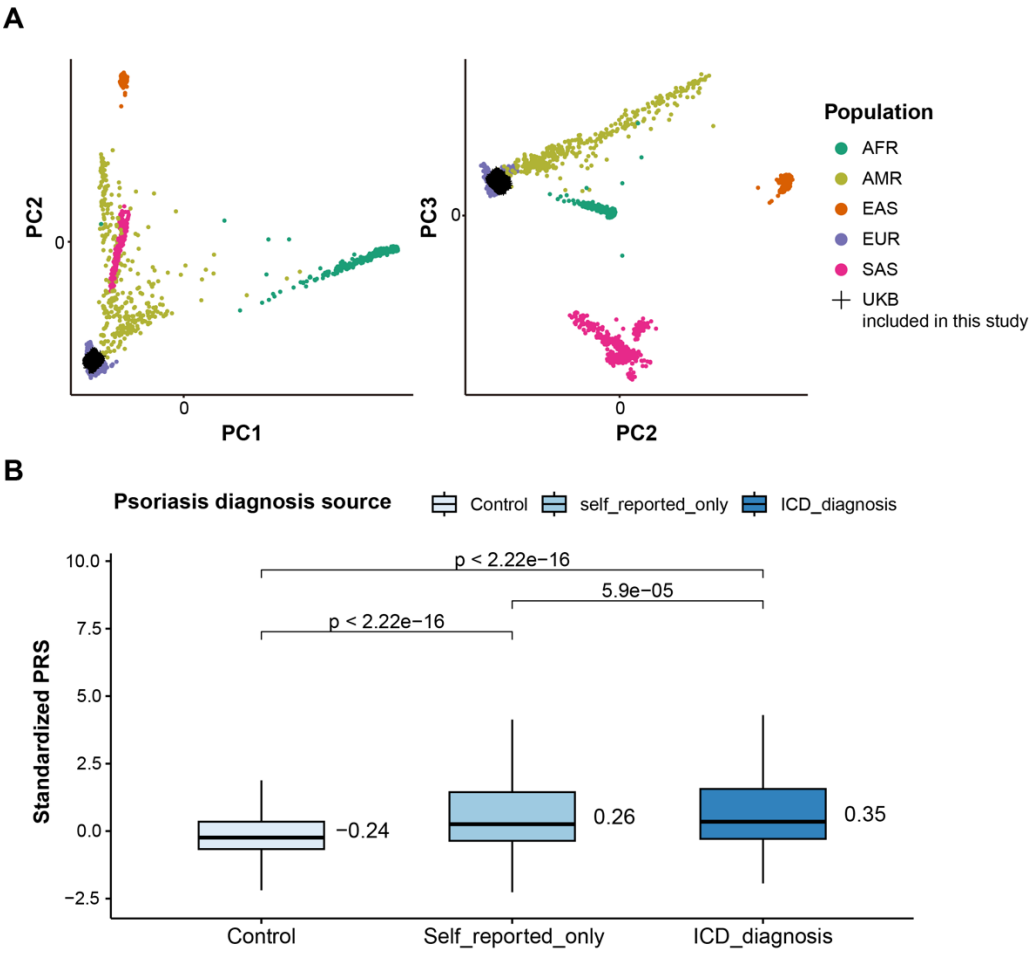
Supplementary Figures

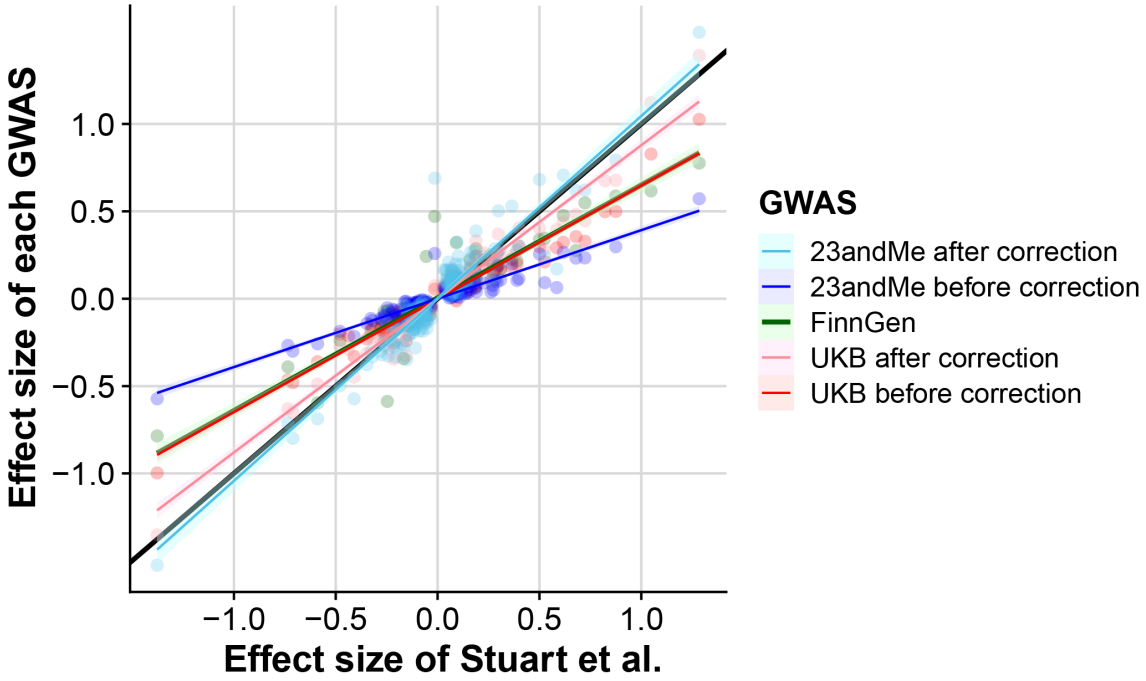
Supplementary Figure 1. UK Biobank samples used in this study.

(A) Principal components of UK Biobank samples projected onto the 1000 Genomes (1kG) Project reference panel, which includes multi-ancestry samples. **(B)** Polygenic risk scores (PRSs) of UK Biobank samples stratified by psoriasis status, including ICD-diagnosed cases, or self-reported only cases, and healthy controls. Meta-analysis of FinnGen r10 and Stuart et al. GWAS was used to calculate UK Biobank PRSs. The center line in each box plot denotes the median value, the box bounds denote the 25th and 75th percentiles, and the whiskers extend to 1.5 × the interquartile range from the box bounds.

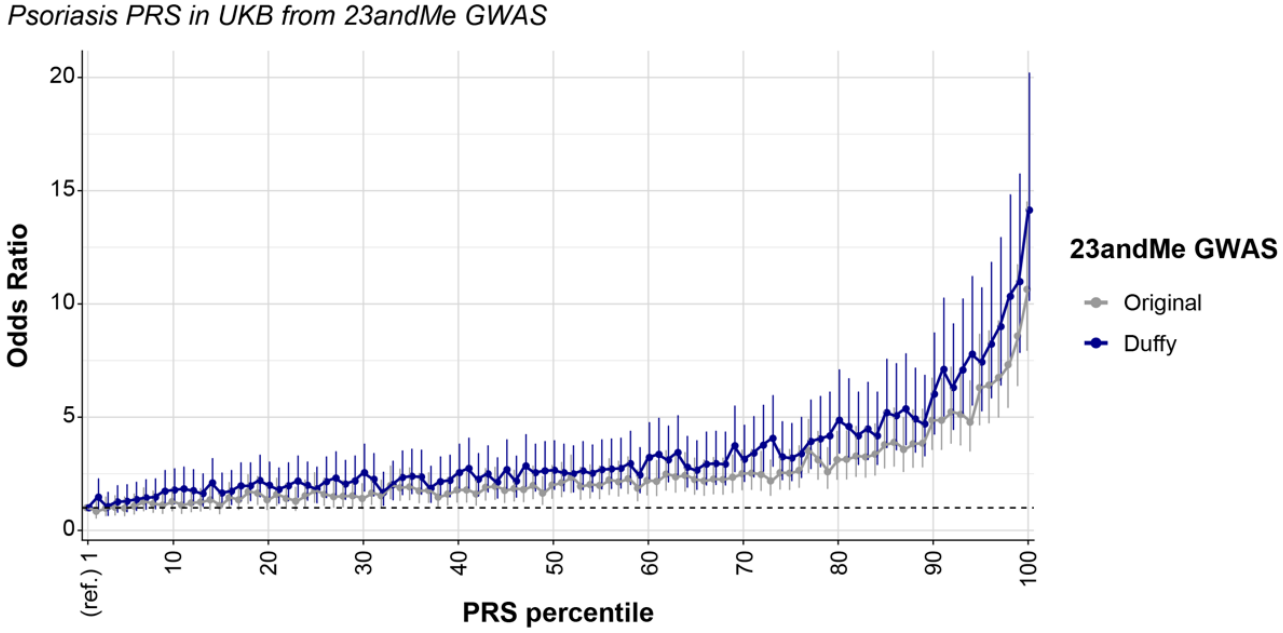


Supplementary Figure 2. Effects of Duffy's adjusted approach in UK Biobank and 23andMe.

This plot shows the effect sizes of the 198 COJO SNPs identified in our GWAS for psoriasis risk variants across individual GWAS summary statistics. Effect sizes in UKB, 23andMe, and Finngen were compared with the corresponding SNPs from Stuart et al. as a reference. For UK Biobank and 23andMe, both raw and misclassification-corrected effect sizes are shown. Each line represents the fitted regression line for the corresponding GWAS dataset.

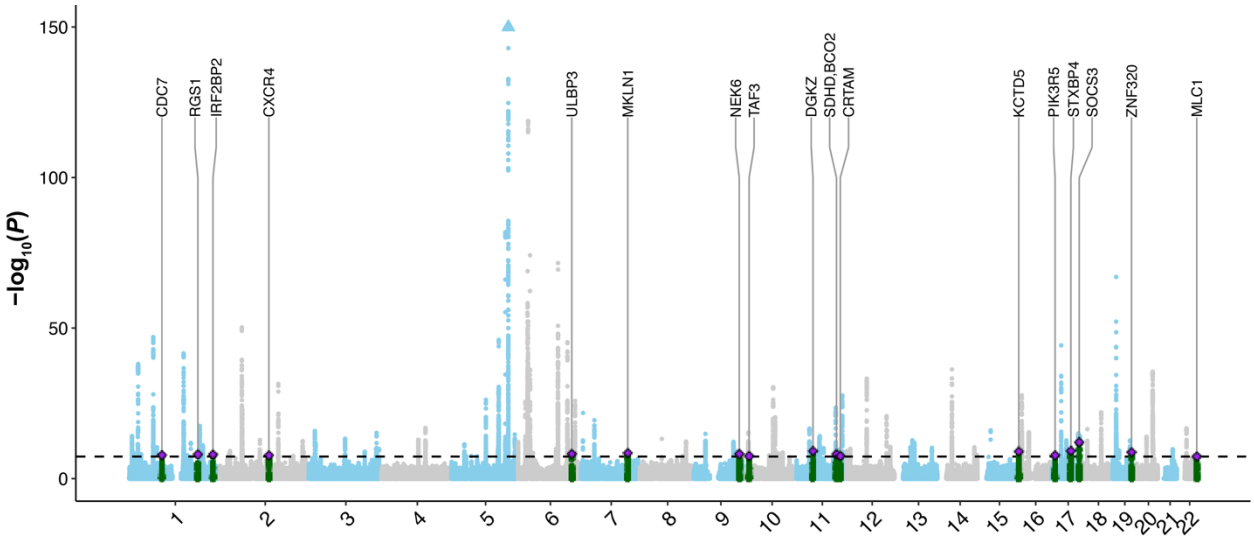


Supplementary Figure 3. PRS analysis evaluating the effect of Duffy's adjustment.
Polygenic risk scores (PRSs) were calculated for UK Biobank samples using both the original 23andMe GWAS and the Duffy-adjusted 23andMe GWAS summary statistics. The PRS results were stratified by percentile, and odds ratios were estimated using the lowest percentile group as the reference. Each point represents the odds ratio and error bars represent the 95% confidence intervals.

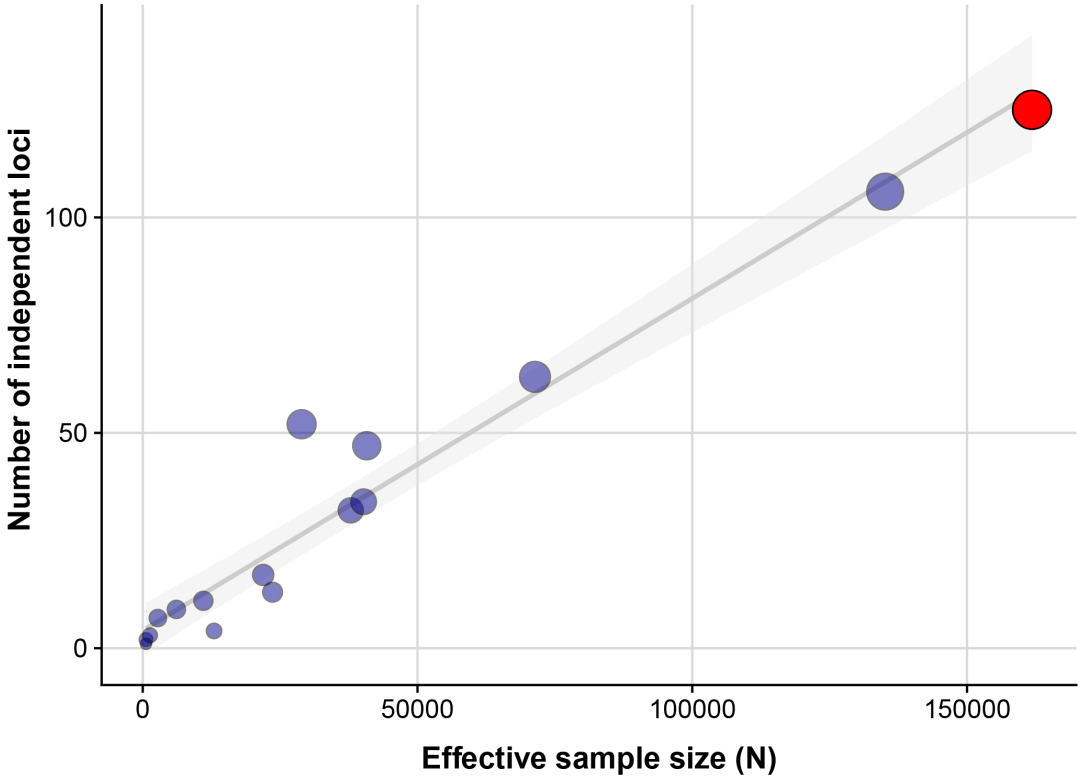


Supplementary Figure 4. Manhattan plot of psoriasis meta-GWAS.

Newly identified loci are shown as dark green points. The lead SNP in each region is shown as a purple diamond, and SNPs with *p*-values < 1×10^{-150} are clipped and shown as triangles. SNPs in the MHC region were excluded from the analysis. The mapped genes represent the genes nearest to the lead SNP.

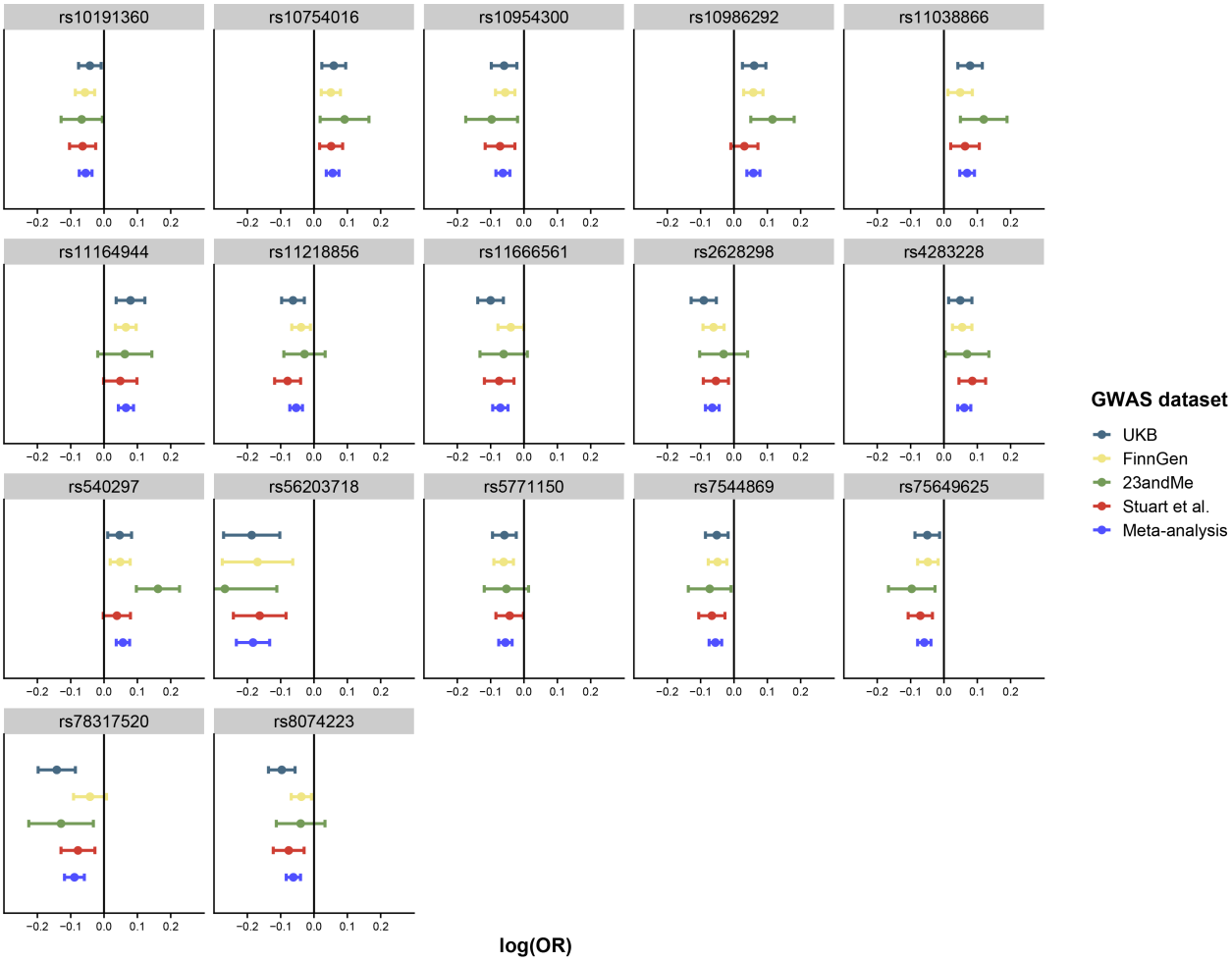


Supplementary Figure 5. Identified independent loci counts corresponding to effective sample size in psoriasis GWAS. The red circle represents the GWAS result from our study. Dot sizes are proportional to the effective sample sizes. Information on the psoriasis GWAS included in this plot is summarized in **Supplementary Data 4**.



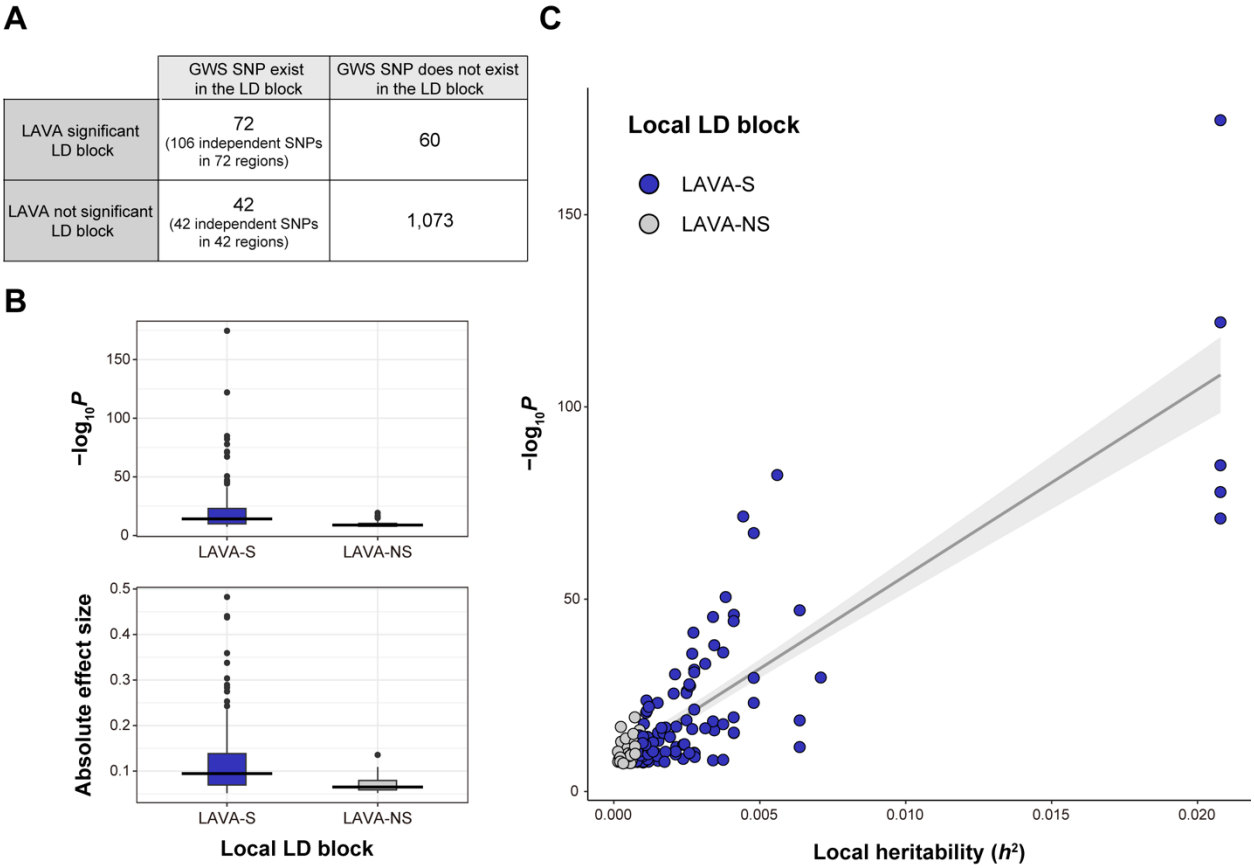
Supplementary Figure 6. Forest plots of effect sizes for newly identified loci.

Newly identified 17 lead SNPs from individual genome-wide association study (GWAS) data and the result of our meta-analysis are shown. The effect size and 95% confidence intervals (calculated as 1.96 × standard error) are represented. OR, Odds ratio.



Supplementary Figure 7. The relationship between Local heritability and genome-wide significance.

(A) Contingency table of LD blocks categorized by the significance of local heritability (LAVA) and the presence of genome-wide significant (GWS) SNPs. **(B)** Comparison of GWAS p-values and effect sizes between 106 independent SNPs located in LAVA-significant (LAVA-S) LD blocks and 42 independent SNPs in LAVA-not significant (LAVA-NS) LD blocks. This analysis was restricted to independent SNPs within LD blocks having at least one GWS SNP. In box plots, the center line denotes the median value, the box bounds denote the 25th and 75th percentiles, and the whiskers extend to 1.5 × the interquartile range from the box bounds. **(C)** Scatter plot showing the relationship between local heritability and psoriasis association *p*-value of LAVA-S and LAVA-NS independent SNPs described in **(B)**.

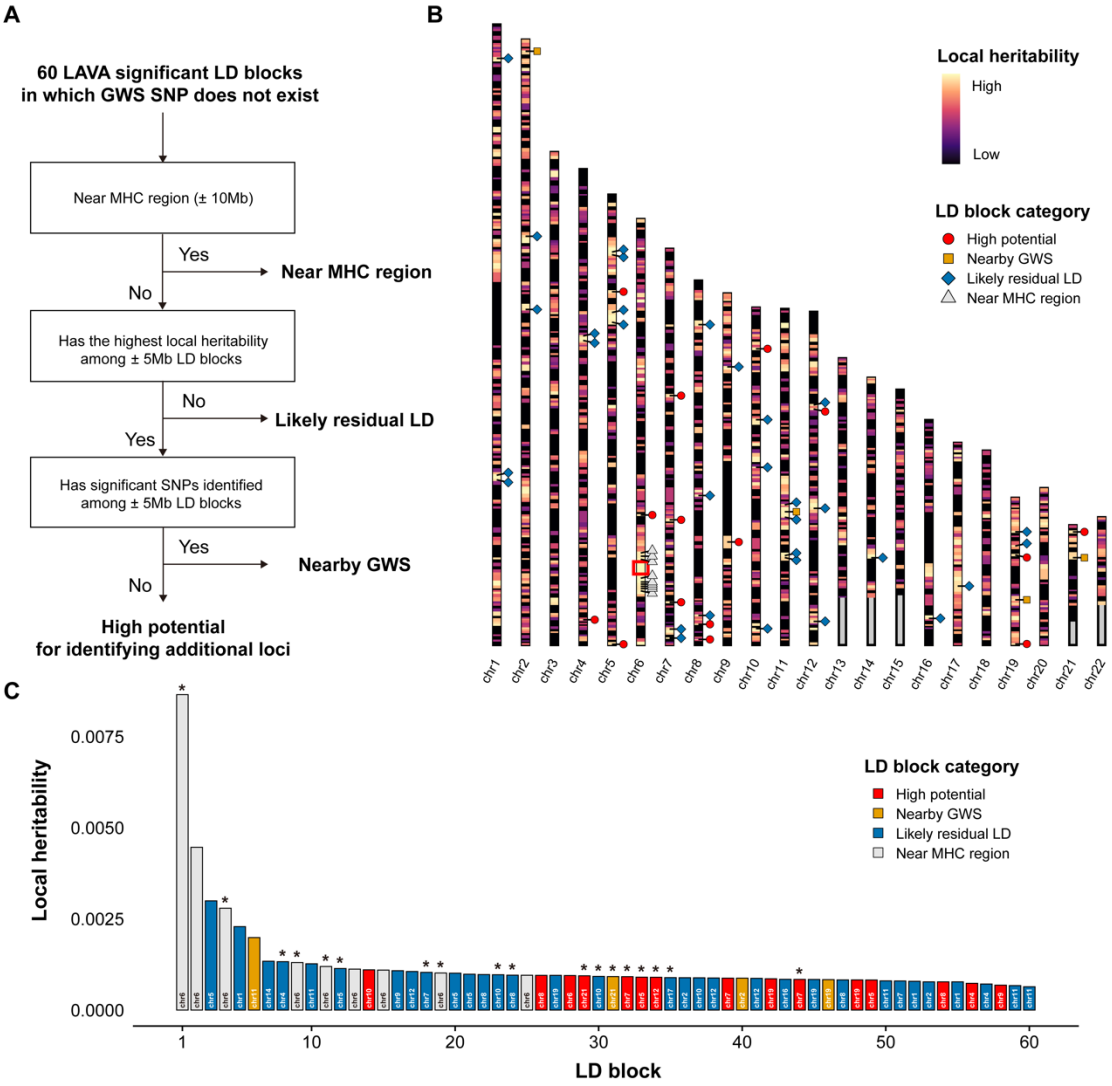


Supplementary Figure 8. Estimating the potential novel discovery of LD blocks that have not reached genome-wide significance in current GWAS.

(A) Flow diagram categorizing LAVA significant regions where no genome-wide significant SNPs were identified.

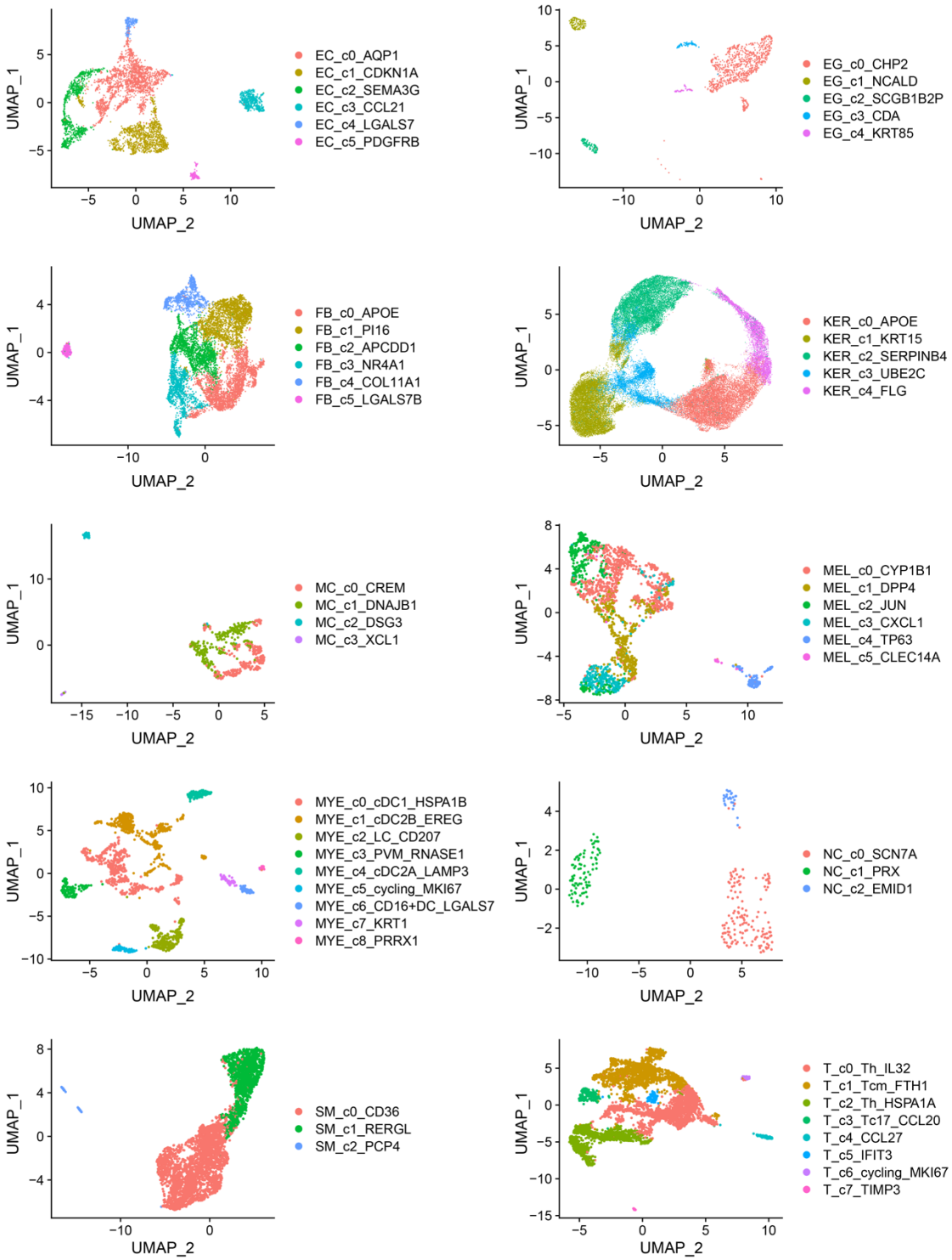
(B) Karyotype plot for the psoriasis-associated SNP discoverability with four categories defined from (A).

(C) Ranked LD blocks with local heritability. Upper asterisk of each block denotes previously reported psoriasis-susceptibility regions.



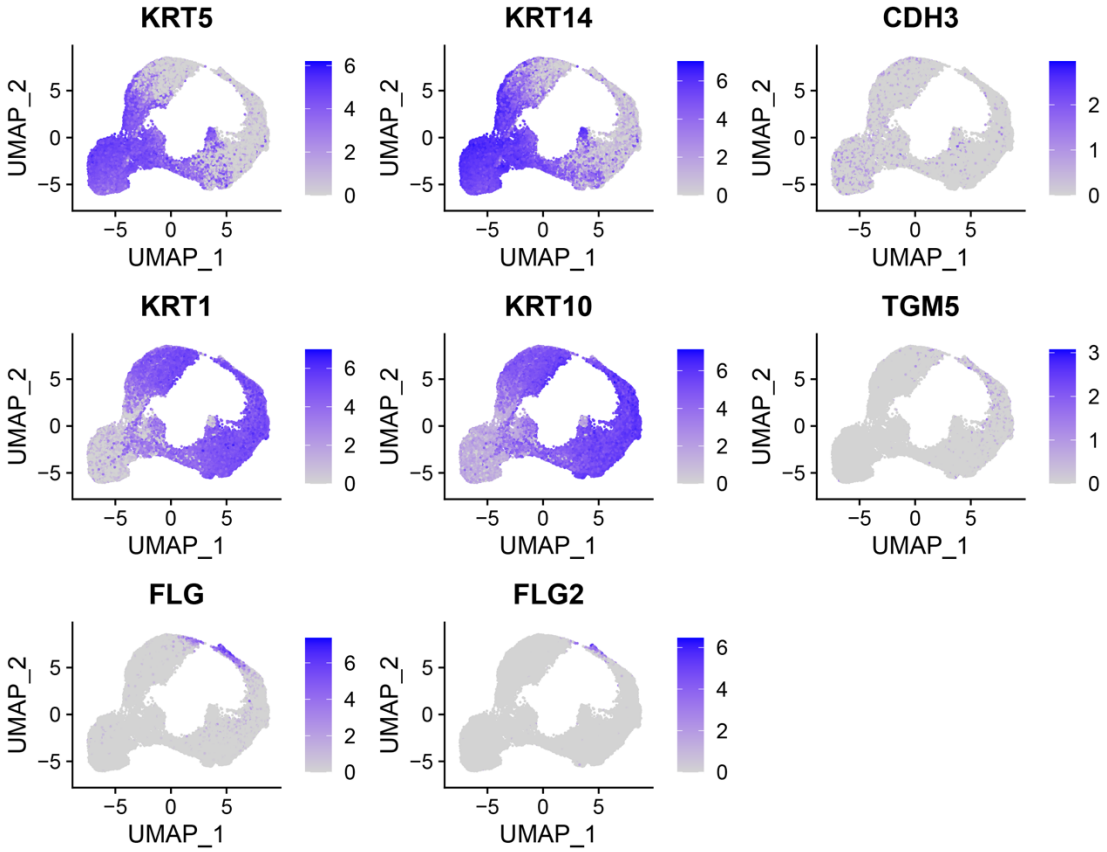
Supplementary Figure 9. UMAPs of cell subtypes.

UMAP analysis were performed independently for each cell type.



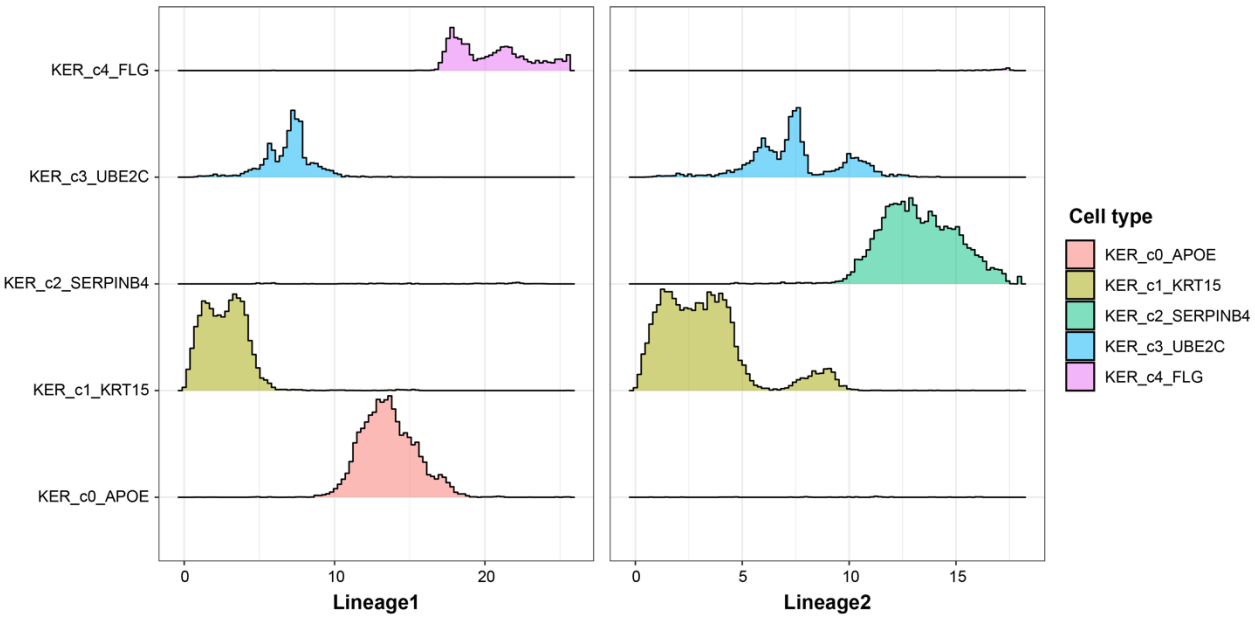
Supplementary Figure 10. Keratinocyte marker expression.

Gene expression of representative markers for the keratinocyte basal (*KRT5*, *KRT14*, and *CDH3*), spinous (*KRT1*, *KRT10*, and *TGM5*), and outer granular (*FLG* and *FLG2*) layers are shown in the UMAP space. Gene expression was adjusted using a size factor and normalized by log transformation.

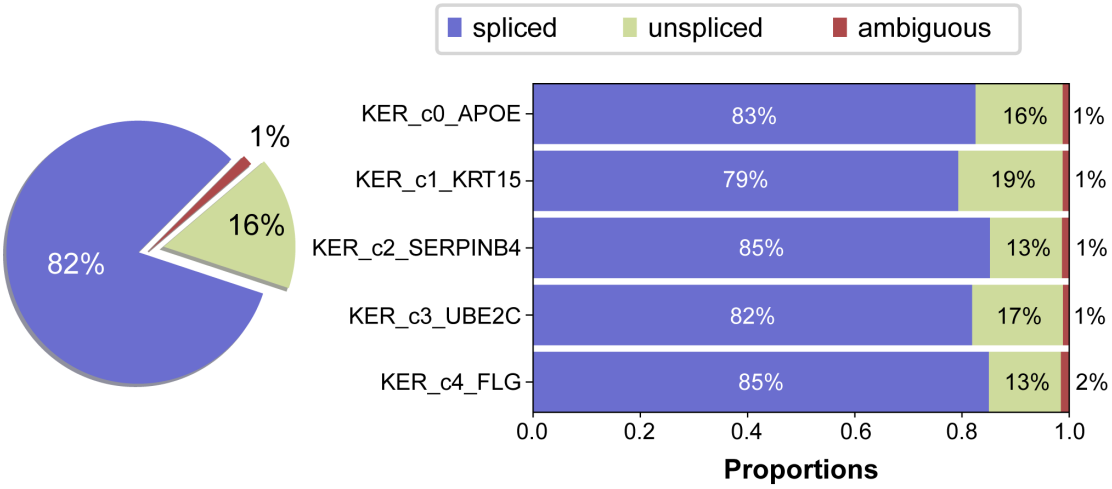


Supplementary Figure 11. Keratinocyte pseudotime analysis.

This plot represents the distribution of pseudotime of cells assigned to the lineages for each cluster by Slingshot analysis.

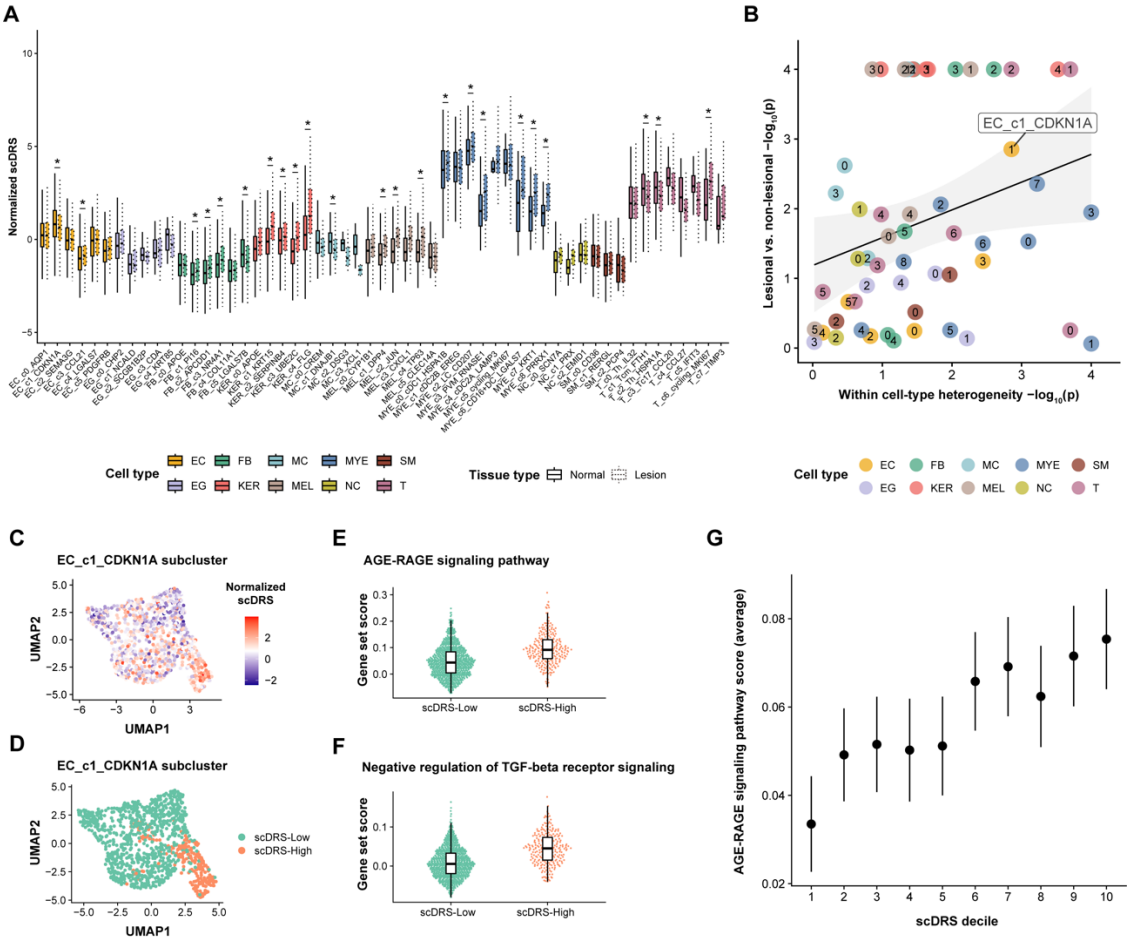


Supplementary Figure 12. The proportion of unspliced and spliced reads per cluster in RNA velocity analysis of keratinocyte clusters.



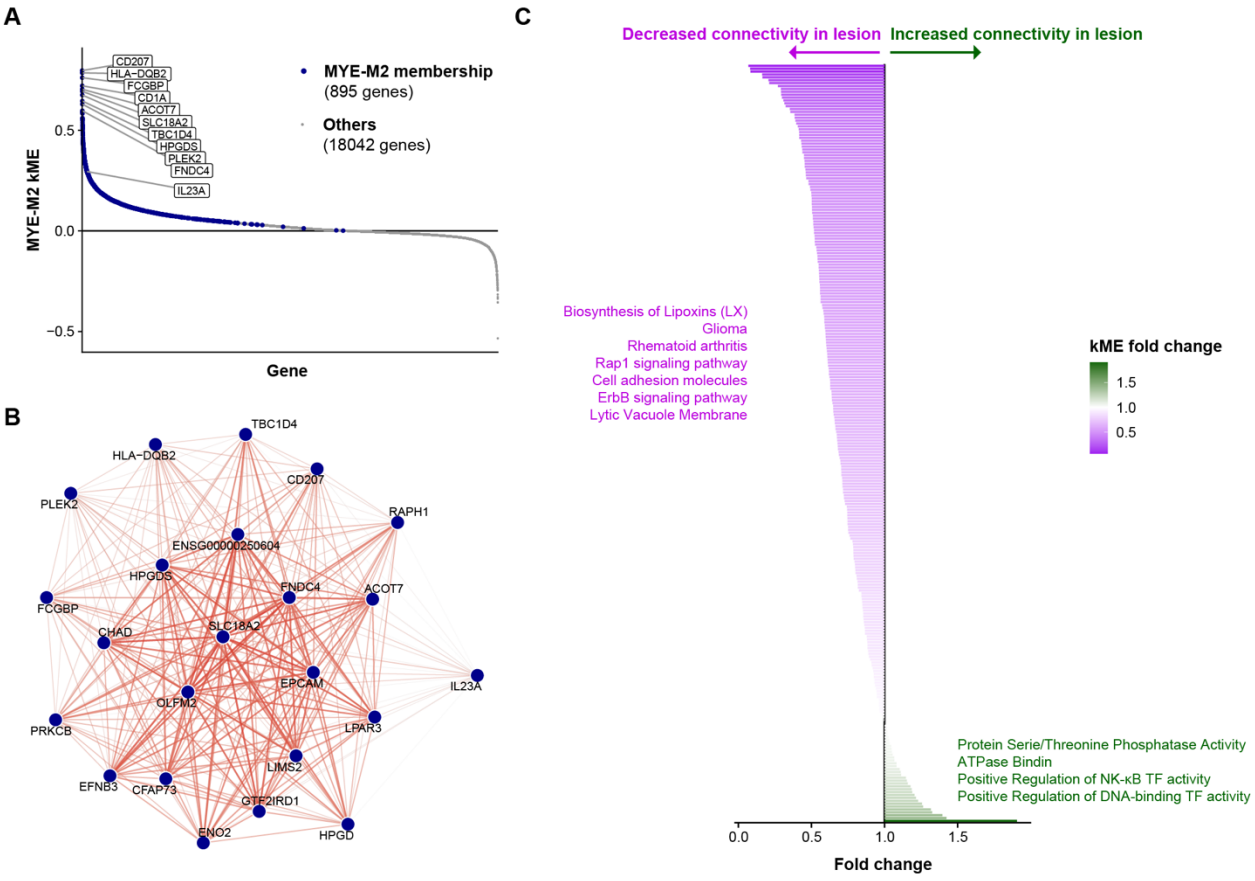
Supplementary Figure 13. scDRS heterogeneity-based analysis.

(A) Distributions of scDRS scores for each cell type stratified by tissue type (normal and lesion). Asterisks denote cell types satisfying both scDRS heterogeneity false discovery rate (FDR) < 0.10 and scDRS score difference FDR < 0.10. *P*-values for scDRS heterogeneity and for scDRS score difference between tissues were calculated using two-sided permutation tests (10,000 permutations). **(B)** Comparison between scDRS heterogeneity *p*-values and scDRS score difference *p*-values. A solid black line represents a linear fit between two variables and the surrounding shaded band denotes the 95% confidence intervals (linear regression slope = 0.399, *p*-value = 0.032). Detailed statistical results are provided in Supplementary Data 15. **(C)** scDRS score distribution of the endothelial cluster EC_c1_CDKN1A in the UMAP space. **(D)** Subclustering of the endothelial cluster EC_c1_CDKN1A. Distributions of gene set scores of two EC_c1_CDKN1A subclusters representing **(E)** the AGE-RAGE signaling pathway and **(F)** negative regulation of the TGF-beta receptor signaling pathway. **(G)** Average gene set scores per scDRS decile group of cells in EC_c1_CDKN1A. Error bars represent 95% confidence intervals. In all box plots, the center line denotes the median value, the box bounds denote the 25th and 75th percentiles, and the whiskers extend to 1.5 × the interquartile range from the box bounds.



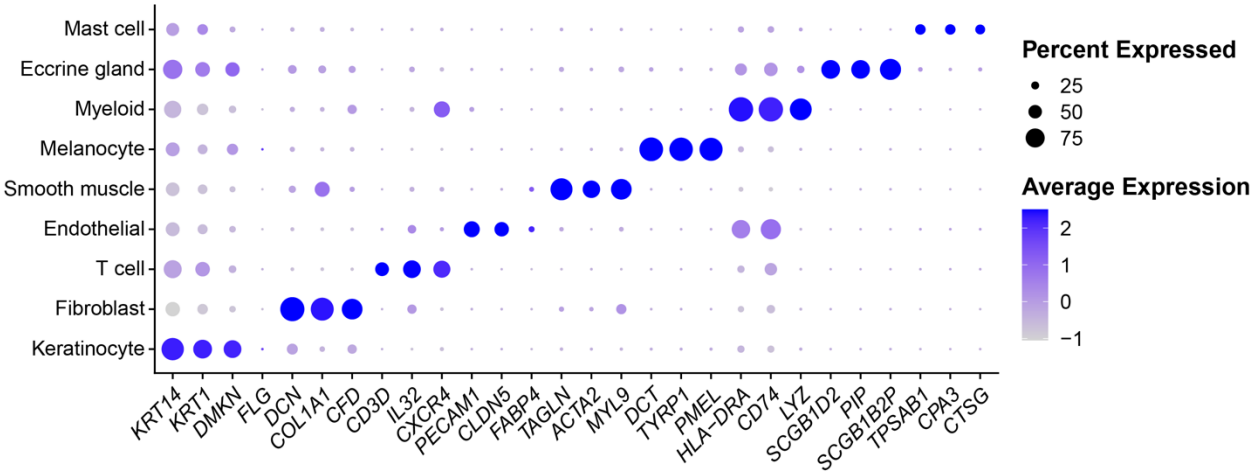
Supplementary Figure 14. MYE-M2 module connectivity analysis.

(A) Scatter plot of genes ranked by module connectivity (kME) and kME scores. The top-10 genes with the highest kME values and IL23A are annotated. **(B)** Network plot showing genes co-expressed with *IL23A*. Genes were filtered based on a TOM pairwise similarity > 0.10 with *IL23A*. **(C)** Comparison of gene connectivities between lesional samples and healthy control samples, ranked by fold change. Genes with fold changes below 1.0 indicate decreased connectivity in lesional samples. Only genes with kME > 0.25 were included in the analysis. Gene sets with increased and decreased connectivity were both used for pathway analysis, and representative pathways with adjusted *p*-value < 0.10 are shown.



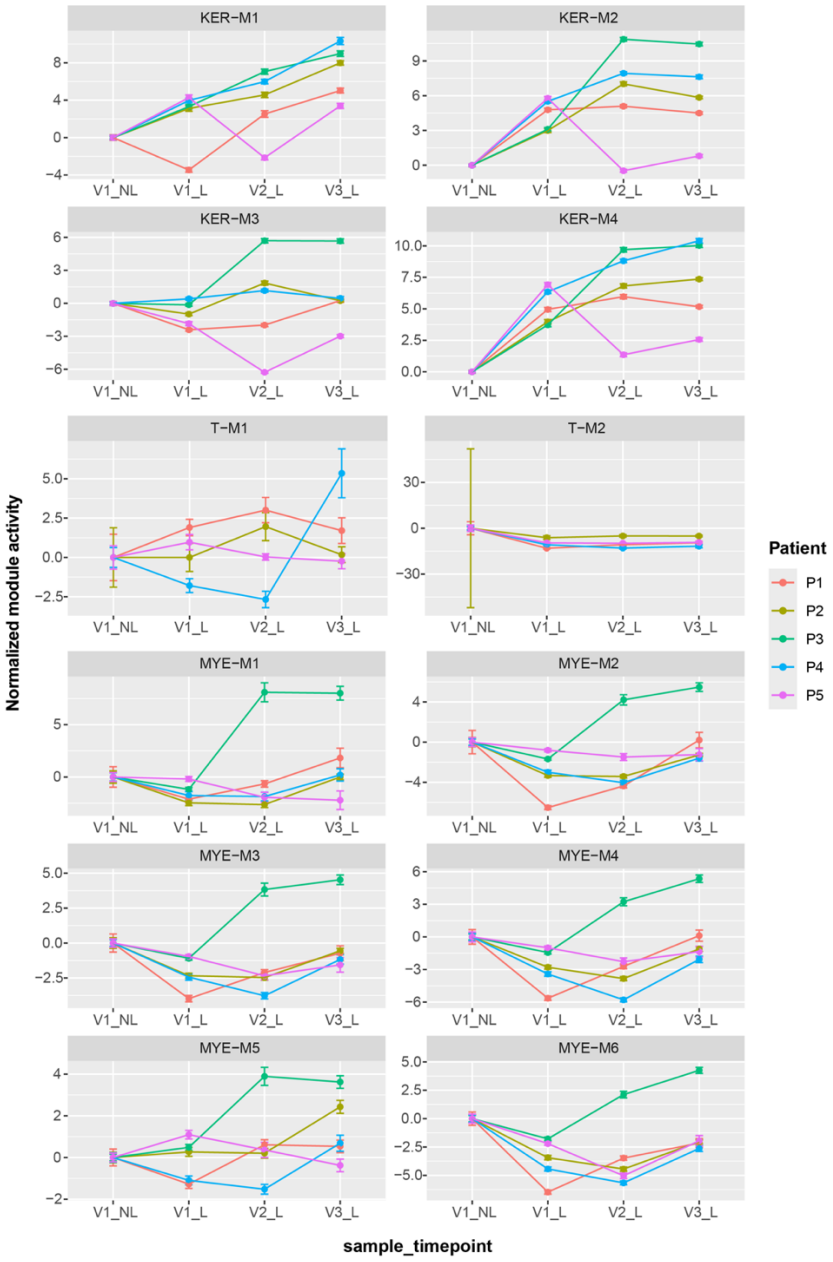
Supplementary Figure 15. Gene expression of representative markers in IL-23 targeted treatment data (Francis et al.).

Representative markers of keratinocyte (*KRT14*, *KRT1*, *DMKN*, and *FLG*), fibroblast (*DCN*, *COL1A1*, and *CFD*), T cell (*CD3D*, *IL32*, and *CXCR4*), endothelial cell (*PECAM1*, *CLDN5*, and *FABP4*), smooth muscle (*TAGLN*, *ACTA2*, and *MYL9*), melanocyte (*DCT*, *TYRP1*, and *PMEL*), myeloid (*HLA-DRA*, *CD74*, and *LYZ*), eccrine gland (*SCGB1D2*, *PIP*, and *SCGB1B2P*), and mast cell (*TPSAB1*, *CPA3*, and *CTSG*) were shown.



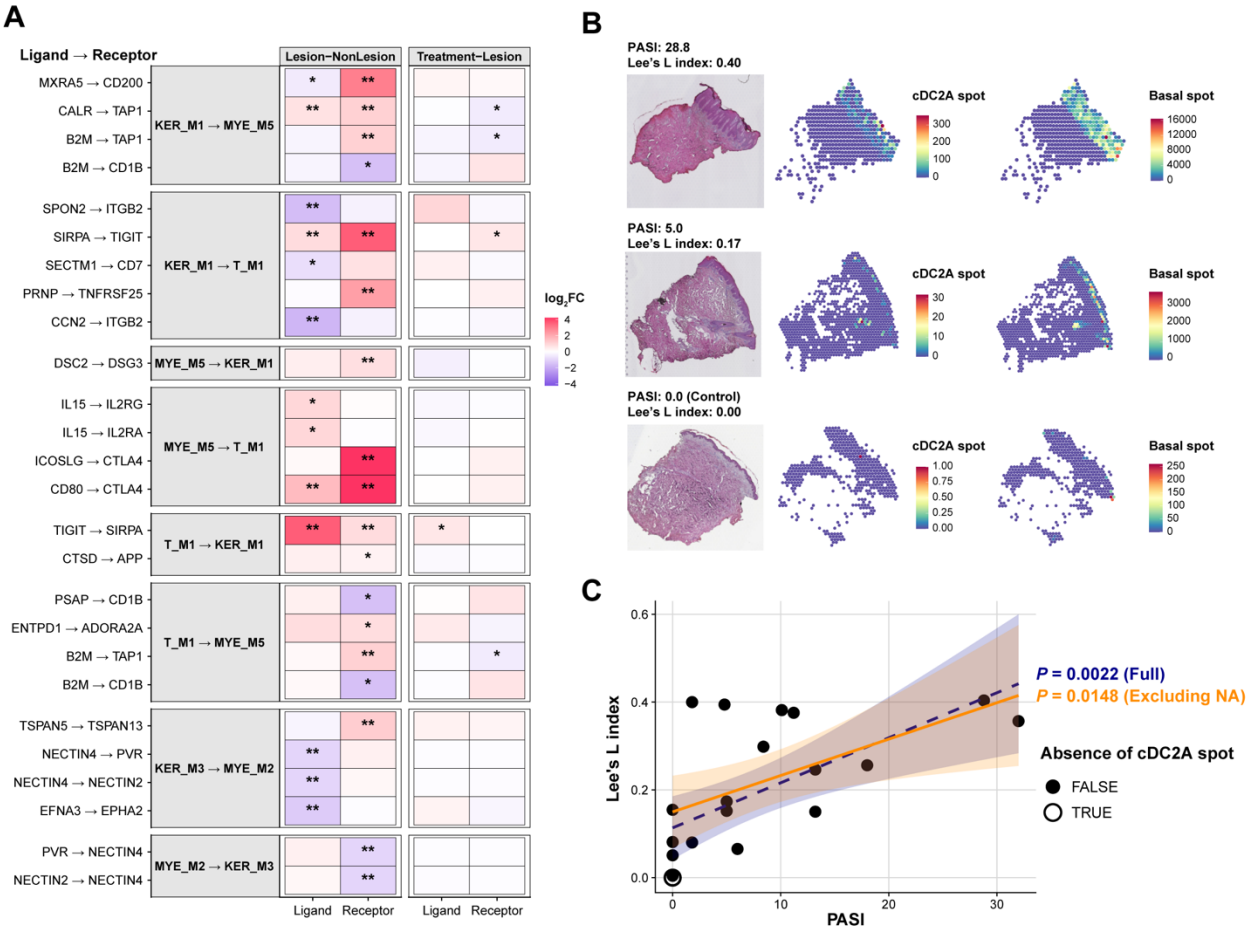
Supplementary Figure 16. Module eigengenes across time points.

The modules shown in Figure 6G were visualized for each patient. Module activities were zero-normalized based on Day 0 non-lesional samples, and values are presented without maximum value scaling. V1_NL, Day 0 Non-lesion; V1_L, Day 0 Lesion, V2_L, Day 3 Lesion; V3_L, Day 14 Lesion. Each point represents the average module score, and error bars represent the 95% confidence intervals.



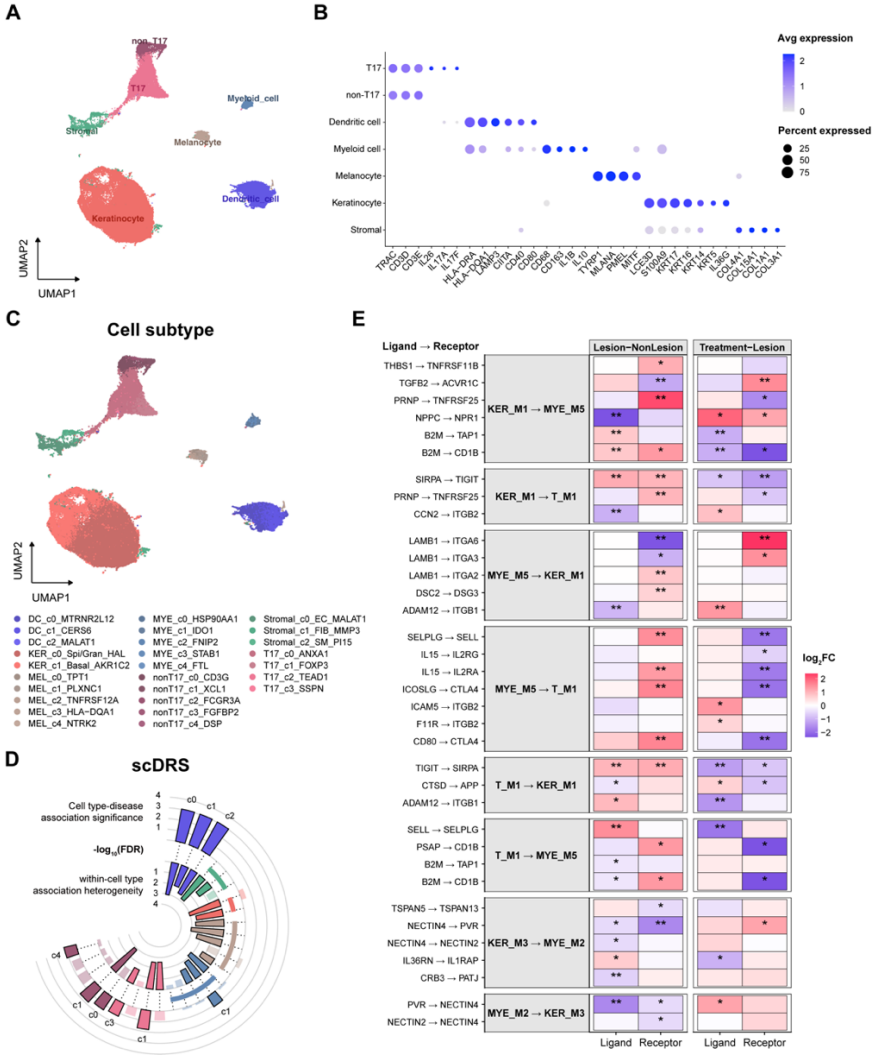
Supplementary Figure 17. Module-level cell-cell interaction analysis among keratinocytes, myeloids, and T cells.

(A) Ligand-receptor interactions that exhibit pairwise differential expression between lesion and non-lesion samples and treatment and lesion samples. The heatmap shows the log2-transformed fold changes of the gene expression between two conditions. Each panel name represents the directionality of the ligand module to receptor module. Double asterisks denote the adjusted *p*-value < 0.05, and single asterisks denote the nominal *p*-value < 0.05. **(B)** Spatial expression plots of cDC2A spots (co-expressing LAMP3 and DSC2) and basal keratinocyte spots (co-expressing KRT5 and DSG3). **(C)** Evaluating associations between Psoriasis Area and Severity Index (PASI) and Lee's L index. Two regression lines were fitted: one excluding samples of non-detected cDC2A spots (orange) and one using all samples with non-detected cDC2 spots imputed as zero (darkblue). Surrounding shaded bands denote the 95% confidence intervals.



Supplementary Figure 18. Replication analysis of single-cell analysis using Kim et al. dataset.

(A) UMAP plot of single cells with major cell type annotation. **(B)** Dot plot showing expression of representative cell markers. **(C)** UMAP plot of cell subtype annotation of each major cell type. **(D)** Cell-subtype level scDRS result. Bar plots in the outer circle represent the FDR-adjusted *p*-values of cell subtype-disease association and bar plots in the inner circle represent the FDR-adjusted *p*-values of within-cell type heterogeneity. **(E)** Ligand-receptor interactions that exhibit pairwise differential expression between lesion and non-lesion samples and treatment and lesion samples. The heatmap shows the log2-transformed fold changes of the gene expression between two conditions. Each panel name represents the directionality of the ligand module to receptor module. Double asterisks denote the adjusted *p*-value < 0.05, and single asterisks denote the nominal *p*-value < 0.05.



Supplementary Figure 19. Schematic illustration of proposed two layer-specific mechanisms of psoriasis pathogenesis.

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