



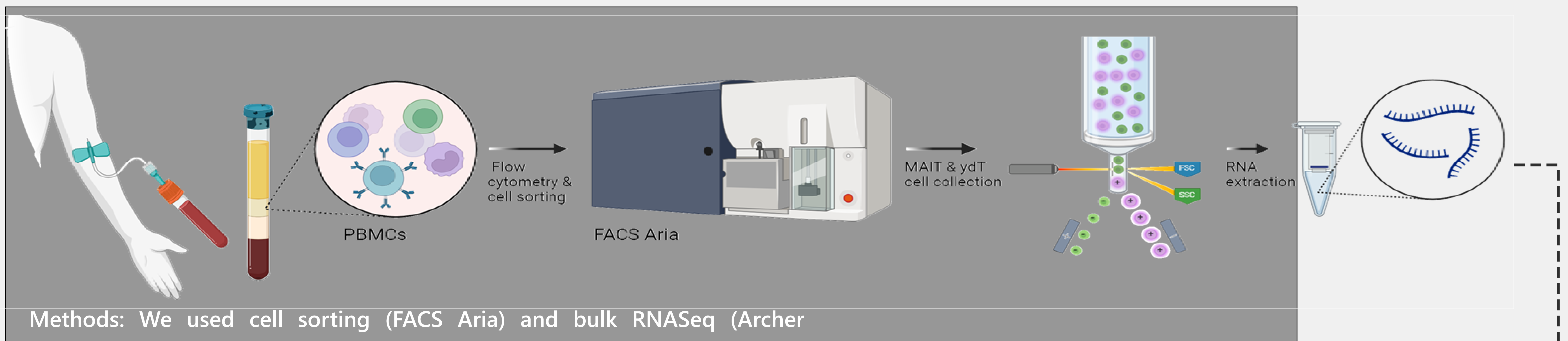
The peripheral MAIT cell TCR α/β repertoires alter with age of psoriasis vulgaris patients.



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Purpose: Psoriasis vulgaris (PV) is a chronic autoinflammatory skin disease characterised by dysregulated T cell activation. Adaptive $\alpha\beta$ T cells are typically involved, but a role for innate-like, mucosal-associated invariant T (MAIT) cells has also been proposed. These unconventional cellular actors mediate potent immune responses against non-peptide antigens in MR1-restricted manner, using semi-invariant TCRV α 7.2 T cell receptor (TCR), tailored by the limited number of TRAV (TRAV1-2) and TRAJ (TRAJ33, TRAJ12 or TRAJ22) genes, in combination with more diverse TRBV/D/J gene segments. Despite the seemingly limited repertoire, novel evidence supports greater MAIT TCR diversity in terms of alternative TRAV/J gene usage and high TRB clonality, but its relevance in PV has only been partially addressed.



Methods: We used cell sorting (FACS Aria) and bulk RNASeq (Archer Immuniverse™-HS TCR assay, NextSeq Illumina platform) with MiXCR, VDJTools and Immunarch pipelines to decipher TCR α and TCR β repertoires of flow-sorted MAIT cells (MR1-5-OP-RU tetramer+ TCRV α 7.2+) from 26 PV patients and 12 healthy controls.

Results: In total, 12219 unique TRA and 60478 TRB clonotypes were observed in PV patients and controls, with similar and predominant expression of TRAV1-2-TRAJ33/20/12 and TRBV20-1/TRBV6-4/TRBV6-1/TRBV6-2/TRBV4-2 variants (Fig.1). The TCR β chain was highly polyclonal and private, contrasting oligoclonal and frequently shared TCR α repertoires (Fig.2). No significant differences in diversity, V/(D)/J gene usage, or clonotype distribution were observed in case-control comparisons. Age, however, emerged as a notable negative predictor of both, TRA and TRB repertoire size in PV, but not healthy subjects (Fig.3a-b). This age-associated reduction of TRA and TRB variety likely reflects decline of the low-frequent clonotypic variants in PV (Fig.3c-d). The diminished TRB diversity was further accentuated by an increased proportion of hyperexpanded clonotypes (Fig.4b), occupying > 5% of the total repertoire. Hyperexpanded TRB clonotypes in PV group did not overlap between individual repertoires and displayed diverse CDR3 properties, supporting influence of individually unique epitopes in MAIT repertoire arrangement.

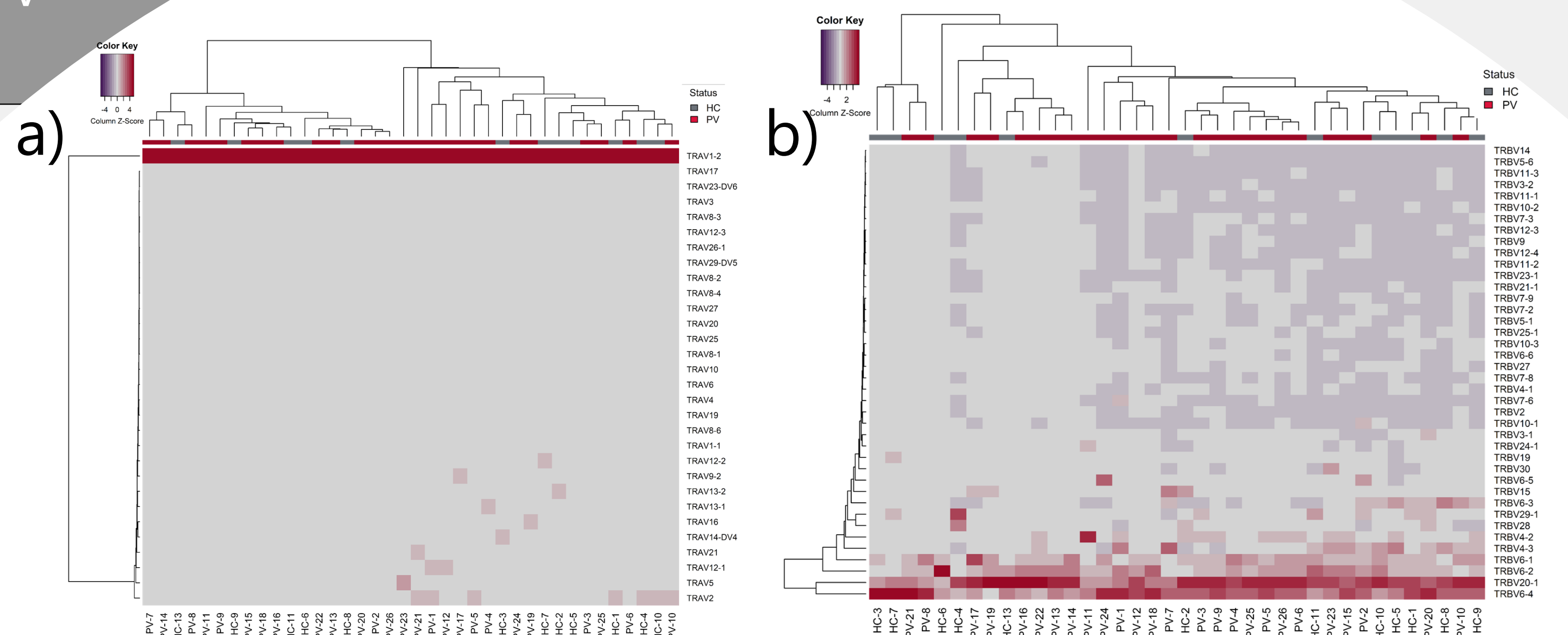


Figure 1. Hierarchical clustering of (A) TRAV and (B) TRBV gene usage in MAIT cells of PV and healthy controls. Data were calculated according to default settings of the VDJTools *CalcSegmentUsage* function.

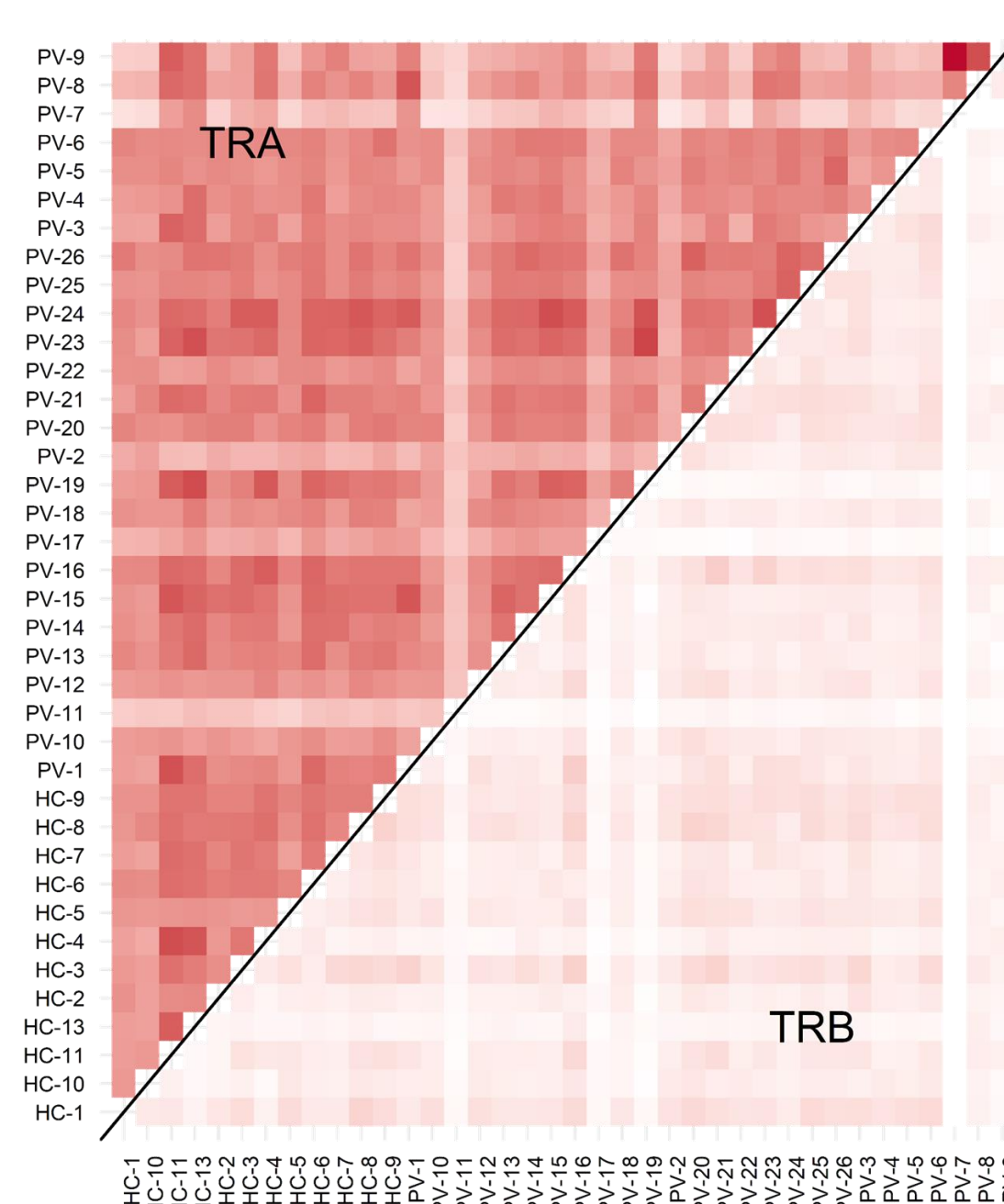


Figure 2. Heatmap of the Jaccard index indicating higher (dark red) or lower (light red) TRA and TRB gene overlap between PV and control samples.

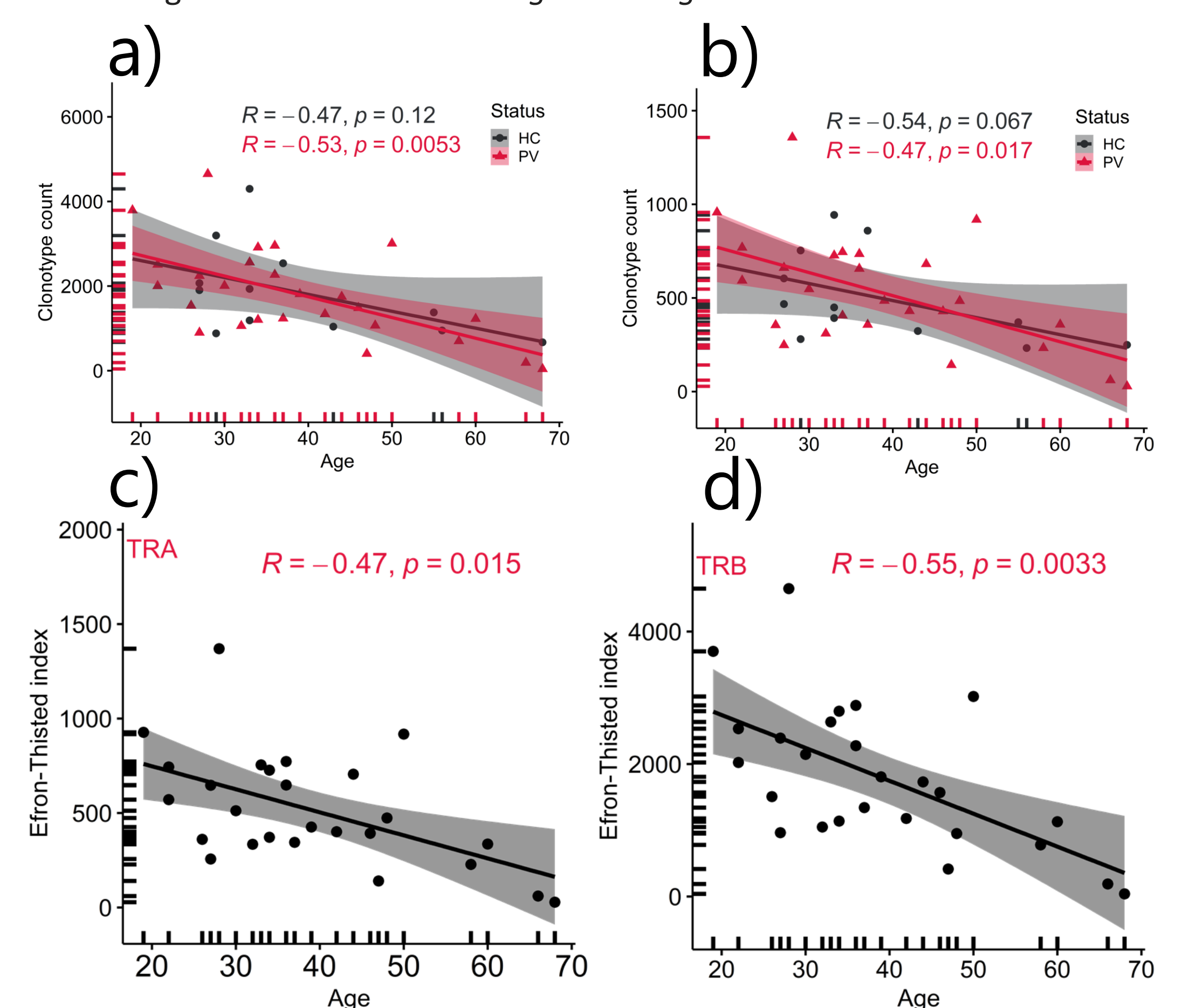


Figure 3. Correlation between age (years) and (a) TRA or (b) TRB clonotype count, and (c-d) Efron-Thisted diversity indexes. Spearman's rank correlation test.

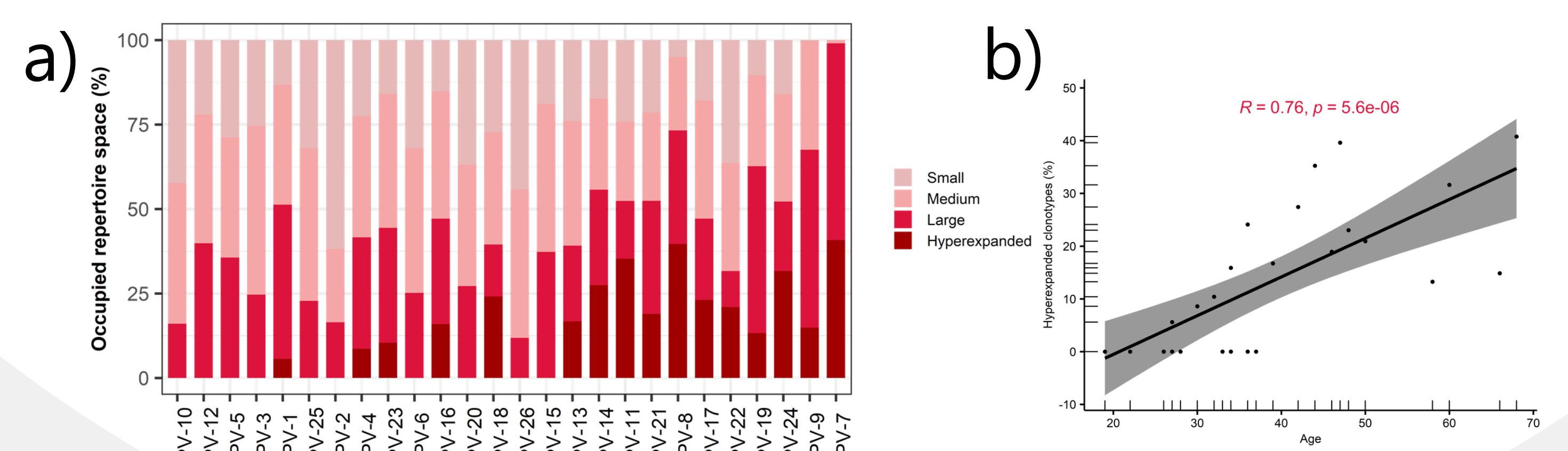


Figure 4. Stacked barplots and correlation plot demonstrating increase of hyperexpanded clonotypes with age. (a) Repertoires are ordered by patients' increasing age on the X-axis. Categories of clonotype frequency in relative frequencies: "small" (<0.0005), "medium" (0.0005–0.005), "large" (0.005–0.05) and "hyperexpanded" (0.05–1). (b) Spearman's correlation test.

Conclusion: Our results support substantial diversity of MAIT TCR β repertoire and highlight the influence of age in diminished diversity of TCR α and TCR β repertoires in psoriasis.