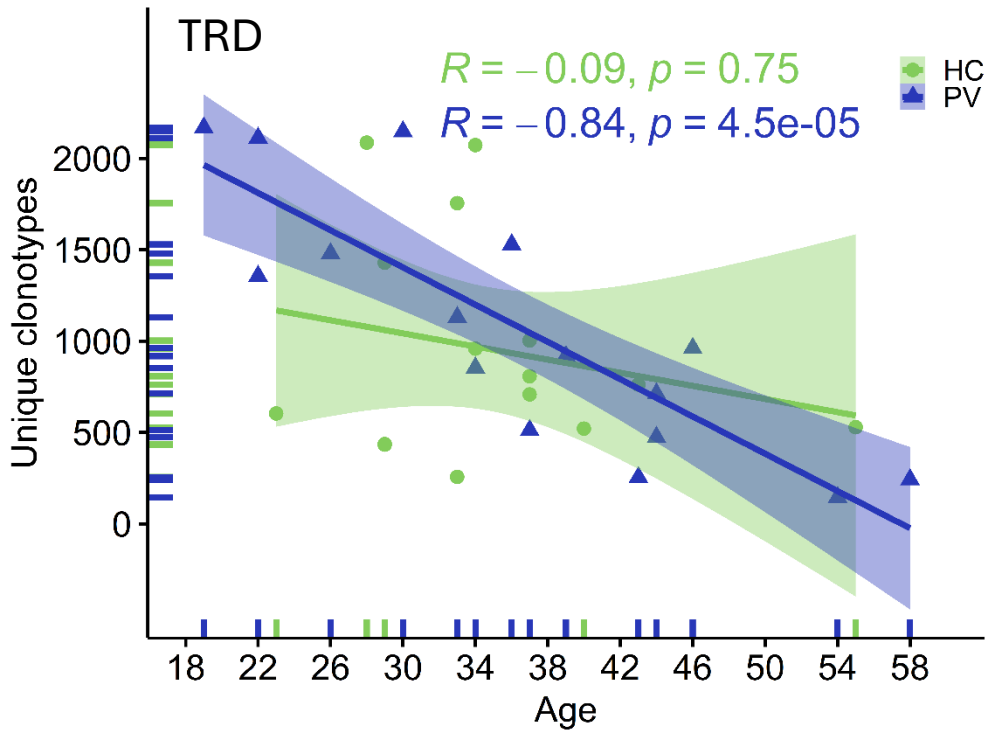
➢ **TRDV2-TRDJ1** and **TRGV9-TRGJP** clonotypes dominated the repertoire in most samples, with no significant differences between cases and controls



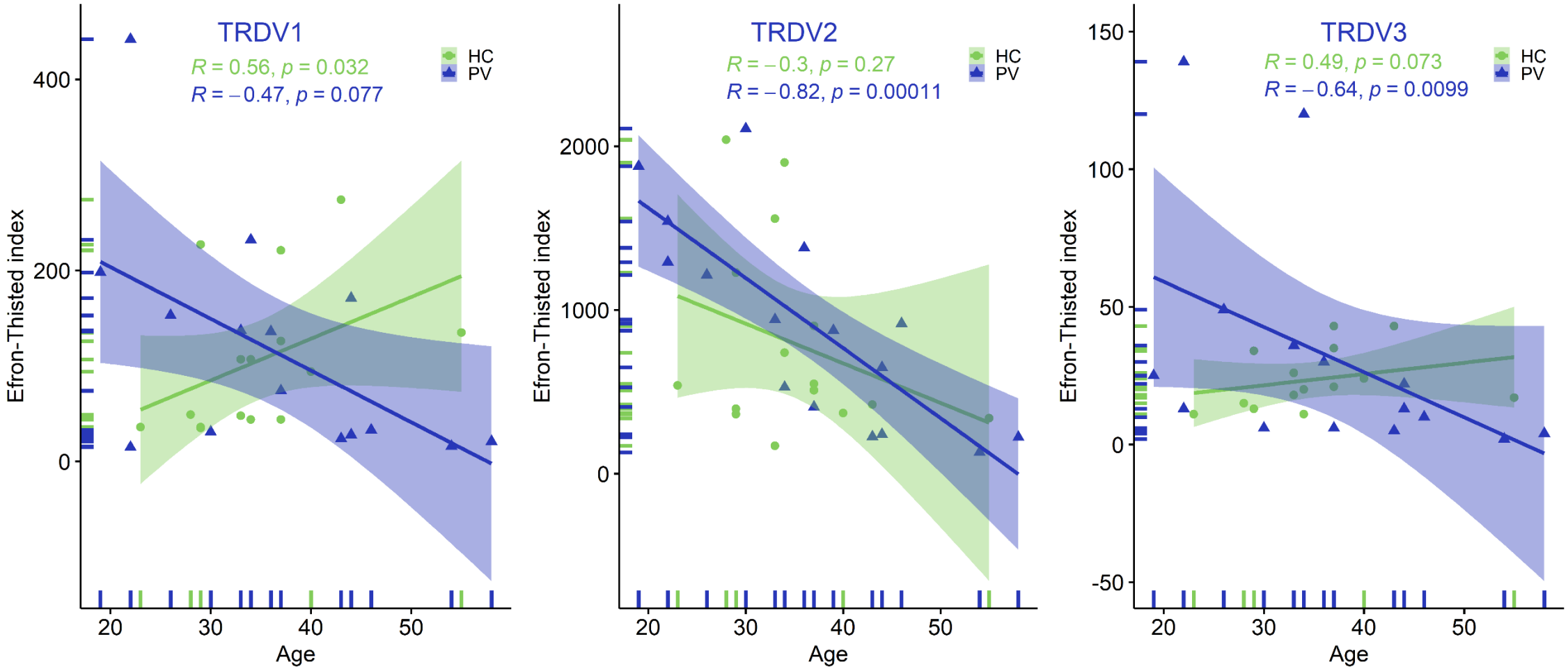


➢ **TRG AND TRD REPERTOIRE DIVERSITY SIGNFICANTLY DECREASES WITH AGE IN PV**, BUT **REMAINS STABLE IN AGE-MATCHED HEALTHY CONTROLS**

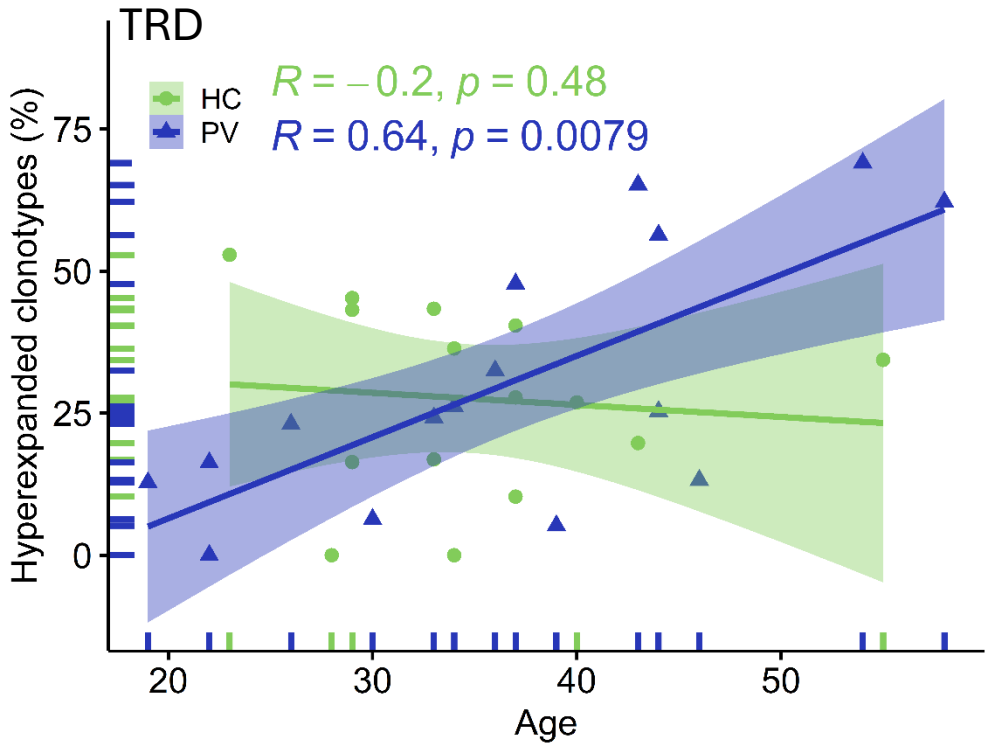


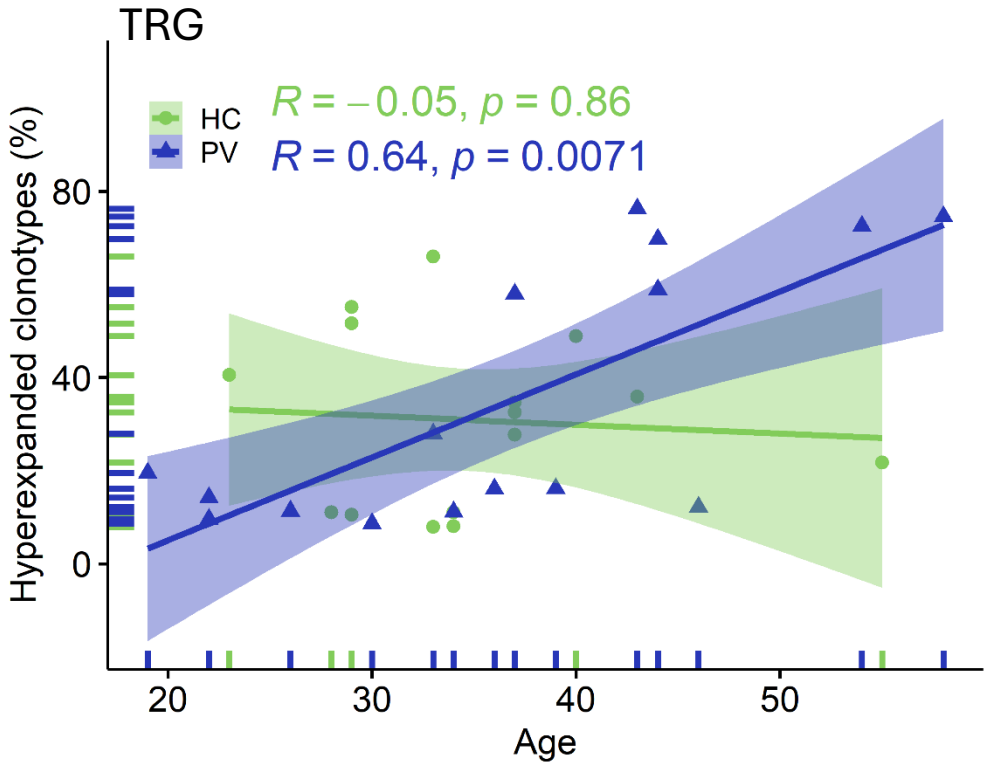


➢ SIGNIFICANT **AGE-RELATED LOSS OF RARE TCRδ CLONOTYPES IN PV, CONTRASTING INCREASED TRDV1 AND TRDV3 DIVERSITY IN HEALTHY CONTROLS**



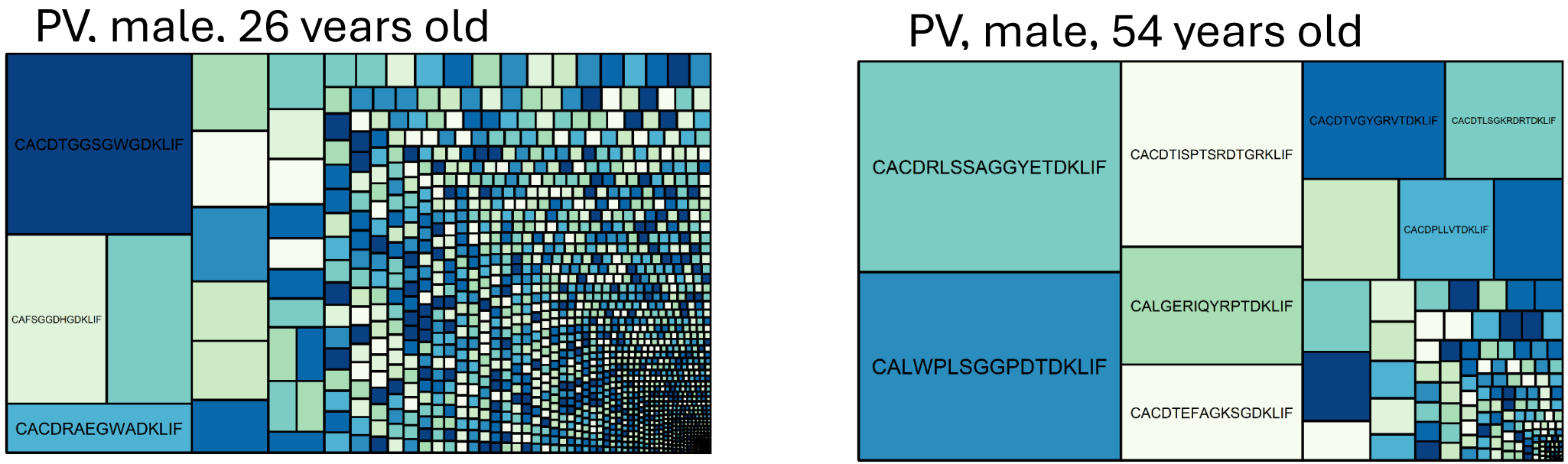
➢ IN PV PATIENTS, **AGING** IS LINKED TO A **SIGNIFICANT INCREASE IN THE FREQUENCY OF HYPEREXPANDED* CLONOTYPES**



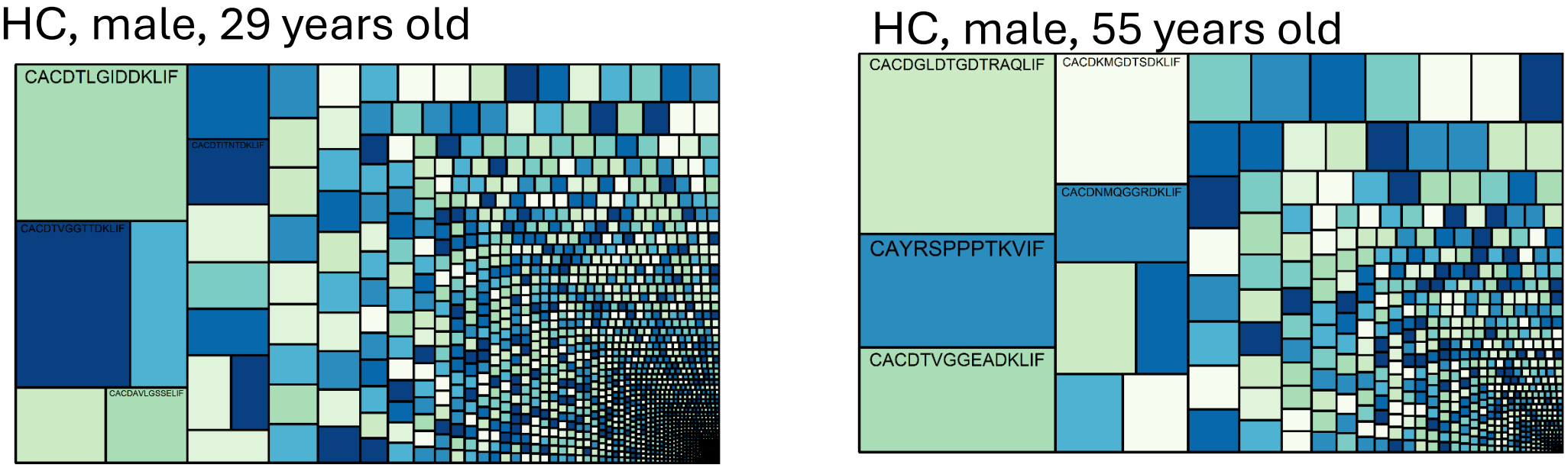


*clonotypes that occupy >5% of the repertoire

A

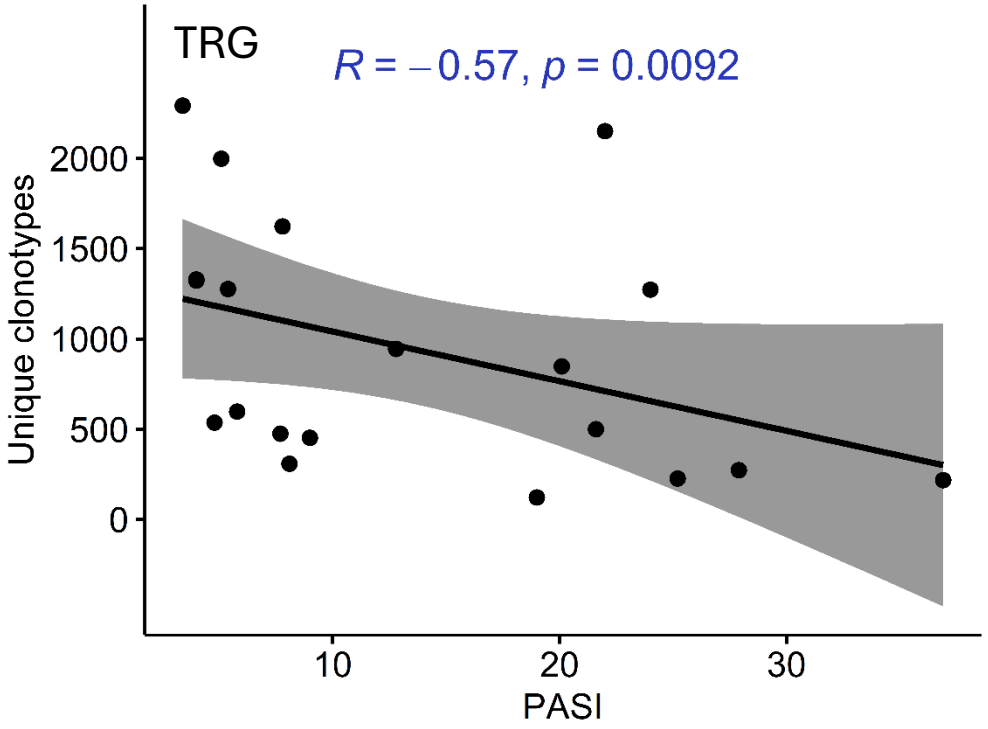


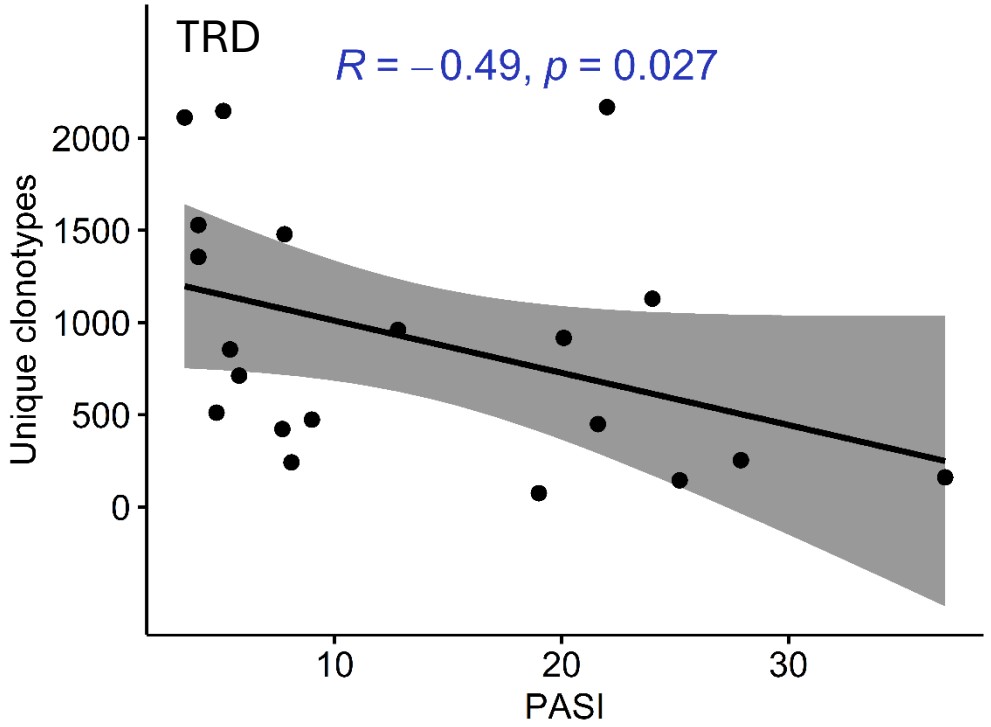
B



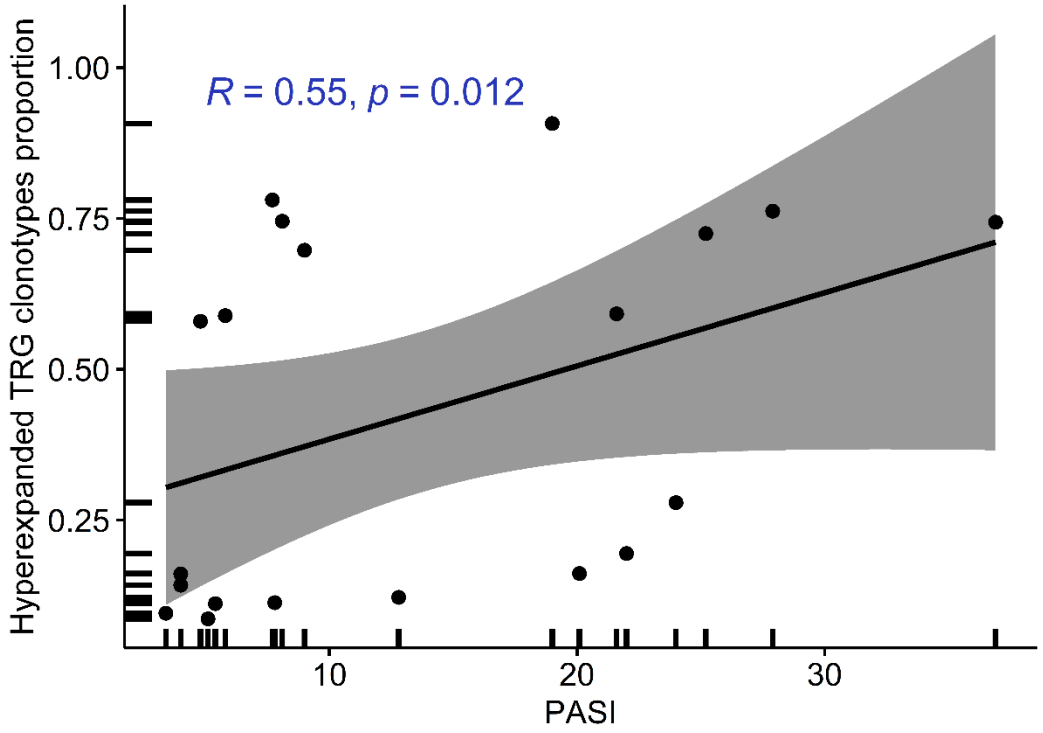
Representative treemap plots showing TCRδ clonotypes of younger and older age-matched PV patients (A) and healthy controls (B)

➢ DISEASE SEVERITY NEGATIVELY CORRELATES WITH TRG AND TRD CLONOTYPE DIVERSITY

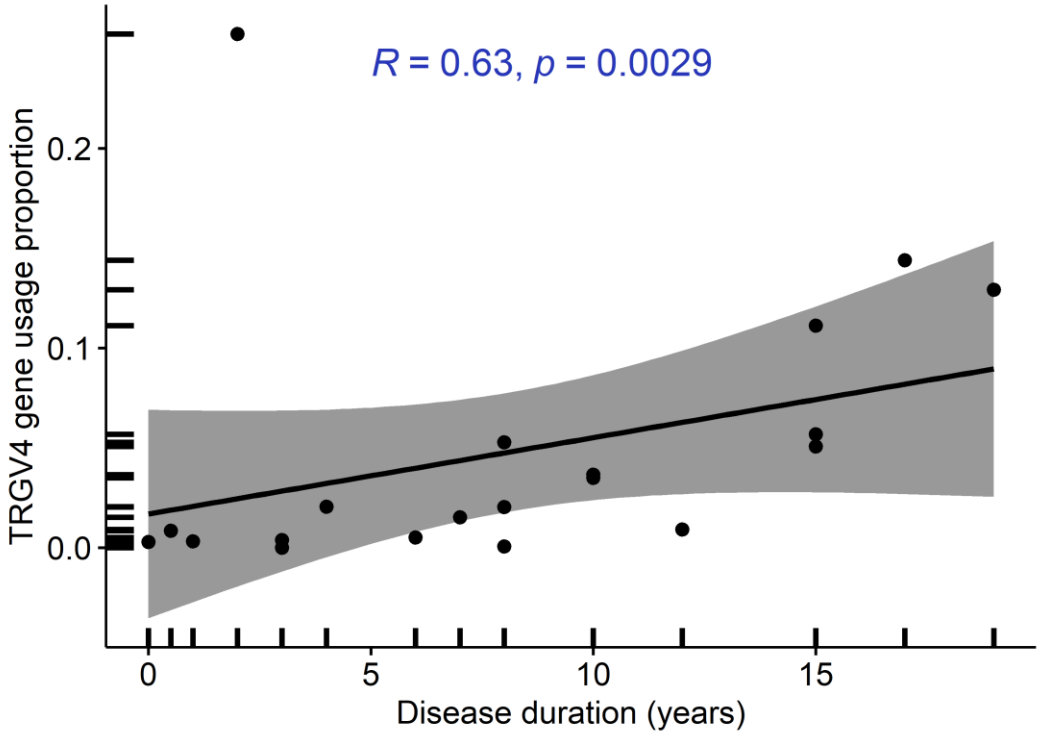




- **DISEASE SEVERITY** IS ASSOCIATED WITH **HIGHER EXPANSION OF TRG CLONOTYPES**



- **DISEASE DURATION** IS ASSOCIATED WITH A **HIGHER PREVALENCE OF TRGV4 CLONOTYPES**



Conclusion

The proportions, gene expression, and the diversity of TCR repertoires of peripheral γδ T cells are altered in psoriasis vulgaris patients

Impact of the duration and severity of the disease

Age and sex associated differences

Future aims: spectral flow cytometry and single-cell sequencing

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