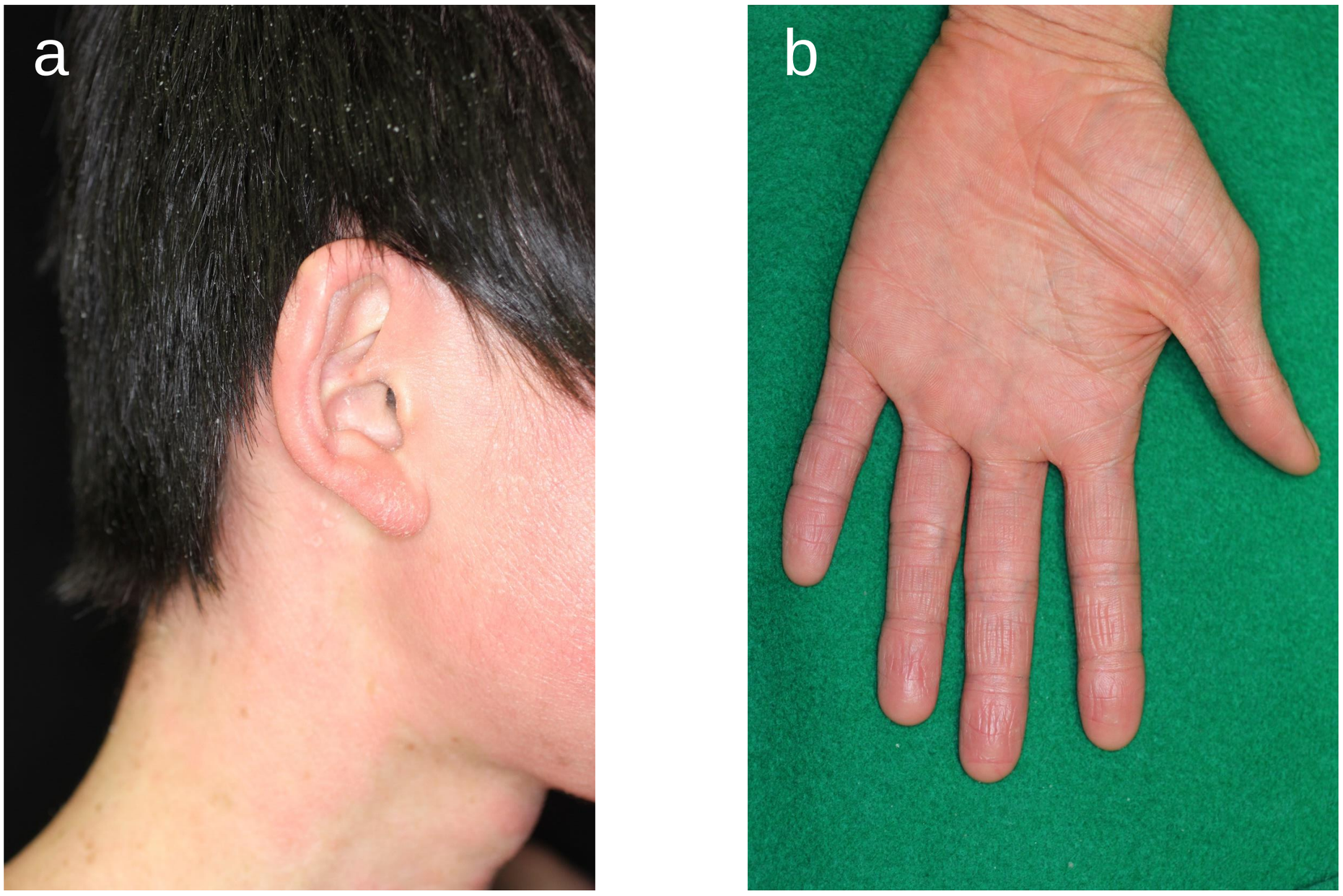
Supplementary Figures

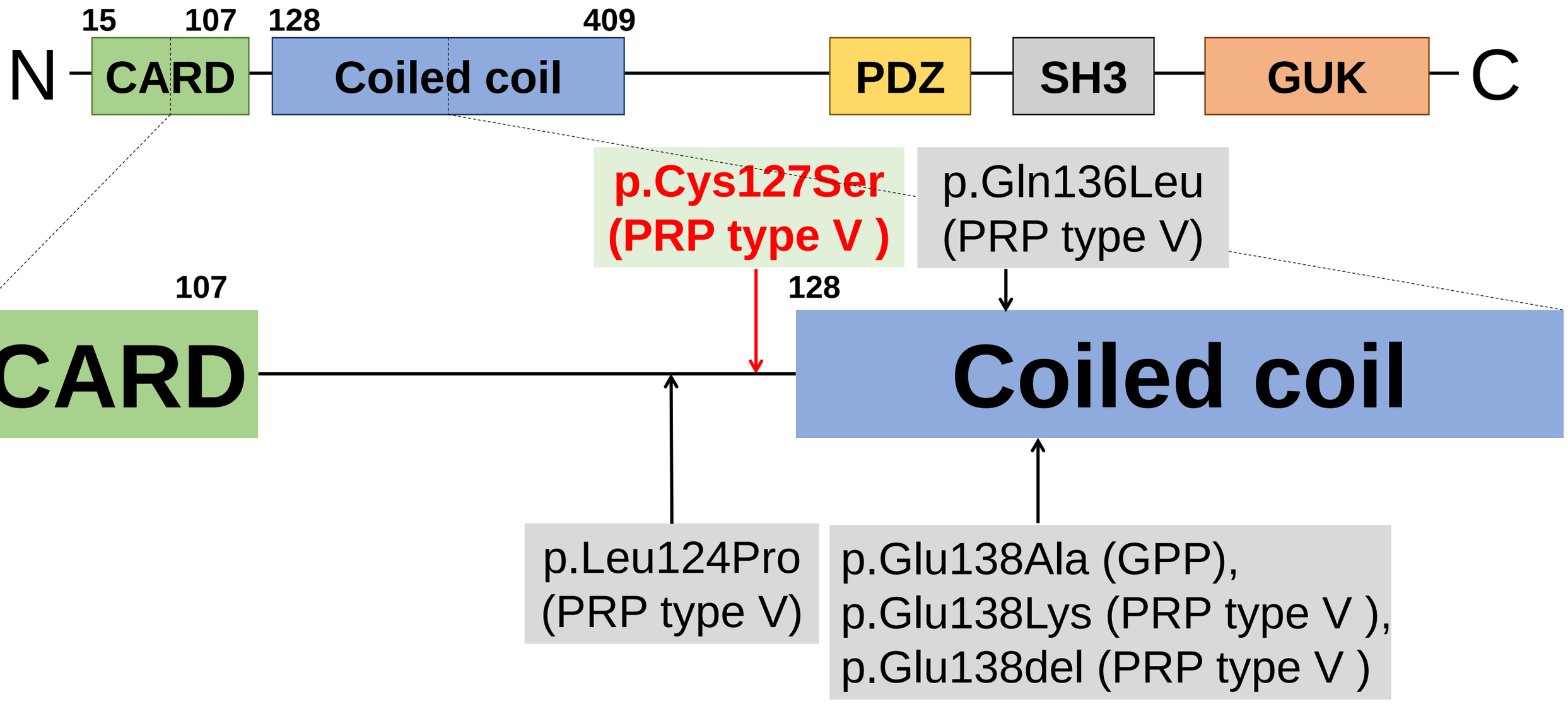
PP.1-7

Supplementary Fig. 1



Supplementary Fig. 1 Clinical features of the patient with pityriasis rubra pilaris associated with the mutation c.380G>C (p.Cys127Ser) in *CARD14.*
(a) At age 20, the patient shows characteristic hyperkeratotic scaly erythema on the right cheek, ear, and neck. Small, fine, whitish scales are seen on the hair. (b) Moderate hyperkeratosis is seen on the left palm, and marked hyperlinearity is observed on the palm and the flexor side of the fingers.

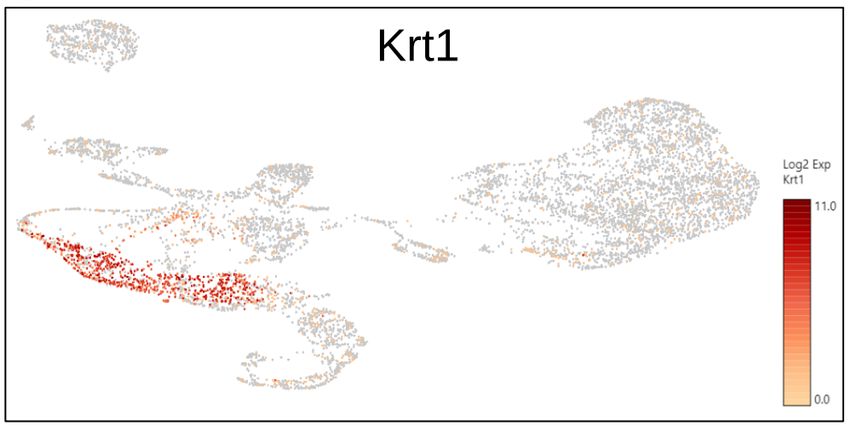
Supplementary Fig. 2

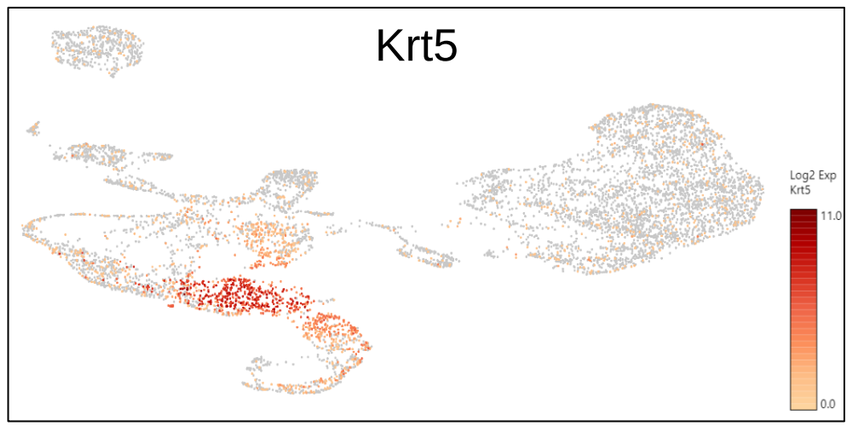


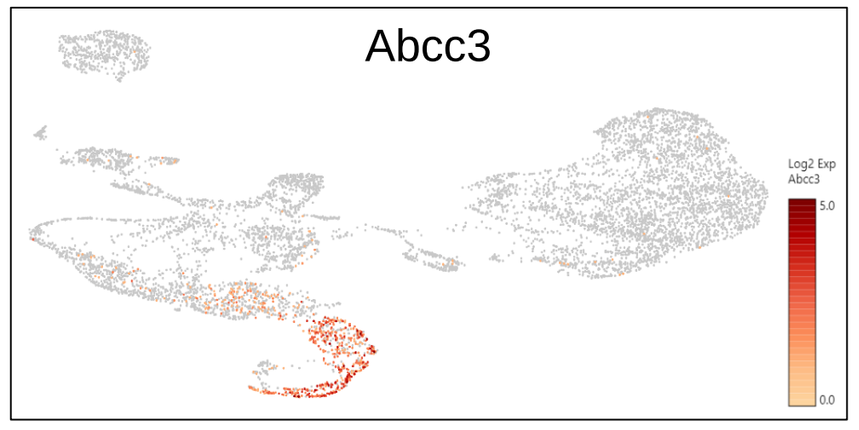
Supplementary Fig. 2 The CARD14 domain structure with the mutation sites indicated.
p. Cys127Ser (red arrow) lies between the CARD domain and the coiled-coil domain of the CARD14 protein, close to residues that correspond to the pathogenic mutations in GPP and in type V PRP.

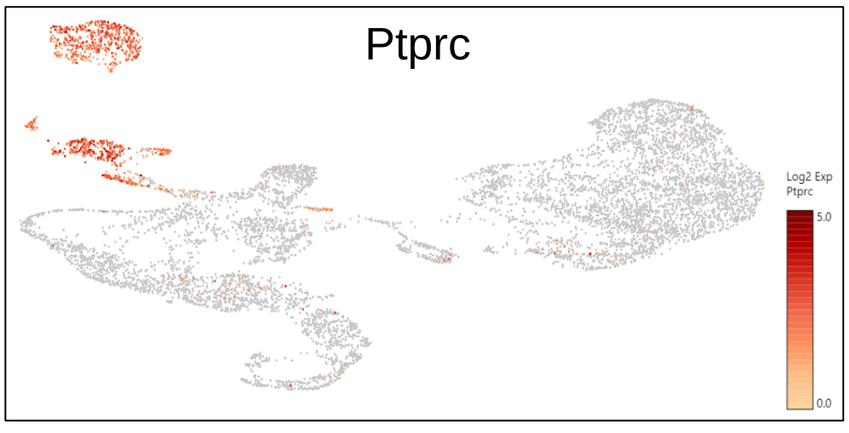
Supplementary Fig. 3

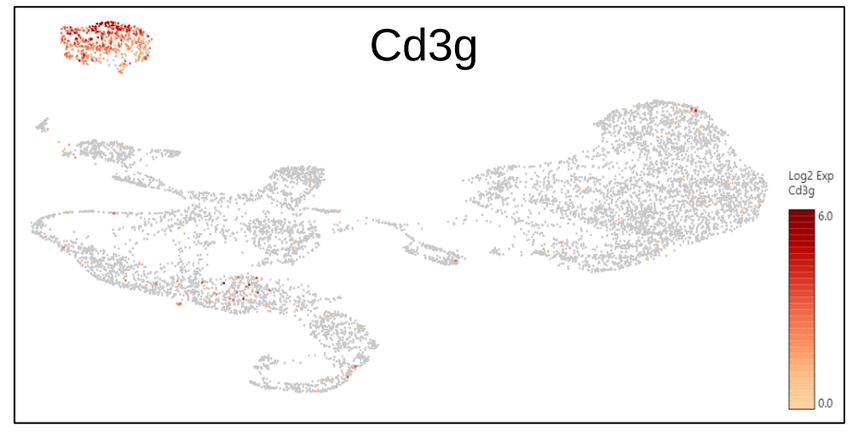
a

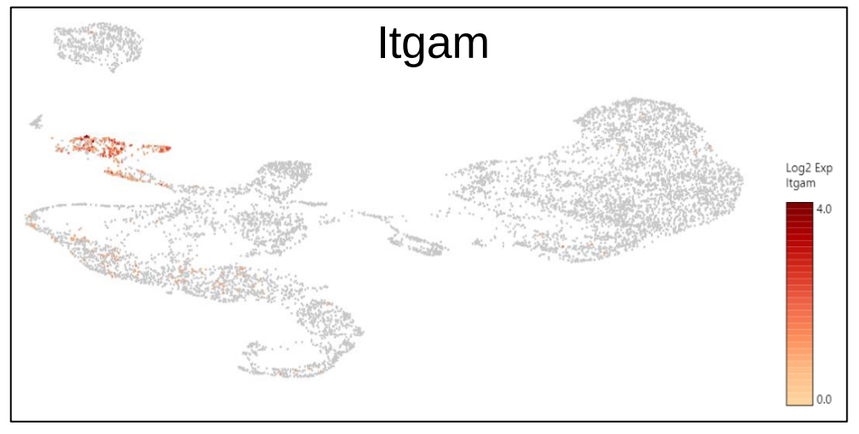


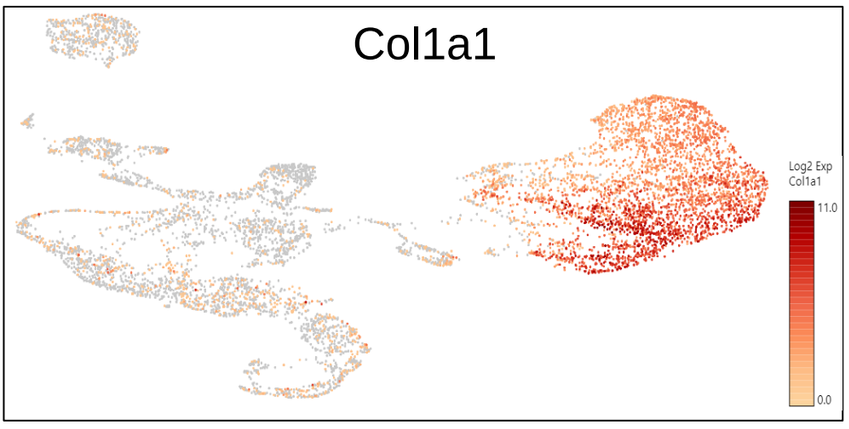


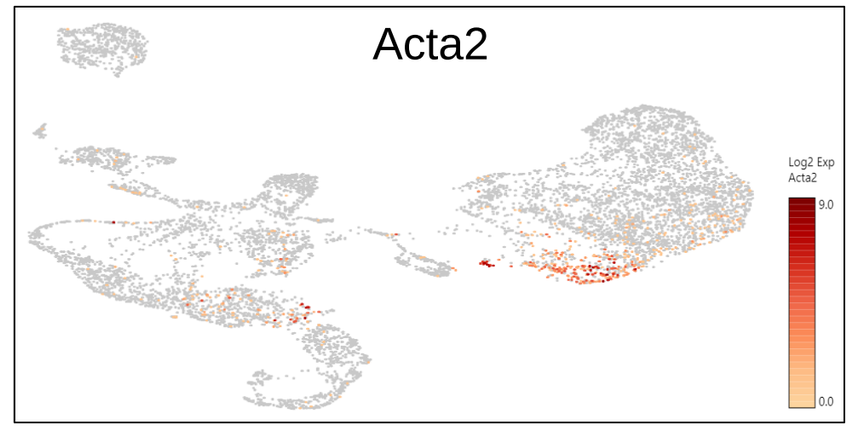


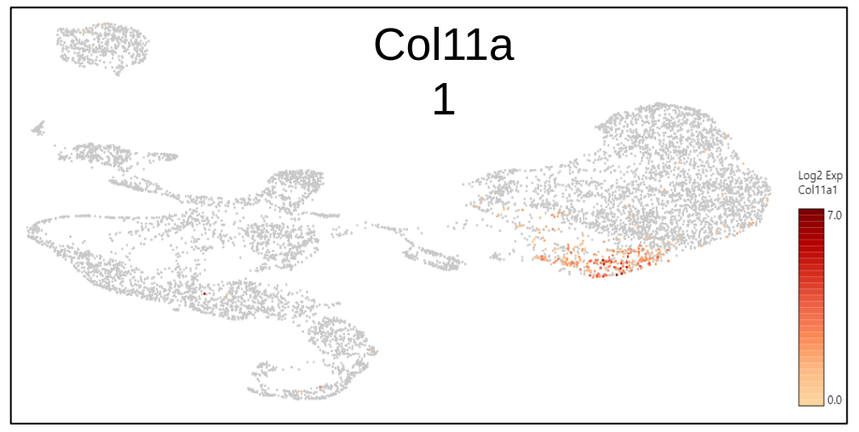


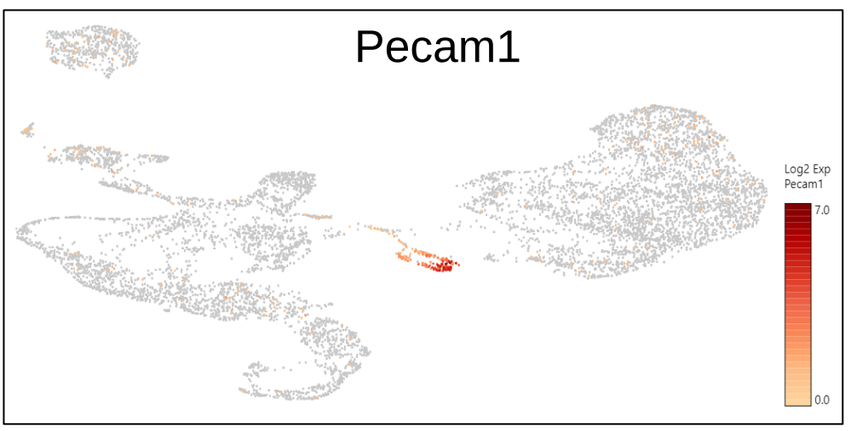


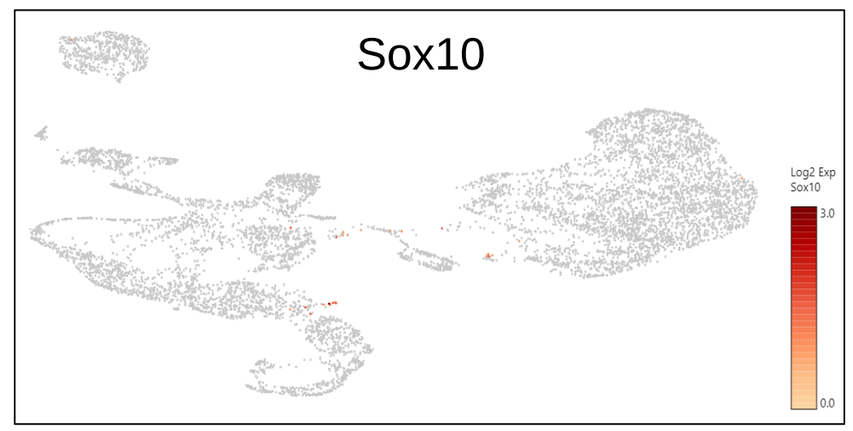


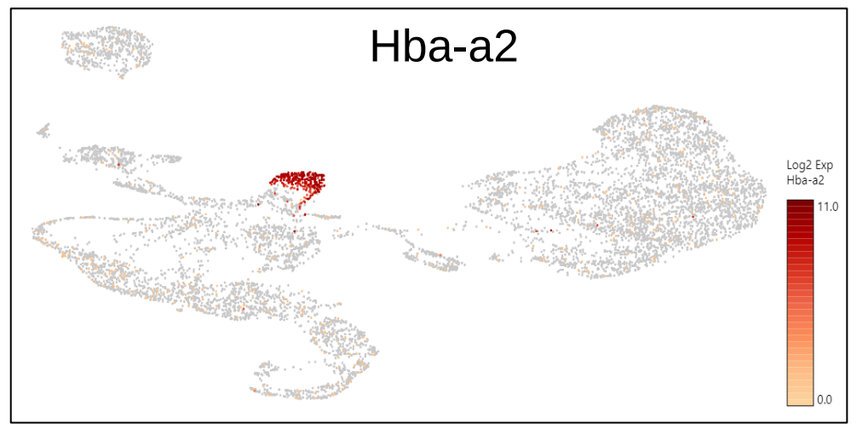












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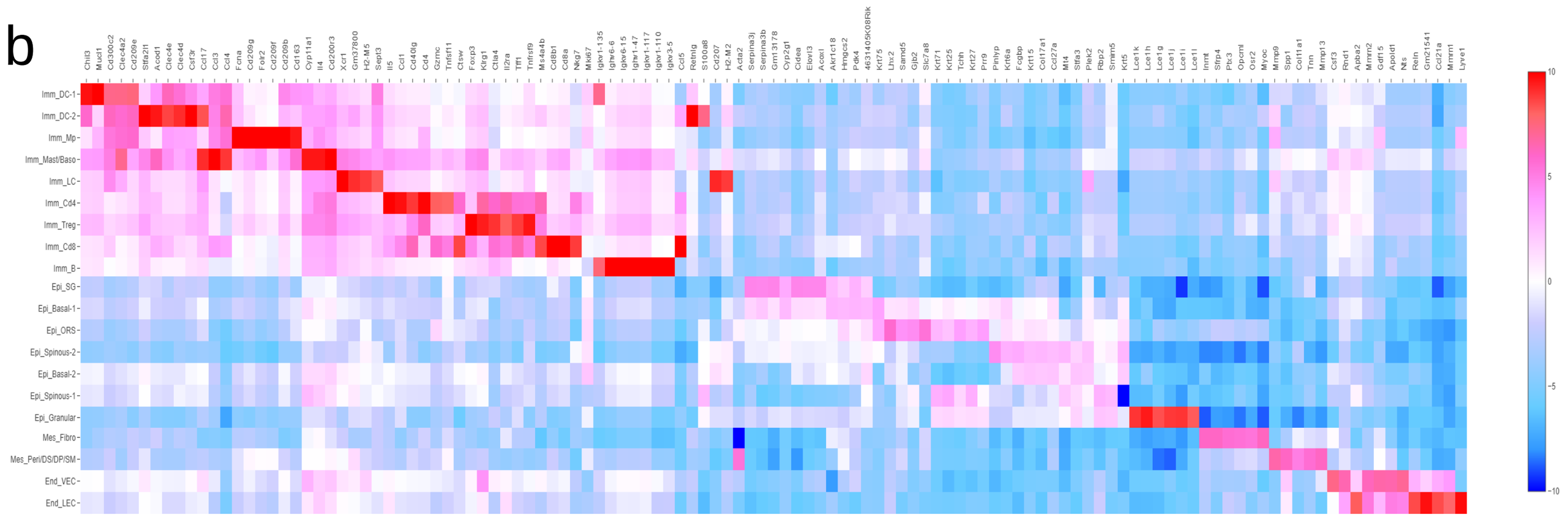
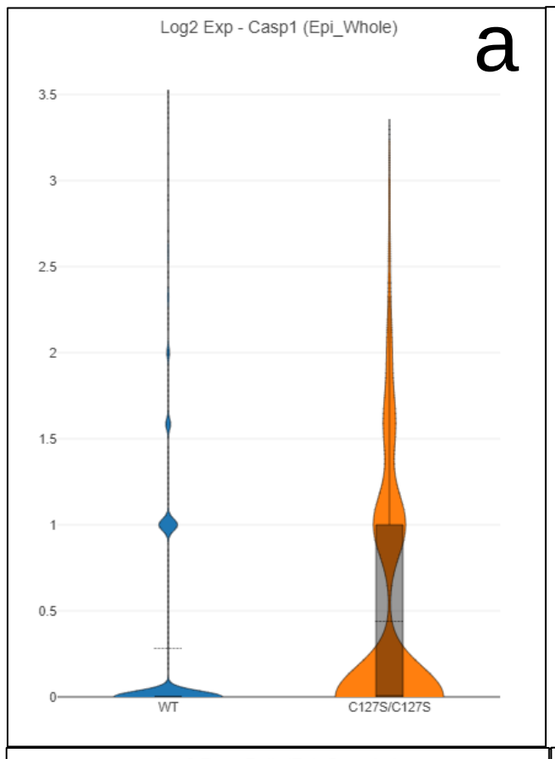


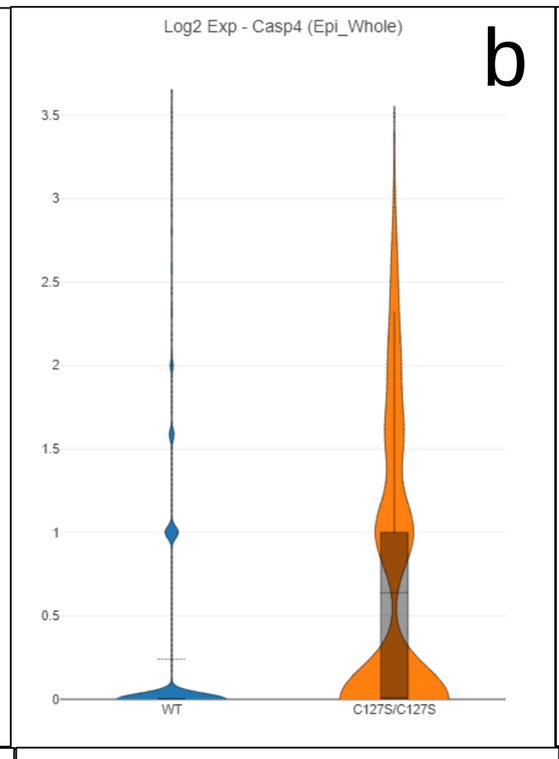
Supplementary Fig. 3 Marker genes to identify clusters and differentially expressed genes (DEGs) in subclusters with scRNA-seq.

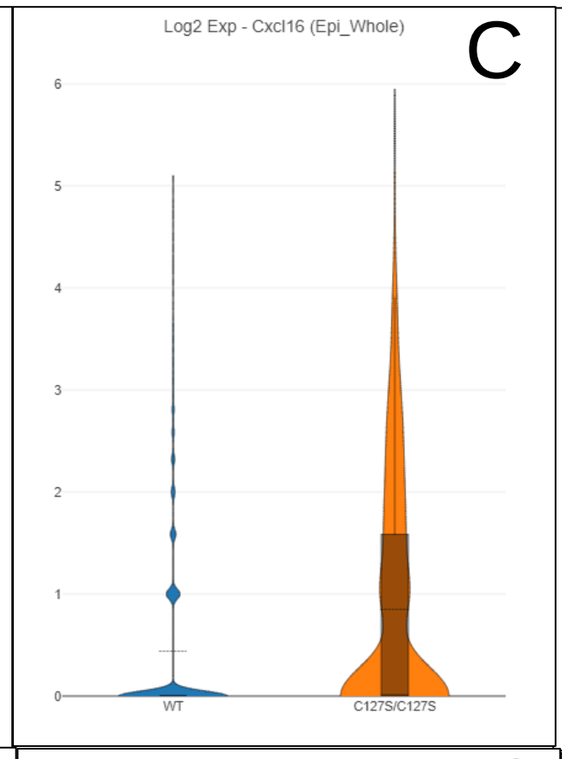
(a) UMAP plots show differential expression levels of well-known markers, which were useful for main- and sub-clustering.

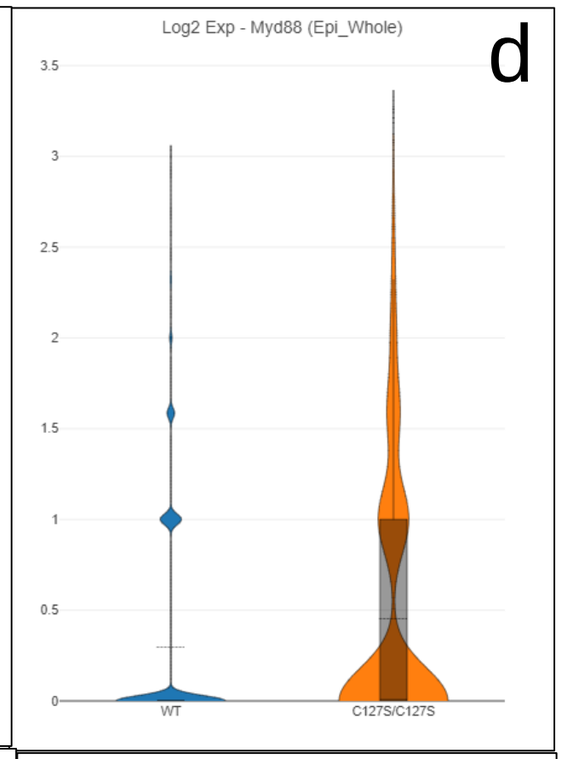
(b) A heatmap shows DEGs in 20 subclusters from Epi_Whole, Imm_Whole, Mes_Whole, and End_Whole. Epi_Whole.

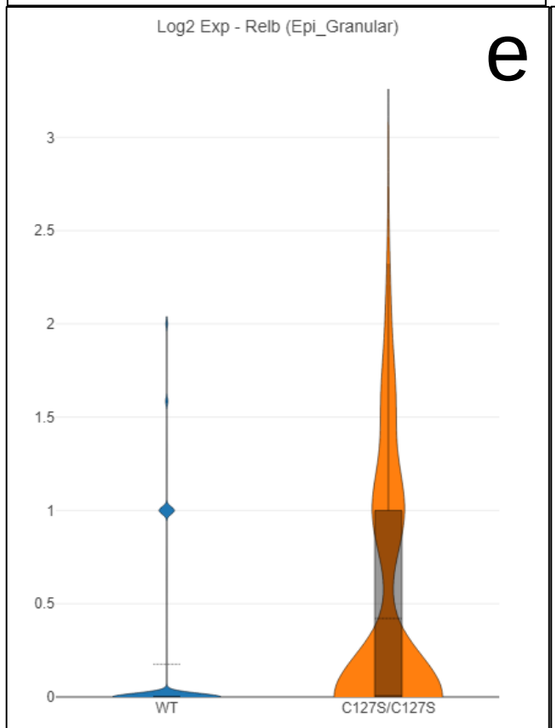
Supplementary Fig. 4

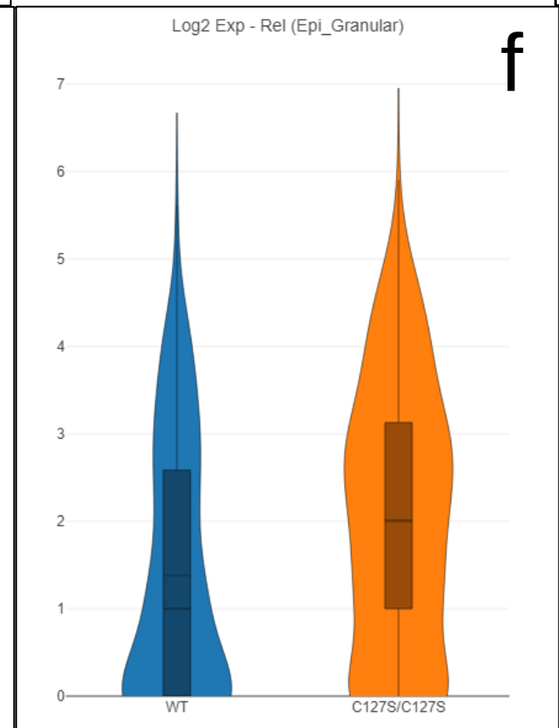


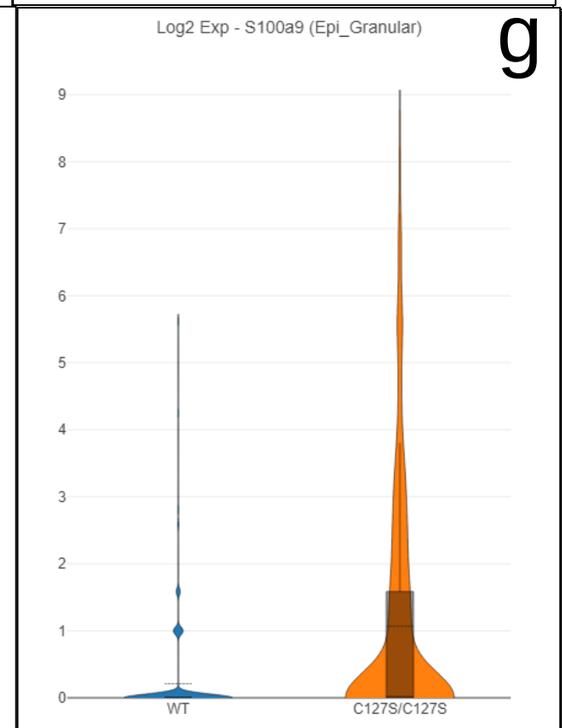


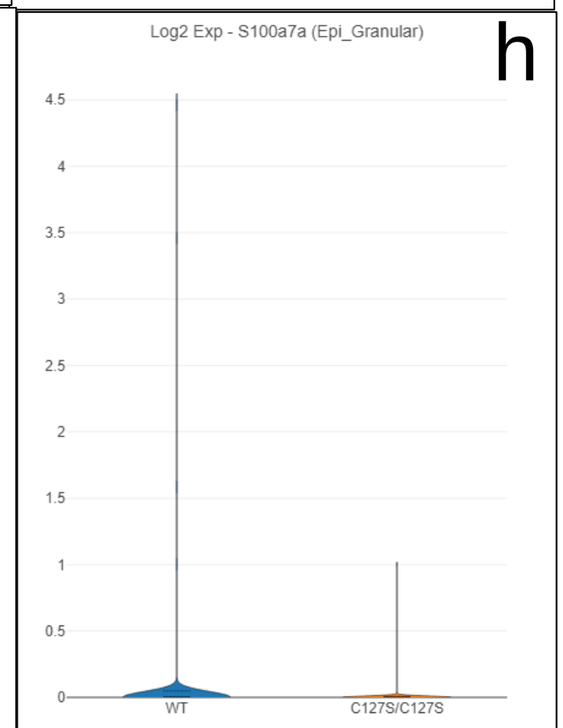


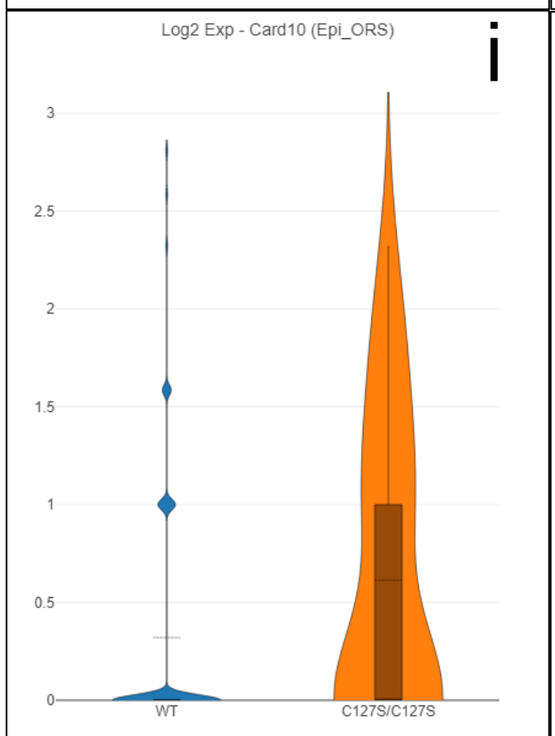


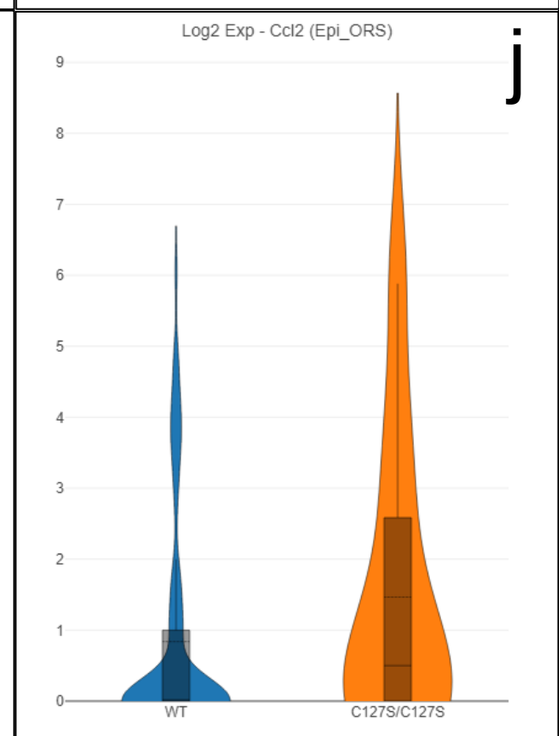


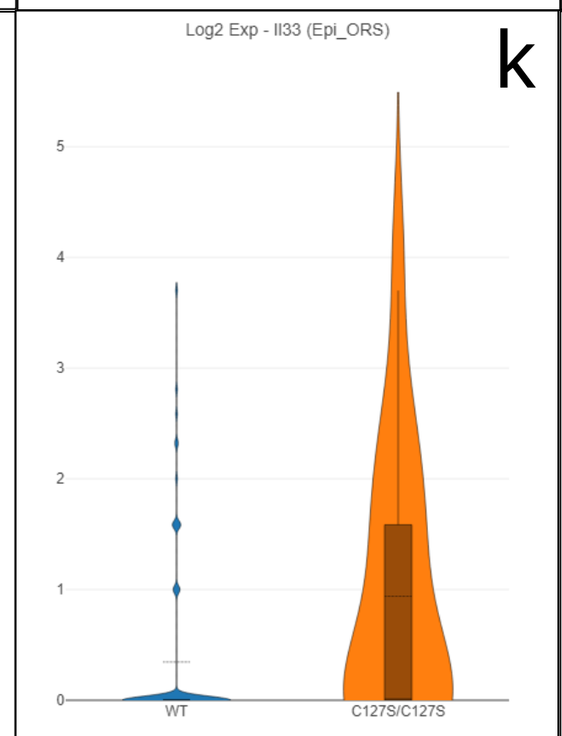


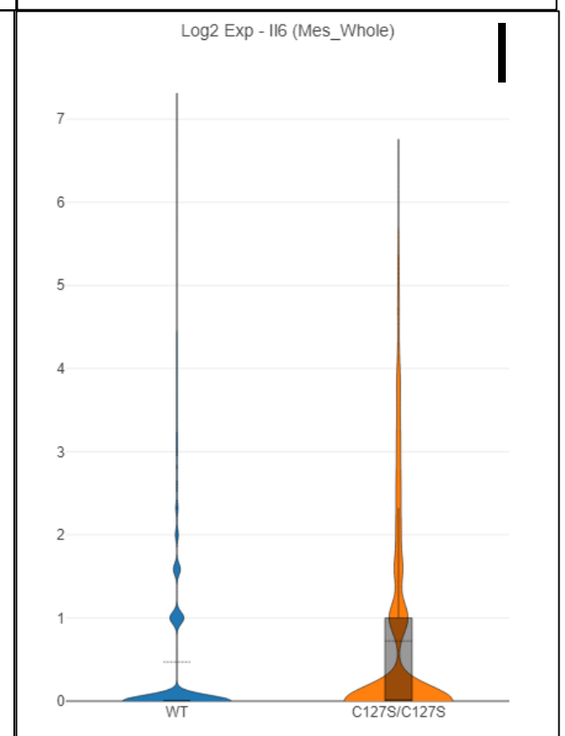


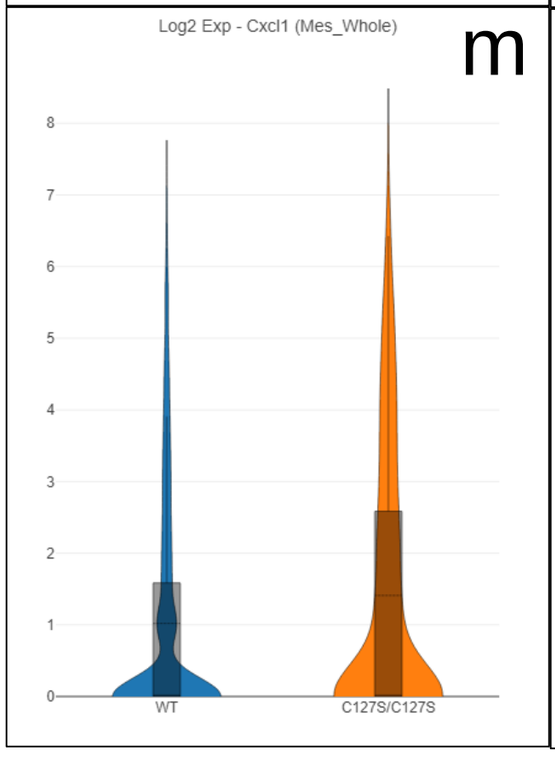


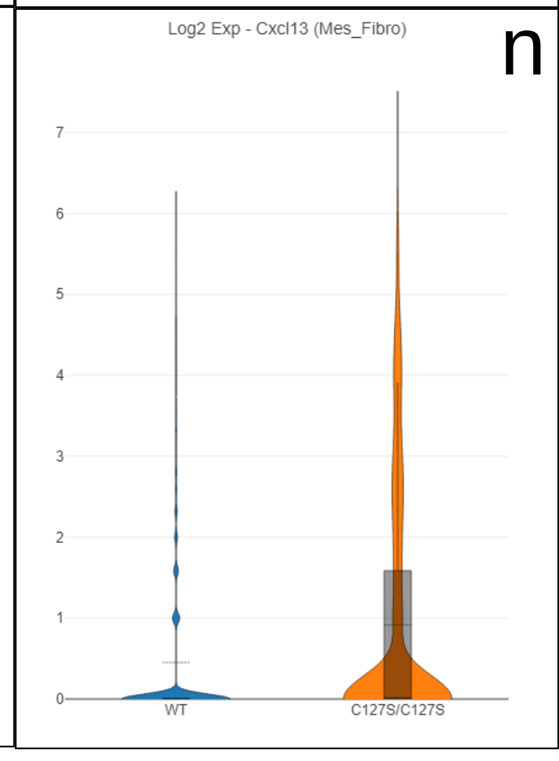


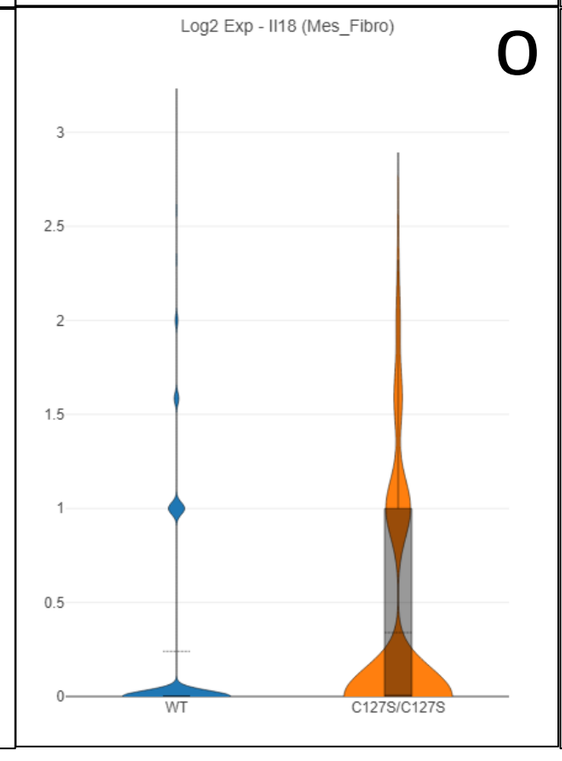


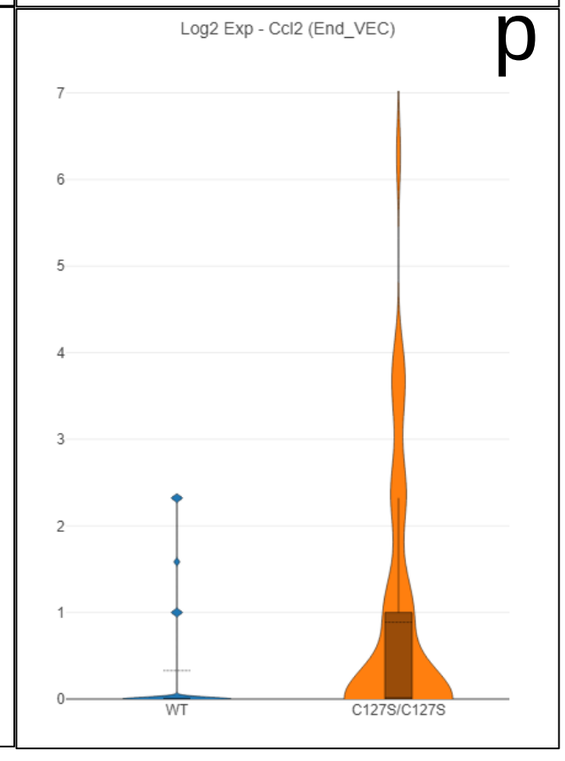








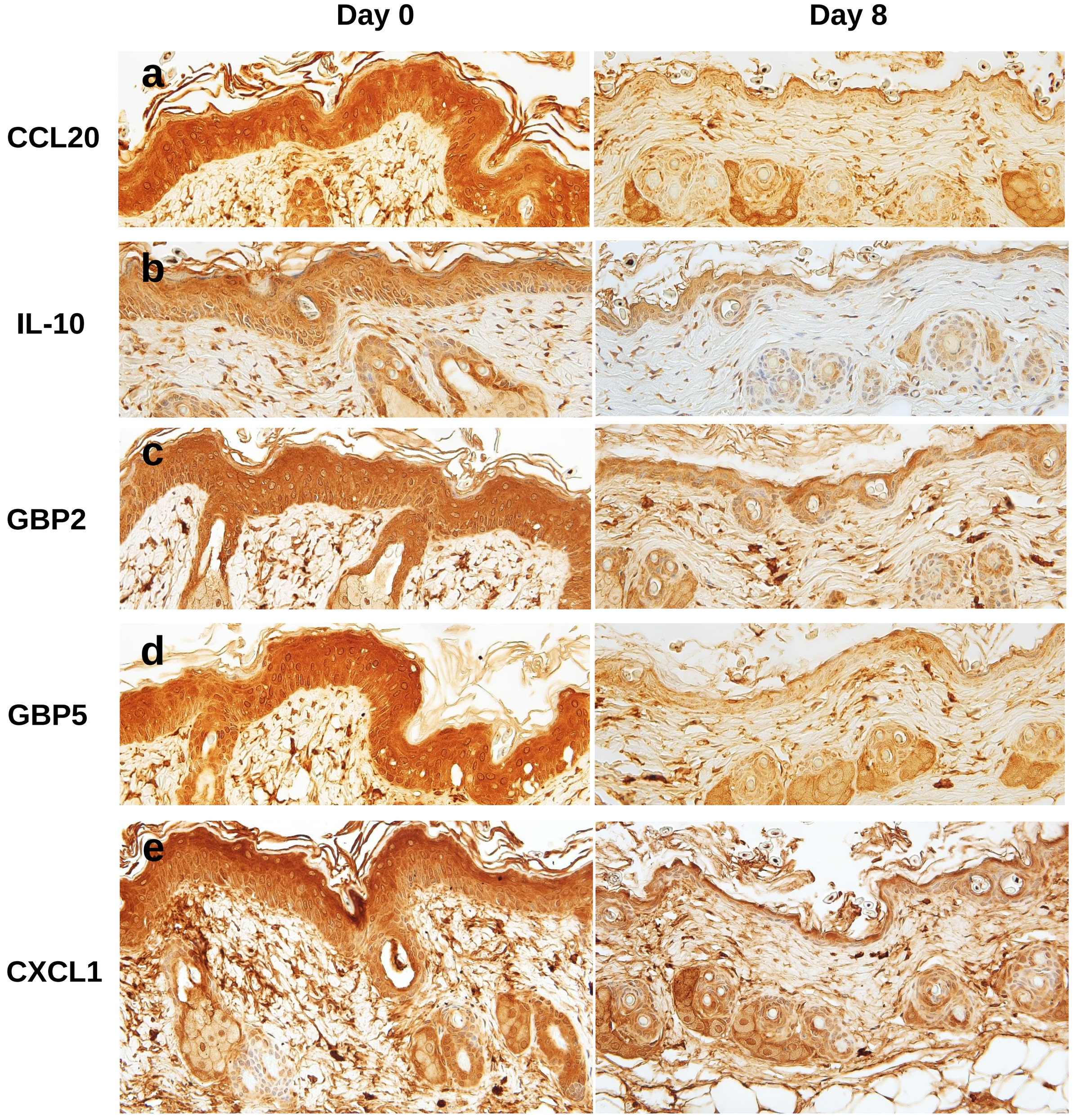




Supplementary Fig. 4 Violin plots showing the selected DEGs between the WT mouse and the *Card14*$^{C127S/C127S}$ mouse.

(a-p) The relative expression of selected DEGs in subclusters is visualized as violin plots. The plots of samples from the WT and the *Card14*$^{C127S/C127S}$ mice are shown in blue and orange, respectively. (a–d) The expression of *Casp1*, *Casp4*, *Cxcl16*, and *Myd88* is significantly up-regulated in the Epi_Whole of the *Card14*$^{C127S/C127S}$ mouse. (e–h) The expression of *Relb*, *Rel*, and *S100a9* is significantly up-regulated, and the expression of *S100a7a* is down-regulated in Epi_Granular of the *Card14*$^{C127S/C127S}$ mouse. (i–k) The expression of *Card10*, *Ccl2*, and *Il33* is significantly up-regulated in Epi_ORS of the *Card14*$^{C127S/C127S}$ mouse. (l, m) The expression of *Il6* and *Cxcl1* is significantly up-regulated in Mes_Whole of the *Card14*$^{C127S/C127S}$ mouse. (n, o) The expression of *Cxcl13* and *Il18* is significantly up-regulated in Mes_Fibro of the *Card14*$^{C127S/C127S}$ mouse. (p) The expression of *Ccl2* is significantly up-regulated in End_VEC of the *Card14*$^{C127S/C127S}$ mouse.

Supplementary Fig. 5



Supplementary Fig. 5 Histological features, immunohistochemistry results of the *Card14*$^{C127S/C127S}$ mice at 8 days of therapy.

(a–e) Immunohistochemical staining using anti-CCL20, IL-10, guanylate-binding protein (GBP) 2, GBP5, and CXCL1 antibodies was performed on skin tissue from the back before treatment and at 8 days of therapy. The back skin samples show weaker anti-CCL20, CXCL1, IL-10, GBP2, and GBP5 antibody staining in the cytoplasm of keratinocytes at Day 8 than at Day 0. (e) CXCL1 staining is intense not only in keratinocytes, but also in dermal fibroblasts at Day 0, and the CXCL1 staining is apparently reduced at Day 8 of treatment.

Supplementary Tables

PP.8-12

Supplementary Table 1. Frequencies of *Card14KI* genotypes in pups derived from intercrosses between *Card14*$^{C127S/+}$ mice and *Card14*$^{C127S/+}$ mice.

WT	*Card14*$^{C127S/+}$	*Card14*$^{C127S/C127S}$	Total
19	46	17	82

Supplementary Table. 2 Upregulated DEGs and enriched pathways in CARD$^{14C127S/C127S}$ mice at P5.

Enriched pathway	Upregulated genes
Cytokine-cytokine receptor interaction	*Ifng, Il1a, Il1b, Il1rn, Il1rl2, Il2ra, Il4ra, Il6, Il7r, Il12b, Il13ra1, Il17a, Il17b, Il17c, Il17f, Il18rap, Il19, Il20, Il20ra, Il21r, Il22, Il23a, Il33, Il36a, Il36b, Il36g, Ccl2, Ccl3, Ccl4, Ccl6, Ccl7, Ccl8, Ccl12, Ccl17, Ccl19, Ccr2, Ccr4, Ccr5, Cxcl1, Cxcl5, Cxcl9, Cxcl10, Cxcl16, Cxcr2, Csf2, Csf2rb, Csf2rb2, Epi3, Osm, Osmr, Tnf*
IL-17 signaling pathway	*Ifng, Il1b, Il6, Il17a, Il17b, Il17c, Il17f, Ccl2, Ccl7, Ccl12, Ccl17, Cxcl1, Cxcl5, Cxcl10, Csf2, Fosb, Fosl1, Defb3, Defb6, S100a8, S100a9, Lcn2, Mmp3, Muc5b, Nfkbia, Ptgs2, Tnf, Tnfaip3*
NOD-like receptor signaling pathway	*Birc3, Casp4, Card9, Ccl2, Ccl12, Cxcl1, Cxcl2, Cxcl3, Defa1, Defa2, Defa3, Defa27, Defa36, Defa40, Defa-rs4, Defb3, Defb6, Defb14, Gbp2, Gbp2b, Gbp3, Gbp5, Gbp7, Ifi204, Ifna16, Il1b, Il6, Irak4, Nirp1a, Mcu, Mefv, Myd88, Nfkbia, Nod2, Oas2, Oas3, Rnasel, Sting1, Tnf, Tnfaip3, Txn2*
Th17 differentiation	*Ebi3, H2-Aa, H2-Ab1, H2-Eb1, H2-Dma, H2-Dmb1, H2-Dmb2, H2-Ob, Ifng, Il1b, Il2ra, Il4ra, Il6, Il17a, Il17f, Il21r, Il22, Il23a, Nfkbia, Stat3*
TNF signaling pathway	*Bcl2, Birc3, Ccl2, Ccl12, Cxcl1, Cxcl2, Cxcl3, Cxcl5, Cxcl10, Csf2, Icam1, Ifi47, Irf1, Il1b, Il6, Mmp3, Mmp9, Nfkbia, Nod2, Ptgs2, Socs3, Tnf, Tnfaip3*
Hematopoietic cell linage	*Csf2, Dntt, Fcgr1, H2-Aa, H2-Ab1, H2-Eb1, H2-Dma, H2-Dmb1, H2-Dmb2, H2-Ob, Itgam, Il1a, Il1b, Il2ra, Il4ra, Il6, Il7r, Tnf, Ifng*
Antigen processing and presentation	*Cd74, Ctss, Ciita, H2-K1, H2-M1, H2-M9, H2-Ob, H2-Aa, H2-Ab1, H2-Eb1, H2-Dma, H2-Dmb1, H2-Dmb2, H2-Ob, Ifng, Gm11127, Tap2, Tnf*

Supplementary Table. 3 DEGs on microarray analysis. (Dataset. 1)

Supplementary Table. 4 Specific markers for extracting subclusters.

Main Clusters	Subclusters	Markers
Epi_Whole	Basal-1	Krt5, Krt14 / Krt1-, Krt10-, Cd34-
Epi_Whole	Basal-2	Krt5, Krt14, Krt1, Krt10 / Grhl1-, Cd34-
Epi_Whole	Spinous-1	Krt1, Krt10, Grhl1 / Krt5-, Krt14-, Cd34-
Epi_Whole	Spinous-2	Krt1, Krt10, Krt5, Krt14, Grhl1/ Cd34-
Epi_Whole	Granular	Flg, Flg2, Krt1, Krt10/ Cd34-
Epi_Whole	SG	Abcc3, Apoc1, Acsl5, Myc, Sox9, Elovl5, Fasn, Rdh11
Epi_Whole	ORS	Cd200, Cd34, Lnx2, Krt6a, Krt15, Krt16
End_Whole	VEC	Pecam1, Itgav, Pid1, ube2t, E2f1 / Lyve1-
End_Whole	LEC	Pecam1, Lyve1
Mes_Whole	Fibro	Pdgfrb, Lum, Dcn, Col1a1, Col3a1, Col5a1, C3/ Col11a1-
Mes_Whole	Peri/DS/DP/SM	Acta2, Pcp4, Col11a1, Dcn, Sox2, Actc1
Imm_Whole	Cd4	Ptprc,Cd3g,Cd3e,Cd4
Imm_Whole	Cd8	Ptprc,Cd3g,Cd3e,Cd8a, Cd8b1,Ctla4
Imm_Whole	Treg	Ptprc,Cd3g,Cd3e,Cd4, Ctla4,Foxp3,Il2ra
Imm_Whole	B	Ms4a1 (Cd20), Cd79a
Imm_Whole	DC-1	Il1b, Cd209a, Cd80, Thbd, Cdh1, Gpr157, Dusp4
Imm_Whole	DC-2	Il1b, Cd209a, Cd86, Id1, Dusp5, Thbd,
Imm_Whole	LC	Cd207, Cldn1, Plek2
Imm_Whole	Mast/Baso	Ptprc, Cd200r3, Ms4a2
Imm_Whole	Mp	Cd163, Cd68, Itgam, Lgmn, Ms4a4a, Ccl4, F13a1, Folr2, Thbd
Neu	none	Sox10, Mlana, Mlph, Tyrp1
Ery	none	Hba-a2, Hbb-bt
Death_1 (Immune cells origin)	none	Expressing a lot immunogloblin associated genes and mitochondrial genes
Death_2 (keratinocytes origin)	none	Expressing Apoc1, Fasn, Elovl5 and a lot mitochondrial genes

Supplementary Table. 5 DEGs in epidermal cells. (Dataset. 2)

Supplementary Table. 6 DEGs in mesenchymal cells. (Dataset. 3)

Supplementary Table. 7 DEGs in endothelial cells. (Dataset. 4)

Supplementary Table. 8 List of loci and primers for potential off-target cleavage sites predicted by CRISPOR.

Chrom	Locus	Primer sequence
chr5	intron: Spdyb	TGTTGGTGTTTGGGTGAAGA
		AAGCAAACGAGGGACCTTCT
chr15	intron: Mtbp	CCTTCATCAGATTGGCCTGT
		GAAGTCAAGGCGGGTACTCA
chr8	intergenic: Gm10638/Siah1a-N4bp1	TCCCACACTTGACAGACAGC
		ATAATCGCGGAGACAAATGC
chr8	intergenic: Gm26878-Fendrr	TATCTACCGCCTTCCACAGG
		GCTAACCATCACCCCAAAGA
chr7	intergenic: Cyp2b10-Cyp2b13	CCCAAGAGCCTGAGAAACAG
		GGGGGATGTAGGGTTAATGG

Supplementary Table. 9 The sequences of primers and UPL probes used for qRT-PCR.

Gene	Primer sequence	UPL#
Hprt1	TGATAGATCCATTCCTATGACTGTAGA	22
	AAGACATTCTTTCCAGTTAAAGTTGAG	
Il1b	TGTAATGAAAGACGGCACACC	78
	TCTTCTTTGGGTATTGCTTGG	
Il1f5	CTGAGTGGGGCACTATGCTT	20
	ACCTTCTCTGCGTGCAGTC	
Il1f6	CACGTACATGGGAGTGCAAA	96
	CATTTCCATTATGTTCCCTTCC	
Il1f8	CTTCGATCCCAGAGACAAGACT	69
	ATTCGGTTCCCACATTTGAA	
Il1f9	GGACACCCTACTTTGCTGCTA	77
	AACAGGAATGGCTTCATTGG	
Il6	GCTACCAAACTGGATATAATCAGGA	6
	CCAGGTAGCTATGGTACTCCAGAA	
Il12a	CCAGGTGTCTTAGCCAGTCC	62
	GCAGTGCAGGAATAATGTTTCA	
Il12b	TGAACTGGCGTTGGAAGC	74
	GCGGGTCTGGTTTGATGA	
Il13	CCTCTGACCCTTAAGGAGCTTAT	17
	CGTTGCACAGGGGAGTCT	
Il17a	TGTGAAGGTCAACCTCAAAGTC	50
	GAGGGATATCTATCAGGGTCTTCA	
Il17f	CCCAGGAAGACATACTTAGAAGAAA	46
	CAACAGTAGCAAAGACTTGACCA	
Il18	CAAACCTTCCAAATCACTTCCT	46
	TCCTTGAAGTTGACGCAAGA	
Il19	TGGAGAACCTCAGGAGCATT	18
	GAATGTCAGCAGGTTGTTGG	
Il22	TGACGACCAGAACATCCAGA	94
	AATCGCCTTGATCTCTCCAC	
Il23a	TCCCTACTAGGACTCAGCCAAC	19
	AGAACTCAGGCTGGGCATC	
Tnf	TCTTCTCATTCCTGCTTGTGG	49
	GGTCTGGGCCATAGAACTGA	
Ifna1	CTGCTGCATGGAATACAACC	22
	AGACAGCCTTGCAGGTCATT	
Ifnb1	CTGGCTTCCATCATGAACAA	18
	AGAGGGCTGTGGTGGAGAA	
Ifng	ATCTGGAGGAACTGGCAAAA	21
	TTCAAGACTTCAAAGAGTCTGAGG	
Pla2g4d	GTCACCCGAGAGACTACATGG	79
	ACAGTGAGCCGGCAGAAG	
Pla2g4e	GTGGAGTTCCTACTCGAAGAGAAT	9
	GAACCTCCAGGCAAGAGACTT	
Pla2g4f	GGGGCCTCATCATTGAGTATT	79
	CGTTTCTTGCTGGTCTGACA	
Alox8	TTTAACTTCCGCAAGACTCCA	4
	ACTGGGAGGCGAAGAAGG	
Sprr1b	ACACTACCTGTCCTCCATATACCAG	17
	TGTTTCACTTGTTGCTCATGC	
Sprr2d	GGCCGAGACTACTTTGGAGA	75
	ACAAGGCTCAGGGCACTTC	
Krt6a	GCCAAGGCAGACAGTCTAACA	55
	CAGGCTACGGTTGTTGTCC	
Krt6b	GGAAATTGCCACCTACAGGA	12
	GGTGGACTGCACCACAGAG	
Krt9	TCAGGAATACAGCATTCTGCTC	19
	CCAGCTCCAGACGATTCAA	
Krt16	ATGGCGAGAATATCCACAGCTC	SYBR
	TGGTTGAACCTTGCTCCTTGA	
Krt17	AGGAGCTGGCCTACCTGAA	63
	ACCTGGCCTCTCAGAGCAT	
S100a7a	TGGATAGTGTGCCTCGCTTC	SYBR
	CCGGAACAGCTCTGTGATGTA	
S100a8	AATGGTCACTACTGAGTGTCCTC	SYBR
	CTCTGCTACTCCTTGTGGCT	
S100a9	CACCCTGAGCAAGAAGGAAT	31
	TGTCATTTATGAGGGCTTCATTT	
Casp1	CCCACTGCTGATAGGGTGAC	103
	GCATAGGTACATAAGAATGAACTGGA	
Casp4	GGGCAACCTTGACGAGATATT	72
	GAGATTCAGTTGCTTGTTGCTTT	
Casp14	AGGATCCATCTTAGAACTGACAGAA	4
	TCAGGGTTCACTTTCCTTGG	
Flg	GGAGGAAGAAACACTGAGCAA	96
	CGATGTCTTGGTCATCTGGA	
Flg2	TGAGCAAGGATGAGCTAAAGG	67
	GTGTCTGGATCATCTGGATTCTT	
Rnase2a	GGGAGCCACAAAGCAGACT	50
	AGCAGCAGGAGACAAAGTCG	
Rnase2b	CAACCCCTTCCCAGAAGTTT	42
	CGCATTGCATCATCACATTT	
Epgn	GGCTCTGGGGGTTCTGATAG	34
	CCTCTGCTTCTTCGCTCAGT	