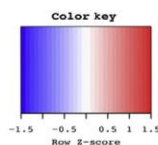


APPENDIX



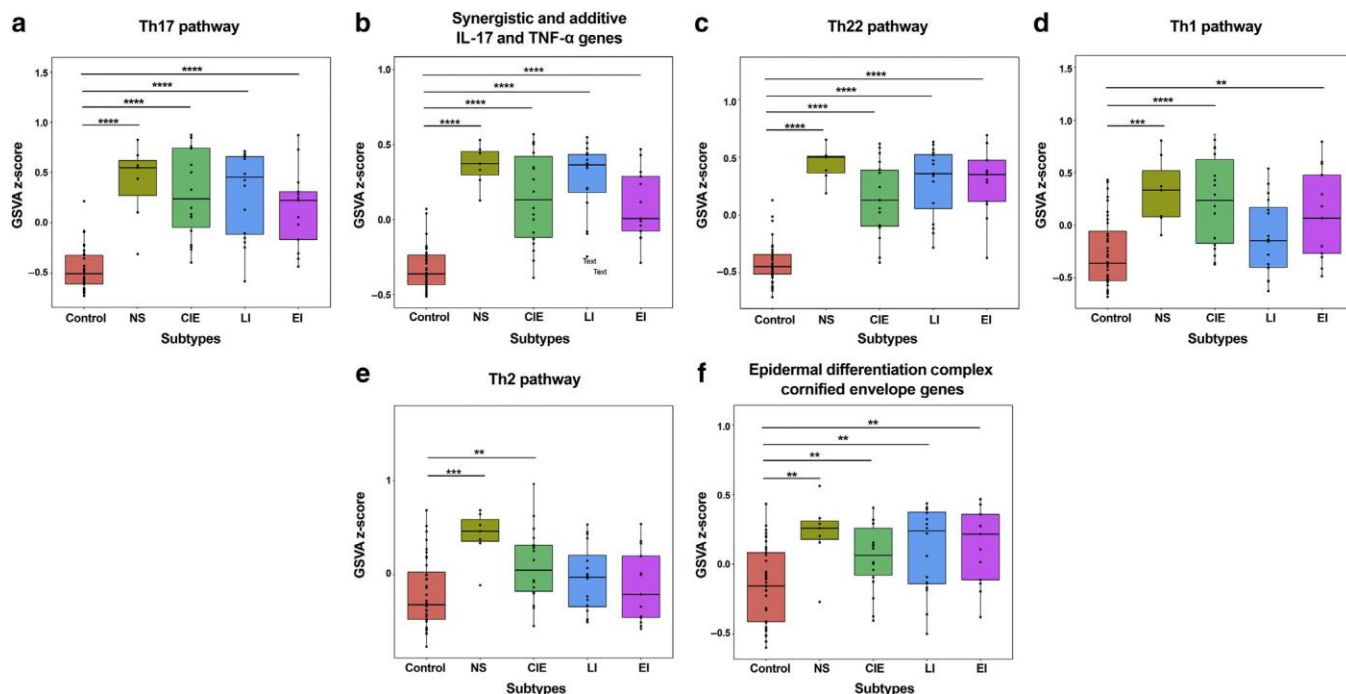
IL-17/TNF- α -related genes

N	NS	CIE	LI	EI	Markers	NS versus N	CIE versus N	LI versus N	EI versus N
					SERPIN3	52.30**	49.80**	48.80**	30.80**
					EIF	6.38**	5.99**	5.89**	4.75**
					LCE3D	34.20**	29.00**	26.90**	17.20**
					SPRR2A	519.00**	243.00**	441.00**	173.00**
					SPRR2B	290.00**	190.00**	290.00**	98.20**
					S100A9	273.00**	120.00**	156.00**	86.40**
					S100A8	176.00**	80.60**	95.10**	53.40**
					SERPIN4	585.00**	316.00**	354.00**	130.00**
					TMEM45B	4.25**	3.57**	3.53**	2.94**
					GRHL3	3.63**	3.14**	3.47**	2.49**
					SPRR2D	36.10**	22.60**	32.20**	13.40**
					SPRR2F	521.00**	248.00**	342.00**	74.80**
					SPRR2E	13.10**	11.00**	11.80**	6.48**
					S100A7	223.00**	85.50**	125.00**	46.40**
					FUT2	4.37**	3.36**	3.88**	2.92**
					S100A7A	2200.00**	497.00**	813.00**	176.00**
					ZC3H12A	8.52**	3.98**	5.18**	3.19**
					PDZK1IP1	2.82**	2.25**	3.02**	2.18**
					EP3	2.98**	1.77**	2.29**	1.71**
					ZSWIM4	2.38**	2.04**	2.47**	1.97**
					TGM1	2.75**	2.15**	2.15**	1.32**
					SPRR2G	36.80**	23.25**	23.20**	13.20**
					S100A12	194.00**	80.70**	87.10**	40.40**
					GJB2	7.59**	5.49**	5.36**	3.98**
					MPPEL2	4.79**	3.75**	3.38**	2.94**
					TMPPRS11D	98.80**	36.80**	34.50**	16.50**
					SPRR2C	379.00**	97.00**	75.60**	27.90**
					CNFN	6.71**	4.27**	4.42**	4.16**
					PI3	222.00**	90.50**	93.10**	87.80**
					GAT6	5.10**	3.33**	3.07**	3.18**
					A2ML1	4.67**	4.83**	6.98**	3.10**
					LCN2	12.40**	14.10**	24.40**	7.81**
					KIF11	7.70**	8.37**	10.90**	5.48**
					VNN3	106.00**	90.40**	162.00**	33.80**
					NFKB12	2.43**	2.54**	2.85**	1.85**
					IRAK2	2.94**	3.03**	3.69**	1.87**
					SDCBP2	2.88**	2.98**	3.88**	1.84**
					NOD2	3.08**	2.49**	3.15**	1.99**
					GFOD2	2.04**	1.87**	2.08**	1.47**
					RFC3	10.80**	6.48**	10.20**	2.90**
					TGM3	8.12**	3.67**	3.64**	1.45**
					PRDM1	2.51**	2.26**	2.26**	1.31**
					FLA2G3	4.66**	3.78**	3.22**	1.98**
					DCUH1D3	2.09**	1.71**	1.52**	1.42**
					AZF12A	9.44**	18.30**	24.40**	11.28**
					CCL20	16.10**	18.30**	7.80**	17.70**
					IL17C	5.42**	10.20**	22.40**	5.18**
					CRABP2	1.75**	2.64**	3.75**	1.03**
					TNFR79	1.93**	2.64**	3.01**	0.81**
					ALOX12B	3.31**	2.72**	3.32**	2.95**
					FOXO1	18.40**	7.96**	11.80**	10.10**
					GPR110	43.30**	39.10**	55.20**	40.50**
					GLTP	2.10**	2.00**	2.44**	2.24**
					ATP10B	2.43**	2.55**	2.94**	2.89**
					SOX7	2.96**	2.57**	3.41**	3.04**
					KRTDAP	1.84**	0.95**	1.48**	0.86**
					CSTA	2.77**	2.60**	3.25**	2.55**
					CYP2S1	2.49**	2.39**	2.15**	1.55**
					SLC6A14	4.55**	4.41**	4.68**	3.71**
					CHE1	7.76**	7.86**	8.68**	3.31**
					DUOX1	2.82**	2.02**	1.27**	0.87**
					RLK10	4.13**	4.74**	5.75**	3.75**
					C9orf169	4.13**	2.95**	3.79**	2.75**
					SULT2B1	2.12**	1.71**	2.11**	2.36**
					FIT1	2.20**	1.66**	1.60**	2.90**
					FMEPA1	-1.77**	-1.72**	-1.11**	-1.91**
					PANX2	-2.21**	-2.21**	-2.96**	-2.27**
					ADRB2	-2.17**	-2.40**	-2.75**	-2.52**
					FUT8	-1.75**	-1.59**	-2.05**	-1.91**
					GGT1	-1.70**	-1.50**	-2.09**	-1.93**
					LOX	-2.04**	-2.10**	-2.95**	-3.16**
					PDGFRL	-2.26**	-2.64**	-3.27**	-4.19**
					PIK3IP1	-2.64**	-2.29**	-2.92**	-2.84**
					PDE1A	-2.16**	-1.68**	-2.04**	-2.45**

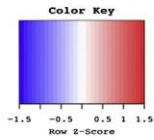
Supplementary Figure S1. IL-17/TNF- α -associated markers are strongly upregulated in all subtypes.

Heatmap representing differentially expressed genes synergistically upregulated by IL-17 and/or TNF- α in ichthyosis subtypes and in healthy controls. Criteria for differential gene expression include FCH > 2 and FDR < 0.05. From left to right, heatmap columns represent N, NS, CIE, LI, and EI. The table shows FCHs in NS versus N, CIE versus N, LI versus N, and EI versus N

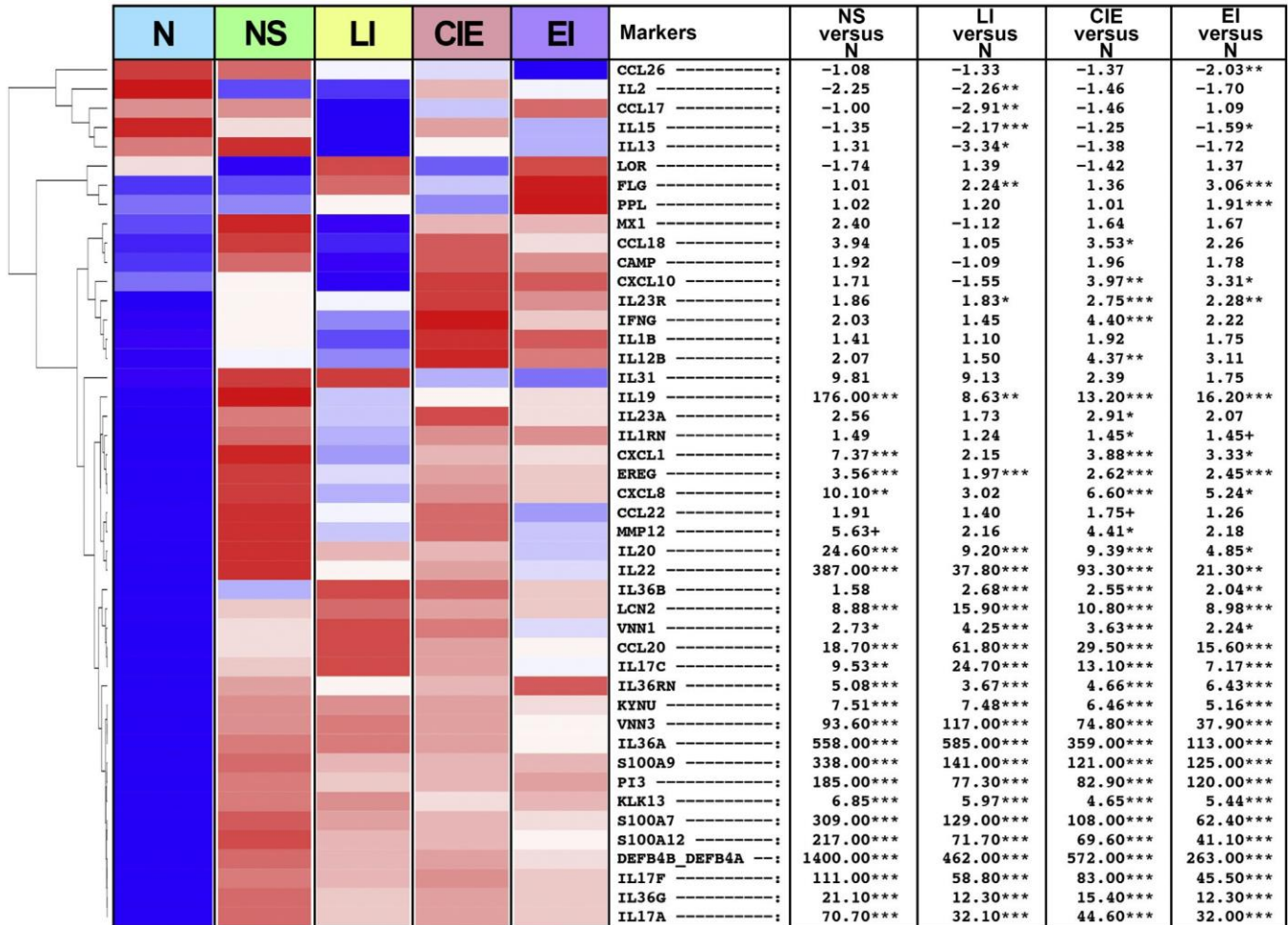
N. **FDR < 0.01, *FDR < 0.05, and ⁺FDR < 0.1. N denotes normal. CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; FCH, fold change; FDR, false discovery rate; LI, lamellar ichthyosis; NS, Netherton syndrome.



Supplementary Figure S2. Th17/Th22 and EDC/CE are strongly upregulated in all subtypes, whereas Th1 and Th2 show comparatively modest and variable modulation. Boxplots of mean GSVA z-score depicting the pathways of genes related to a selection of immune axes. (a) Th17, (b) genes synergistically upregulated by IL-17 and/or TNF- α , (c) Th22, (d) Th1, (e) Th1, and (f) EDC and CE. **** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, and * $P < 0.05$. CE, cornified envelope; CIE, congenital ichthyosiform erythroderma; EDC, epidermal differentiation complex; EI, epidermolytic ichthyosis; GSVA, gene set variation analysis; LI, lamellar ichthyosis; NS, Netherton syndrome; Th, T helper.

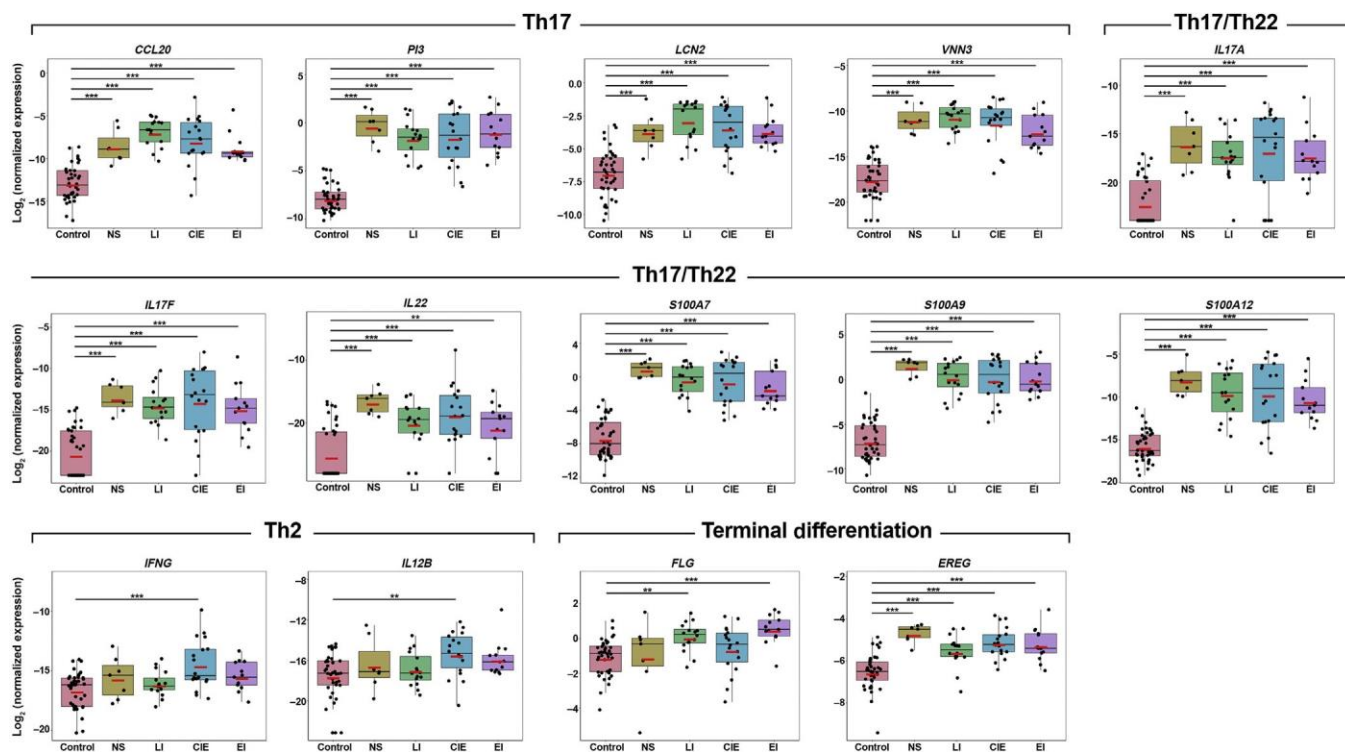


RT-PCR

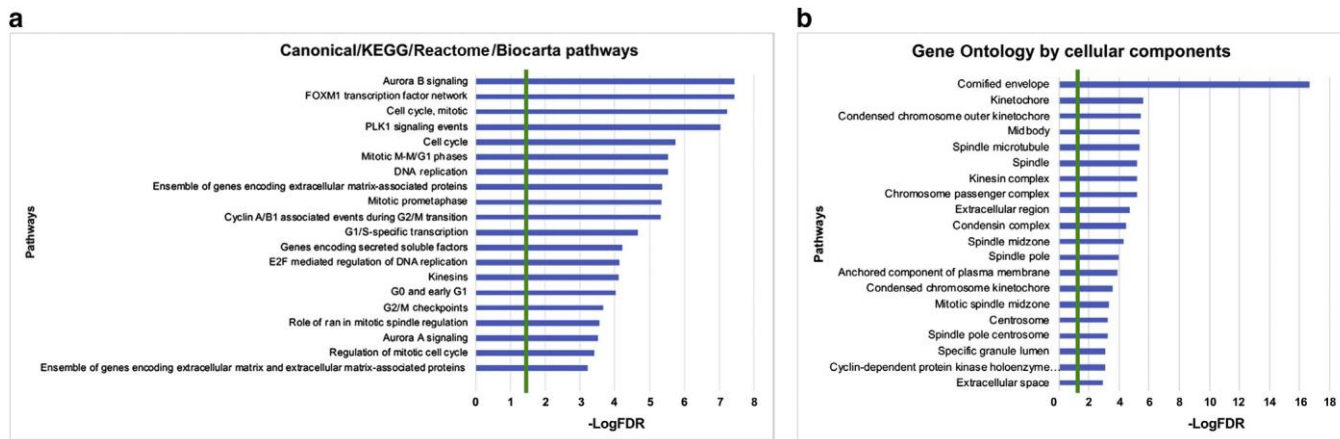


Supplementary Figure S3. RT-PCR analysis supports RNA-seq data. Heatmap representing the genes sequenced with RT-PCR from biopsied skin of patients with the various ichthyosis subtypes and healthy controls. Criteria for differential gene expression include FCH > 2 and FDR < 0.05. From left to right, heatmap columns represent N, NS, CIE, LI, and EI. The table shows FCHs in NS versus N, CIE versus N, LI versus N, and EI versus N. N denotes normal. **FDR < 0.01,

*FDR < 0.05, and +FDR < 0.1. CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; FDR, false discovery rate; LI, lamellar ichthyosis; NS, Netherton syndrome; RNA-seq, RNA-sequencing.



Supplementary Figure S4. RT-PCR analysis supports RNA-seq of immune and terminal differentiation marker expression. Boxplots of \log_2 -normalized expression of a selection of genes sequenced with RT-PCR, representing Th17-specific, Th17/Th2, Th2, and terminal differentiation pathways. **** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, and * $P < 0.05$. CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; LI, lamellar ichthyosis; NS, Netherton syndrome; RNA-seq, RNA-sequencing; Th, T helper.



Supplementary Figure S5. Pathway enrichment analysis highlights cellular proliferation signaling. Barplots of $-\log$ false discovery rates of all DEGs within the pathways from validated databases. (a) Enriched pathways from the canonical, KEGG, Reactome, and BioCarta databases. (b) Further localization of DEGs to cellular components is shown through the Gene Ontology database. DEG, differentially expressed gene; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Supplementary Table S1. Ichthyosis Cohort Demographics

Subject No.	Subtype	Gene	Age (y)	Sex	Race	Flow Cytometry Performed
1	LI	<i>TGM1</i>	56.9	F	White/Caucasian	
2	LI	<i>TGM1</i>	37	F	Black/African American	
3	NS	<i>SPINK5</i>	6.3	F	Other	
4	EI	<i>K10</i>	11.6	M	White/Caucasian	Y
5	CIE	<i>NIPAL4</i>	14.1	F	White/Caucasian	Y
6	NS	<i>SPINK5</i>	19.2	M	White/Caucasian	Y
7	LI	<i>TGM1</i>	28	M	White/Caucasian	Y
8	EI	<i>K10</i>	17.9	M	White/Caucasian	Y
9	CIE	<i>CerS3</i>	29.8	M	Asian/Pacific Islander	Y
10	EI	<i>K10</i>	40.3	F	White/Caucasian	
11	CIE	<i>ALOX12B</i>	16.6	M	White/Caucasian	
12	NS	<i>SPINK5</i>	12.5	F	Black/African American	Y
13	LI	<i>TGM1</i>	9.2	F	White/Caucasian	Y
14	LI	<i>TGM1</i>	10.8	M	White/Caucasian	Y
15	CIE	<i>ALOXE3</i>	42.9	F	White/Caucasian	
16	EI	<i>K10</i>	55	F	White/Caucasian	
17	NS	<i>SPINK5</i>	23	F	White/Caucasian	
18	LI	<i>TGM1</i>	19	F	Other	Y
19	CIE	<i>ALOX12B</i>	11	M	White/Caucasian	Y
20	EI	<i>K10</i>	13	F	White/Caucasian	Y
21	LI	<i>TGM1</i>	35	F	White/Caucasian	Y
22	CIE	<i>ALOX12B</i>	7	M	White/Caucasian	Y
27	CIE	<i>PNPLA1</i>	6	M	Asian/Pacific Islander	Y
28 ¹	CIE	<i>ABCA12</i>	4	M	Black/African American	Y
29	EI	<i>K1</i>	2.2	M	White/Caucasian	Y
30	CIE	<i>GJA1</i>		M	White/Caucasian	Y
31	CIE	<i>GJA1</i>	31.56	F	Black/African American	
32	CIE	<i>NIPAL4</i>	46.94	M	White/Caucasian	
33 ¹	CIE	<i>ABCA12</i>	7.4	M	Other	
34	EI	<i>K1</i>	1.1	F	Asian/Pacific Islander	
35	EI	<i>K10</i>	17.7	M	Black/African American	
36	EI	<i>K10</i>	34	F	White/Caucasian	
39	LI	<i>TGM1</i>	41.3	F	White/Caucasian	Y
40	NS	<i>SPINK5</i>	43.2	F	White/Caucasian	Y
41	LI	<i>TGM1</i>	23.7	F	White/Caucasian	Y
42	CIE	<i>ALOX12B</i>	15.1	F	White/Caucasian	Y
43	EI	<i>K10</i>	70.8	M	White/Caucasian	
44	NS	<i>SPINK5</i>	41.2	F	White/Caucasian	Y
47	LI	<i>TGM1</i>	24.7	F	White/Caucasian	Y
48	LI	<i>TGM1</i>	26.2	M	White/Caucasian	
49	LI	<i>TGM1</i>	42.7	F	Other	Y
50	EI	<i>K10</i>	57.9	F	White/Caucasian	
51	EI	<i>K10</i>	18	F	Hispanic	Y
52	CIE	<i>ABCA12</i>	32.2	F	White/Caucasian	Y
53	NS	<i>SPINK5</i>	18.9	M	White/Caucasian	Y
54	EI	<i>K10</i>	16.9	M	White/Caucasian	
55	CIE	<i>ALOX12B</i>	17.5	F	American Indian/Alaskan Native	Y
56	LI	<i>TGM1</i>	53.1	M	White/Caucasian	Y
57	LI	<i>TGM1</i>	56.6	F	White/Caucasian	Y
58 ²	CIE	<i>TGM1</i>	48.7	F	White/Caucasian	Y
59	LI	<i>TGM1</i>	10.5	F	White/Caucasian	
60	LI	<i>TGM1</i>	13.1	M	White/Caucasian	
62	CIE	<i>NIPAL4</i>	1	M	White/Caucasian	
64	CIE	<i>CerS3</i>	5.2	M	Other	

¹These patients presented with harlequin ichthyosis.

²This patient was born with LI but presented with CIE at the time of sample collection

Abbreviations: CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; F, female; LI, lamellar ichthyosis; M, male; No., number; NS, Netherton syndrome; Y, yes.

Supplementary Table S2. Comparison of Unique Genes in Subtypes and Common Phenotypes with Previous Work with Microarrays

Subtype Versus Controls	Upregulated RNA-Seq, Previously Insignificant	Downregulated RNA-Seq, Previously Insignificant	Upregulated in RNA-Seq and Previously Insignificant	Downregulated in RNA-Seq and Previously Insignificant	Upregulated RNA-Seq, Not Previously Measured	Downregulated RNA-Seq, Not Previously Measured
Common	171	329	97	41	338	658
NS	38	88	8	6	188	814
CIE	23	6	3	0	249	150
EI	8	54	16	11	185	452
LI	20	80	16	50	152	588

Abbreviations: CIE, congenital ichthyosiform erythroderma; EI, epidermolytic ichthyosis; LI, lamellar ichthyosis; NS, Netherton syndrome; RNA-Seq, RNA-sequencing.

The previous work with microarrays was conducted by [Malik et al. \(2019\)](#)

Supplementary Table S3. Selection of RNA-Seq Marker Versus Clinical Index Correlations

	Marker	TEWL		IASI-E		IASI-S		IASI-SE	
		rho	P-Value	rho	P-Value	rho	P-Value	rho	P-Value
Th2	CCL7	0.334	0.019	0.189	0.171	-0.042	0.760	0.148	0.285
	CCL17	0.316	0.027	-0.091	0.514	-0.099	0.476	-0.147	0.288
	CCL18	0.211	0.146	0.181	0.189	-0.350	0.009	-0.057	0.684
	CXCL13	0.090	0.536	0.327	0.016	-0.153	0.270	0.187	0.177
	CCL23	0.133	0.362	0.316	0.020	-0.351	0.009	0.007	0.962
	CCL22	0.070	0.632	0.288	0.035	-0.139	0.317	0.156	0.261
	IL-4R	0.261	0.070	0.276	0.043	-0.246	0.073	0.094	0.498
	IL-31	-0.167	0.252	-0.164	0.236	0.318	0.019	0.066	0.636
Th17	CXCL3	0.200	0.168	0.144	0.298	-0.314	0.021	-0.036	0.795
	CXCL2	0.170	0.242	0.258	0.060	-0.405	0.002	-0.021	0.882
Th17/Th22	FOXE1	0.254	0.078	0.226	0.101	0.315	0.020	0.397	0.003
	PITX1	0.218	0.132	0.237	0.085	0.209	0.129	0.317	0.020
	IL-23R	-0.232	0.109	0.365	0.007	0.014	0.922	0.292	0.032
	CRABP2	0.197	0.174	0.144	0.299	0.210	0.128	0.273	0.046
	PANX2	0.243	0.093	-0.199	0.150	-0.225	0.101	-0.287	0.036
	EPN3	0.458	<0.001	-0.068	0.624	-0.077	0.579	-0.104	0.454
	FAM43A	0.426	0.002	0.249	0.069	-0.172	0.213	0.113	0.417
	HAS3	0.417	0.003	0.199	0.149	-0.101	0.469	0.137	0.324
	TMPRSS11D	0.385	0.006	0.310	0.022	-0.204	0.139	0.123	0.375
	KLK10	0.381	0.007	0.231	0.092	-0.094	0.498	0.134	0.335
	IL-19	0.366	0.010	0.072	0.604	-0.275	0.044	-0.099	0.476
	SERPINB3	0.338	0.017	0.293	0.032	-0.193	0.161	0.104	0.456
	DCUN1D3	0.296	0.039	0.252	0.066	-0.246	0.073	0.060	0.667
	CCL13	0.294	0.040	0.023	0.870	-0.280	0.040	-0.133	0.337
	CXCL1	0.129	0.378	0.301	0.027	-0.245	0.074	0.124	0.372
	CYP2S1	-0.010	0.945	0.282	0.039	-0.160	0.248	0.142	0.304
	IL-17A	0.003	0.981	0.356	0.008	-0.111	0.426	0.252	0.066
	IL-17F	0.068	0.642	0.283	0.038	-0.205	0.137	0.119	0.392
	IL-36G	0.228	0.116	0.261	0.057	-0.308	0.023	0.037	0.791
	KLK12	0.084	0.565	0.297	0.029	0.055	0.691	0.244	0.075
	PI3	0.156	0.285	0.439	<0.001	-0.161	0.244	0.257	0.060
	S100A12	0.149	0.307	0.320	0.018	-0.281	0.040	0.082	0.557
	S100A7	0.135	0.356	0.253	0.065	-0.279	0.041	0.017	0.905
	S100A7A	0.137	0.348	0.334	0.014	-0.197	0.153	0.162	0.242
	S100A8	0.214	0.140	0.280	0.041	-0.231	0.093	0.077	0.582
	S100A9	0.227	0.117	0.299	0.028	-0.229	0.096	0.096	0.491
	SAA4	0.046	0.753	0.388	0.004	-0.348	0.010	0.060	0.666
	SERPINB4	0.229	0.114	0.365	0.007	-0.231	0.094	0.150	0.279
VNN3	0.068	0.644	0.276	0.044	-0.062	0.654	0.166	0.232	

(continued)

Supplementary Table S3. Continued

	Marker	TEWL		IASI-E		IASI-S		IASI-SE	
		rho	P-Value	rho	P-Value	rho	P-Value	rho	P-Value
Innate immunity	IL-8	0.234	0.105	0.226	0.100	-0.282	0.039	0.035	0.803
Negative regulators	IL-34	-0.011	0.941	-0.377	0.005	0.375	0.005	-0.073	0.601
Lipid metabolism	ACER2	-0.348	0.014	-0.205	0.136	0.083	0.550	-0.123	0.376
	ACSL1	0.119	0.416	-0.300	0.027	0.073	0.598	-0.212	0.125
	CeTP	0.334	0.019	-0.321	0.018	-0.404	0.002	-0.500	<0.001
	FABP7	-0.022	0.883	-0.346	0.010	-0.025	0.855	-0.300	0.028
	FFAR2	0.410	0.003	-0.114	0.410	-0.074	0.595	-0.110	0.429
	KRTDAP	-0.344	0.016	-0.202	0.143	0.035	0.803	-0.169	0.221
	LIPE	0.335	0.019	-0.041	0.766	-0.266	0.052	-0.208	0.131
	PLA2G16	0.279	0.052	-0.207	0.134	-0.240	0.080	-0.314	0.021
	PLA2G3	0.295	0.040	0.328	0.015	-0.250	0.068	0.124	0.373
	PLA2G4D	0.378	0.007	0.353	0.009	-0.151	0.277	0.178	0.198
	SAA1	0.213	0.142	0.285	0.037	-0.184	0.182	0.113	0.417
Tight junctions	CDH12	-0.078	0.596	0.203	0.044	-0.005	0.970	-0.226	0.101
	CDH19	-0.145	0.320	0.030	0.829	-0.388	0.004	-0.105	0.452
	CDH20	-0.110	0.452	-0.275	0.044	0.085	0.542	-0.252	0.066
	CLDN1	-0.415	0.003	-0.277	0.042	-0.298	0.029	-0.216	0.117
	CLDN8	-0.045	0.758	-0.299	0.028	-0.388	0.004	-0.195	0.158
Gap junctions	GJB2	0.436	0.002	0.260	0.058	-0.013	0.925	0.226	0.100
	GJB6	0.457	<0.001	0.202	0.143	-0.145	0.294	0.072	0.605
Keratins	K77	-0.175	0.229	-0.314	0.021	0.219	0.111	-0.120	0.389
Other barrier-related	ANXA6	0.284	0.048	-0.054	0.700	-0.242	0.078	-0.162	0.243
KC differentiation	IL-20	0.184	0.205	0.169	0.223	-0.331	0.015	-0.042	0.765
	SPRR2A	0.085	0.560	0.285	0.037	-0.162	0.243	0.150	0.278
	SPRR2C	0.192	0.185	0.367	0.006	-0.303	0.026	0.111	0.424
	SPRR2F	0.163	0.262	0.287	0.035	-0.193	0.161	0.130	0.349
Terminal differentiation	FLG	0.034	0.816	-0.296	0.030	0.157	0.257	-0.175	0.206
	LCE3D	0.306	0.033	0.163	0.238	-0.288	0.034	-0.124	0.371
	LOR	0.038	0.798	-0.291	0.033	0.225	0.102	-0.067	0.630
	SCEL	-0.103	0.479	-0.307	0.024	0.222	0.107	-0.140	0.311
Clinical indices	IASI_E	-0.095	0.515	N/A	N/A	0.043	0.758	0.765	<0.001
	IASI_S	-0.266	0.064	0.043	0.758	N/A	N/A	0.650	<0.001
	IASI_SE	-0.257	0.075	0.765	<0.001	0.650	<0.001	N/A	N/A
	TEWL	N/A	N/A	-0.095	0.515	-0.266	0.064	-0.257	0.075
Misc.	FURIN	0.467	<0.001	0.143	0.302	-0.080	0.565	0.073	0.600
	GGT1	0.261	0.070	0.253	0.065	-0.457	<0.001	-0.185	0.181
	HIF1A	0.339	0.017	0.096	0.492	-0.197	0.152	0.269	0.049
	MPZL2	0.230	0.112	0.176	0.204	-0.112	0.419	0.274	0.045
	SLPI	-0.099	0.499	0.377	0.005	-0.153	0.268	0.208	0.131
	SOX7	0.047	0.751	0.092	0.507	0.342	0.011	0.288	0.035

Pairs of rho and p-values found to be significant ($P < 0.05$) have been highlighted in bold. Abbreviations: IASI-E, ichthyosis area severity index-erythema; IASI-S, ichthyosis area severity index-scaling; IASI-SE, total ichthyosis area severity index; KC, keratinocyte; LOR, loricrin; Misc., miscellaneous; N/A, not applicable; TEWL, transepidermal water loss; Th, T helper.

Supplementary Table S4. Selection of RNA-Seq Versus Flow Cytometry Spearman Correlations

Gene Set	RNA-Seq Marker	Flow Cytometry T-Cell Markers	Spearman Rho (r)	P-Value
Th22 specific	IL-22	CD4+ IL-22+	0.439	0.012
	IL-22	CD4+ IL-22+ CLA-	0.424	0.016
	SERPINB4	CD4+ IL-22+ CLA-	0.390	0.027
	SERPINB4	CD4+ IL-22+	0.387	0.029
	S100A9	CD4+ IL-22+	0.381	0.032
	S100A8	CD4+ IL-22+ CLA-	0.379	0.032
	S100A8	CD4+ IL-22+	0.371	0.037
	S100A8	CD4+ IL-22+	0.368	0.038
	S100A9	CD4+ IL-22+ CLA-	0.361	0.043
	S100A9	CD4+ IL-22+ CLA-	0.354	0.047
Th17 specific	K1	CD4+ IL-17+ CLA-	-0.375	0.034
	IL-23A	CD4+ IL-22+ CLA-	0.481	0.005
	CAMP	CD4+ IL-22+ CLA-	0.477	0.006
	IL-23A	CD4+ IL-22+	0.465	0.007
	CAMP	CD4+ IL-22+	0.459	0.008
	CAMP	CD4+ IL-17+ CLA-	0.368	0.038
	PI3	CD4+ IL-22+	0.361	0.042
	CAMP	CD4+ IL-17+	0.358	0.048
	CCR6	CD4+ IL-17+ CLA+	-0.465	0.008
Synergistically upregulated by IL-17/TNF- α	DCUN1D3	CD4+ IL-22+	0.525	0.002
	DCUN1D3	CD4+ IL-22+ CLA-	0.503	0.003
	IL-23A	CD4+ IL-22+ CLA-	0.481	0.005
	FAM43A	CD4+ IL-22+	0.478	0.006
	IL-23A	CD4+ IL-22+	0.465	0.007
	FAM43A	CD4+ IL-22+ CLA-	0.459	0.008
	K75	CD4+ IL-22+ CLA+	0.458	0.008
	SPRR2A	CD4+ IL-22+	0.452	0.009
	IL-1B	CD4+ IL-22+	0.448	0.010
	IL-1B	CD4+ IL-22+ CLA-	0.443	0.011
	IL-1RN	CD4+ IL-22+	0.441	0.012
	IL-1RN	CD4+ IL-22+ CLA-	0.440	0.012
	SERPINB3	CD4+ IL-22+ CLA-	0.440	0.012
	SPRR2A	CD4+ IL-22+ CLA-	0.435	0.013
	SERPINB3	CD4+ IL-22+	0.434	0.013
	TMPRSS11D	CD4+ IL-22+	0.408	0.020
	SERPINB3	CD4+ IL-22+	0.407	0.021
	SPRR2D	CD4+ IL-22+	0.405	0.021
	HBEGF	CD4+ IL-22+ CLA+	0.403	0.022
	TMPRSS11D	CD4+ IL-22+ CLA-	0.401	0.023
GSVA Pathway		Flow Cytometry Markers	Spearman Rho (r)	P-Value
Synergistic and additive IL-17 and TNF- α KC		CD4+ IL-22+	0.420	0.017
Synergistic and additive IL-17 and TNF- α KC		CD4+ IL-22+ CLA-	0.398	0.024
Th22/IL-22		CD4+ IL-22+	0.388	0.028
Th22/IL-22		CD4+ IL-22+ CLA-	0.371	0.037
Th17 specific		CD4+ IL-22+	0.361	0.043
Th22/IL-22		CD4+ IL-22+ CLA-	0.360	0.043
Th2 specific		CD4+ IL-22+	0.356	0.045
EDC		CD4+ IL-22+	0.356	0.046

Abbreviations: CLA, cutaneous lymphocyte-associated antigen; EDC, epidermal differentiation complex; GSVA, gene set variation analysis; KC, keratinocyte; RNA-Seq, RNA-sequencing; Th, T helper.

Supplementary Table S5. Pathway Enrichment Analysis of Differentially Expressed Genes in Ichthyosis Versus Controls

Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Aurora B signaling	9.970	<0.001	<0.001	10.000	AURKA, AURKB, BIRC5, BUB1, KIF20A, KIF23, KIF2C, NCAPG, NCAPH, SMC4
FOXO1 transcription factor network	9.820	<0.001	<0.001	10.000	AURKB, BIRC5, CCNA2, CCNB1, CCNB2, CCNE1, CENPF, FOXM1, NEK2, PLK1
Cell cycle, mitotic	7.350	<0.001	<0.001	26.000	AURKA, AURKB, BIRC5, BUB1, BUB1B, CCNA2, CCNB1, CCNB2, CCNE1, CDC20, CDC25A, CDC45, CDC6, ERCC6L, KIF18A, KIF20A, KIF23, KIF2C, MCM10, MYBL2, NEK2, PLK1, PTTG1, RRM2, SKA1, ZWINT
PLK1 signaling events	9.030	<0.001	<0.001	10.000	AURKA, BUB1, BUB1B, CCNB1, CDC20, CLSPN, ERCC6L, KIF20A, PLK1, TPX2
Cell cycle	6.880	<0.001	<0.001	14.000	BUB1, BUB1B, CCNA2, CCNB1, CCNB2, CCNE1, CDC20, CDC25A, CDC45, CDC6, ESPL1, PLK1, PTTG1, TTK
Cell cycle	6.140	<0.001	<0.001	27.000	AURKA, AURKB, BIRC5, BUB1, BUB1B, CCNA2, CCNB1, CCNB2, CCNE1, CDC20, CDC25A, CDC45, CDC6, ERCC6L, HJURP, KIF18A, KIF20A, KIF23, KIF2C, MCM10, MYBL2, NEK2, PLK1, PTTG1, RRM2, SKA1, ZWINT
DNA replication	6.350	<0.001	<0.001	17.000	AURKB, BIRC5, BUB1, BUB1B, CCNA2, CDC20, CDC45, CDC6, ERCC6L, KIF18A, KIF20A, KIF23, KIF2C, MCM10, PLK1, SKA1, ZWINT
Mitotic M-M/G1 phases	6.410	<0.001	<0.001	16.000	AURKB, BIRC5, BUB1, BUB1B, CDC20, CDC45, CDC6, ERCC6L, KIF18A, KIF20A, KIF23, KIF2C, MCM10, PLK1, SKA1, ZWINT
Ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors	5.530	<0.001	<0.001	38.000	A2ML1, CCL20, CCL7, CLEC3A, CLEC7A, CSTA, CXCL1, EREG, FGF1P1, HPSE, HRNR, HYAL4, IFNE, IL17A, IL17C, IL17F, IL20, IL36A, IL36G, IL36RN, LGALS9B, LGALS9C, LMAN1L, PCSK6, PI3, S100A12, S100A2, S100A7, S100A7A, S100A8, S100A9, SERPINB10, SERPINB13, SERPINB3, SERPINB4, TGM1, TLL2, WNT5A
Mitotic prometaphase	6.650	<0.001	<0.001	11.000	AURKB, BIRC5, BUB1, BUB1B, CDC20, ERCC6L, KIF18A, KIF2C, PLK1, SKA1, ZWINT
Cyclin A/B1 associated events during G2/M transition	8.200	<0.001	<0.001	5.000	CCNA2, CCNB1, CCNB2, CDC25A, PLK1
G1/s-specific transcription	7.150	<0.001	<0.001	5.000	CCNE1, CDC25A, CDC45, CDC6, RRM2
Genes encoding secreted soluble factors	5.010	<0.001	<0.001	21.000	CCL20, CCL7, CXCL1, EREG, FGF1P1, HRNR, IFNE, IL17A, IL17C, IL17F, IL20, IL36A, IL36G, IL36RN, S100A12, S100A2, S100A7, S100A7A, S100A8, S100A9, WNT5A
E2F mediated regulation of DNA replication	6.020	<0.001	<0.001	6.000	CCNB1, CCNE1, CDC25A, CDC45, CDC6, RRM2
Kinesins	6.210	<0.001	<0.001	5.000	KIF18A, KIF20A, KIF23, KIF2C, KIF4A
G0 and Early G1	6.060	<0.001	<0.001	5.000	CCNA2, CCNE1, CDC25A, CDC6, MYBL2
G2/m checkpoints	5.330	<0.001	<0.001	6.000	CCNB1, CCNB2, CDC25A, CDC45, CDC6, MCM10
Role of Ran in mitotic spindle regulation	5.980	<0.001	<0.001	3.000	AURKA, KPNA2, TPX2
Aurora A signaling	5.280	<0.001	<0.001	5.000	AURKA, AURKB, BIRC5, DLGAP5, TPX2
Regulation of mitotic cell cycle	4.710	<0.001	<0.001	8.000	AURKA, AURKB, BUB1B, CCNA2, CCNB1, CDC20, PLK1, PTTG1
Ensemble of genes encoding ECM and ECM-associated proteins	3.900	<0.001	0.001	40.000	A2ML1, CCL20, CCL7, CLEC3A, CLEC7A, CSTA, CXCL1, EREG, FGF1P1, HPSE, HRNR, HYAL4, IFNE, IL17A, IL17C, IL17F, IL20, IL36A, IL36G, IL36RN, LGALS9B, LGALS9C, LMAN1L, LRG1, PCSK6, PI3, S100A12, S100A2, S100A7, S100A7A, S100A8, S100A9, SERPINB10, SERPINB13, SERPINB3, SERPINB4, TGM1, TLL2, VWA3A, WNT5A
ATR signaling pathway	4.510	<0.001	0.001	5.000	CCNA2, CDC25A, CDC6, CLSPN, PLK1
Oocyte meiosis	4.180	<0.001	0.001	9.000	AURKA, BUB1, CCNB1, CCNB2, CCNE1, CDC20, ESPL1, PLK1, PTTG1

Supplementary Table S5. Continued

Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
E2F transcription factor network	4.260	<0.001	0.001	7.000	<i>CCNA2, CCNE1, CDC25A, CDC6, E2F7, MYBL2, RRM2</i>
Chemokine receptors bind chemokines	4.340	<0.001	0.001	6.000	<i>CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6</i>
Cell cycle checkpoints	4.060	<0.001	0.001	9.000	<i>BUB1B, CCNB1, CCNB2, CCNE1, CDC20, CDC25A, CDC45, CDC6, MCM10</i>
Amino acid transport across the plasma membrane	4.050	0.001	0.002	4.000	<i>SLC6A14, SLC7A1, SLC7A11, SLC7A5</i>
G1/s transition	3.630	0.001	0.003	8.000	<i>CCNA2, CCNB1, CCNE1, CDC25A, CDC45, CDC6, MCM10, RRM2</i>
Mitotic G1-G1/S phases	3.550	0.001	0.003	9.000	<i>CCNA2, CCNB1, CCNE1, CDC25A, CDC45, CDC6, MCM10, MYBL2, RRM2</i>
Glycosaminoglycan degradation	3.770	0.001	0.004	3.000	<i>HPSE, HS3ST3A1, HYAL4</i>
Activation of ATR in response to replication stress	3.640	0.001	0.004	4.000	<i>CDC25A, CDC45, CDC6, MCM10</i>
IL-23-mediated signaling events	3.560	0.001	0.004	4.000	<i>ALOX12B, CXCL1, IL17A, IL17F</i>
Cyclins and Cell Cycle Regulation	3.540	0.002	0.005	3.000	<i>CCNB1, CCNE1, CDC25A</i>
Cell cycle: g2/m checkpoint	3.430	0.002	0.006	3.000	<i>CCNB1, CDC25A, PLK1</i>
Mitotic G2-G2/M phases	3.230	0.002	0.006	6.000	<i>CCNA2, CCNB1, CCNB2, CDC25A, NEK2, PLK1</i>
APC-Cdc20 mediated degradation of Nek2A	3.330	0.002	0.007	3.000	<i>BUB1B, CDC20, NEK2</i>
Glycosphingolipid biosynthesis - lacto and neolacto series	3.240	0.002	0.007	3.000	<i>FUT2, FUT3, FUT6</i>
Genes encoding enzymes and their regulators involved in the remodeling of the ECM	3.010	0.002	0.007	12.000	<i>A2ML1, CSTA, HPSE, HYAL4, PCSK6, PI3, SERPINB10, SERPINB13, SERPINB3, SERPINB4, TGM1, TLL2</i>
Amine compound SLC transporters	3.150	0.003	0.008	3.000	<i>RHCG, SLC6A11, SLC6A14</i>
Progesterone-mediated oocyte maturation	3.050	0.003	0.008	6.000	<i>BUB1, CCNA2, CCNB1, CCNB2, CDC25A, PLK1</i>
Linoleic acid metabolism	2.980	0.004	0.010	3.000	<i>AKR1B10, PLA2G4B, PLA2G4E</i>
G alpha (i) signaling events	2.840	0.004	0.010	10.000	<i>CCL20, CXCL1, CXCR1, CXCR2, CXCR6, GNAT1, GNAT2, HRH3, MTNR1B, RGS20</i>
P53 signaling pathway	2.890	0.004	0.010	5.000	<i>CCNB1, CCNB2, CCNE1, GTSE1, RRM2</i>
APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	2.890	0.004	0.010	5.000	<i>AURKA, AURKB, CDC20, PLK1, PTTG1</i>
Amino acid and oligopeptide SLC transporters	2.840	0.004	0.011	4.000	<i>SLC6A14, SLC7A1, SLC7A11, SLC7A5</i>
Activation of the pre-replicative complex	2.830	0.005	0.011	3.000	<i>CDC45, CDC6, MCM10</i>
ABC-family proteins mediated transport	2.630	0.006	0.016	3.000	<i>ABCA12, ABCC1, ABCG4</i>
Ion channel transport	2.600	0.007	0.016	4.000	<i>ATP10B, ATP12A, HTR3A, HTR3B</i>
G alpha i Pathway	2.560	0.007	0.017	3.000	<i>EPHB2, PI3, RGS20</i>
P73 transcription factor network	2.500	0.008	0.018	5.000	<i>BUB1, CCNA2, CCNB1, PLK1, S100A2</i>
Validated transcriptional targets of AP1 family members Fra1 and Fra2	2.440	0.009	0.019	3.000	<i>CCNA2, FOSL1, IVL</i>

(continued)

Supplementary Table S5. Continued

Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Glycosphingolipid metabolism	2.440	0.009	0.019	3.000	ARSF, GM2A, NEU2
Arachidonic acid metabolism	2.430	0.009	0.019	4.000	ALOX12B, GPX2, PLA2G4B, PLA2G4E
NOD-like receptor signaling pathway	2.280	0.012	0.025	4.000	GARD6, CCL7, CXCL1, PYDC1
Interferon gamma signaling	2.280	0.012	0.025	4.000	GBP6, OAS2, OAS3, OASL
Retinol metabolism	2.200	0.013	0.027	4.000	ADH7, RDH16, UGT1A10, UGT1A7
IFN- α/β signaling	2.200	0.013	0.027	4.000	IFI27, OAS2, OAS3, OASL
Cytokine-cytokine receptor interaction	2.170	0.015	0.030	11.000	CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6, IFNE, IL17A, IL20, TNFRSF21, TNFRSF9
MHC class II antigen presentation	2.140	0.015	0.030	5.000	KIF18A, KIF20A, KIF23, KIF2C, KIF4A
ABC transporters	2.080	0.016	0.030	3.000	ABCA12, ABCC1, ABCG4
APC/C:Cdc20 mediated degradation of mitotic proteins	2.030	0.018	0.034	4.000	BUB1B, CCNB1, CDC20, PTTG1
Metabolism of xenobiotics by cytochrome P450	2.000	0.019	0.035	4.000	ADH7, CYP2S1, UGT1A10, UGT1A7
Validated transcriptional targets of delta α 63 isoforms	1.950	0.020	0.036	3.000	CCNB2, GPX2, TOP2A
Drug metabolism - other enzymes	1.790	0.026	0.046	3.000	UGT1A10, UGT1A7, XDH
Heparan sulfate/heparin (HS-GAG) metabolism	1.750	0.028	0.049	3.000	B3GAT1, HPSE, HS3ST3A1
Validated targets of C-MYC transcriptional activation	1.730	0.030	0.053	4.000	BIRC5, CCNB1, CDC25A, FOSL1
S phase	1.740	0.031	0.053	5.000	CCNA2, CCNE1, CDC25A, CDC45, CDC6
Validated transcriptional targets of tap63 isoforms	1.680	0.031	0.053	3.000	GPX2, PLK1, S100A2
Glycosaminoglycan metabolism	1.700	0.034	0.056	5.000	B3GAT1, HAS3, HMMR, HPSE, HS3ST3A1
Transmembrane transport of small molecules	1.700	0.038	0.063	14.000	ABCA12, ABCC1, ABCG4, ATP10B, ATP12A, HTR3A, HTR3B, RHCG, SLC5A1, SLC6A11, SLC6A14, SLC7A1, SLC7A11, SLC7A5
Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds	1.470	0.047	0.076	4.000	RHCG, SLC5A1, SLC6A11, SLC6A14
Cyclin E associated events during G1/S transition	1.380	0.050	0.080	3.000	CCNA2, CCNE1, CDC25A
Transport of inorganic cations/anions and amino acids/oligopeptides	1.380	0.055	0.085	4.000	SLC6A14, SLC7A1, SLC7A11, SLC7A5
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	1.320	0.055	0.085	3.000	RAET1E, ULBP1, ULBP2
Recruitment of mitotic centrosome proteins and complexes	1.320	0.055	0.085	3.000	CCNB1, NEK2, PLK1
IFN signaling	1.370	0.061	0.091	6.000	GBP6, IFI27, KPNA2, OAS2, OAS3, OASL
Sphingolipid metabolism	1.270	0.061	0.091	3.000	ARSF, GM2A, NEU2
Epithelial cell signaling in <i>Helicobacter pylori</i> infection	1.240	0.063	0.093	3.000	CXCL1, CXCR1, CXCR2

Supplementary Table S5. Continued
Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Potassium channels	1.270	0.066	0.095	4.000	KCNG3, KCNJ15, KCNK10, KCNK6
Phase 1 - functionalization of compounds	1.210	0.066	0.095	3.000	ADH7, CYP24A1, CYP2S1
Factors involved in megakaryocyte development and platelet production	1.280	0.068	0.097	5.000	KIF18A, KIF20A, KIF23, KIF2C, KIF4A
Drug metabolism - cytochrome P450	1.130	0.075	0.100	3.000	ADH7, UGT1A10, UGT1A7
Metabolism of nucleotides	1.130	0.075	0.100	3.000	GDA, RRM2, XDH
Natural killer cell mediated cytotoxicity	1.150	0.083	0.110	5.000	RAET1E, RAET1G, RAET1L, ULBP1, ULBP2
M/g1 transition	0.940	0.100	0.140	3.000	CDC45, CDC6, MCM10
Peptide ligand-binding receptors	0.964	0.120	0.160	6.000	CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6
Class A/1 (Rhodopsin-like receptors)	0.954	0.130	0.170	9.000	CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6, HRH3, MTNR1B, P2RY1
Chemokine signaling pathway	0.896	0.130	0.170	6.000	CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6
Synthesis of DNA	0.707	0.140	0.180	3.000	CCNA2, CDC45, CDC6
SLC-mediated transmembrane transport	0.752	0.160	0.210	7.000	RHCG, SLC5A1, SLC6A11, SLC6A14, SLC7A1, SLC7A11, SLC7A5
Fc g R-mediated phagocytosis	0.611	0.160	0.210	3.000	PLA2G4B, PLA2G4D, PLA2G4E
GPCR ligand binding	0.749	0.180	0.220	11.000	ADM2, CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6, HRH3, MTNR1B, P2RY1, WNT5A
Genes encoding proteins affiliated structurally or functionally to ECM proteins	0.639	0.180	0.220	5.000	CLEC3A, CLEC7A, LGALS9B, LGALS9C, LMAN1L
Biological oxidations	0.568	0.190	0.230	4.000	ADH7, CYP24A1, CYP2S1, UGT1A7
Vascular smooth muscle contraction	0.291	0.250	0.300	3.000	MYLK2, PLA2G4B, PLA2G4E
Phospholipid metabolism	0.338	0.260	0.310	5.000	ARSF, GM2A, NEU2, PLA2G4D, PLBD1
Neuronal system	0.372	0.270	0.320	7.000	CHRNA5, CHRNA9, KCNG3, KCNJ15, KCNK10, KCNK6, SLC6A11
Purine metabolism	0.263	0.280	0.320	4.000	GDA, POLR3G, RRM2, XDH
Metabolism of carbohydrates	0.307	0.280	0.330	6.000	B3GAT1, HAS3, HMMR, HPSE, HS3ST3A1, SLC5A1
Neurotransmitter receptor binding and downstream transmission in the postsynaptic cell	0.008	0.350	0.400	3.000	CHRNA5, CHRNA9, KCNJ15
Cytokine signaling in immune system	0.030	0.380	0.430	6.000	GBP6, IFI27, KPNA2, OAS2, OAS3, OASL
Transmission across chemical synapses	-0.036	0.390	0.430	4.000	CHRNA5, CHRNA9, KCNJ15, SLC6A11
Metabolism of amino acids and derivatives	-0.175	0.440	0.490	4.000	AASS, ARG1, HAL, KYNU
Hemostasis	-0.369	0.560	0.620	9.000	KIF18A, KIF20A, KIF23, KIF2C, KIF4A, LRP8, P2RY1, SLC7A11, SLC7A5
Neuroactive ligand-receptor interaction	-0.426	0.560	0.620	5.000	CHRNA5, CHRNA9, HRH3, MTNR1B, P2RY1
Immune system	-0.517	0.650	0.700	18.000	CDC20, DEFB4A, GBP6, IFI27, KIF18A, KIF20A, KIF23, KIF2C, KIF4A, KPNA2, NLRX1, OAS2, OAS3, OASL, RAET1E, S100A12, ULBP1, ULBP2
Adaptive immune system	-0.794	0.730	0.790	9.000	CDC20, KIF18A, KIF20A, KIF23, KIF2C, KIF4A, RAET1E, ULBP1, ULBP2
Axon guidance	-1.050	0.790	0.840	3.000	CDK5R1, KIF4A, SCN2A

(continued)

Supplementary Table S5. Continued

Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Metabolism of lipids and lipoproteins	-1.110	0.830	0.870	7.000	ARSF, CYP24A1, GM2A, NEU2, PLA2G4D, PLBD1, TNFRSF21
Innate immune system	-1.260	0.860	0.900	3.000	DEFB4A, NLRX1, S100A12
Developmental biology	-1.260	0.870	0.900	5.000	CDK5R1, HNF1B, KIF4A, PCSK6, SCN2A
GPCR downstream signaling	-1.410	0.910	0.930	12.000	ADM2, CCL20, CXCL1, CXCR1, CXCR2, CXCR6, GNAT1, GNAT2, HRH3, MTNR1B, P2RY1, RGS20
Signaling by GPCR	-1.440	0.910	0.930	14.000	ADM2, CCL20, CCL7, CXCL1, CXCR1, CXCR2, CXCR6, GNAT1, GNAT2, HRH3, MTNR1B, P2RY1, RGS20, WNT5A
Pathways in cancer	-1.610	0.930	0.940	3.000	BIRC5, CCNE1, WNT5A
Metabolism of proteins	-2.500	1.000	1.000	3.000	ARSF, GCNT4, TUBA1C
Gene Ontology by cellular components					
Cornified envelope	16.200	<0.001	<0.001	19.000	CNFN, CSTA, HRNR, IVL, LCE3A, LCE3C, LCE3D, LCE3E, PI3, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR2G, SPRR3, TGM1
Kinetochores	7.550	<0.001	<0.001	11.000	AURKB, BUB1, BUB1B, CENPF, KIF18A, KIF2C, NEK2, PLK1, SKA3, TTK, ZWINT
Condensed chromosome outer kinetochores	9.980	<0.001	<0.001	4.000	BUB1B, CENPF, SKA1, SKA3
Spindle microtubule	7.870	<0.001	<0.001	7.000	AURKA, AURKB, BIRC5, KIF4A, PLK1, SKA1, SKA3
Midbody	6.580	<0.001	<0.001	14.000	ANLN, ASPM, AURKA, AURKB, BIRC5, CENPF, CEP55, KIF14, KIF20A, KIF23, KIF4A, NEK2, PLK1, SHCBP1
Spindle	6.580	<0.001	<0.001	12.000	AURKA, AURKB, BUB1B, CDC20, CENPF, KBTBD8, KIF20A, KIF23, PLK1, SHCBP1, TPX2, TTK
Kinesin complex	7.150	<0.001	<0.001	8.000	KIF14, KIF18A, KIF18B, KIF20A, KIF23, KIF24, KIF2C, KIF4A
Chromosome passenger complex	9.530	<0.001	<0.001	3.000	AURKA, AURKB, BIRC5
Extracellular region	4.900	<0.001	<0.001	63.000	ADH7, ADM2, AKR1B10, ARG1, B3GAT1, C10orf99, CCL20, CHI3L2, CXCL1, DEFB4A, ENDOU, EPHB2, EREG, FABP5, FETUB, FGF2, GM2A, HPSE, HRNR, IGLON5, IL17A, IL17C, IL17F, IL20, IL36A, IL36G, IL36RN, KLK10, KLK13, KLK8, KLK9, LCN2, LRG1, LRP8, PCSK6, PCSK9, PGLYRP2, PGLYRP3, PI3, PLA2G4B, PRSS22, PRSS27, RAET1E, RAET1G, RAET1L, S100A12, S100A7, S100A8, S100A9, SAA4, SERPINB3, SUS4, TCN1, TEX101, TLL2, TMPS11A, TMPS11D, ULBP2, VNN1, VNN3, VWA3A, WFDC12, WNT5A
Condensin complex	7.950	<0.001	<0.001	3.000	NCAPG, NCAPH, SMC4
Spindle midzone	6.650	<0.001	<0.001	5.000	AURKA, AURKB, CDC6, KIF14, PLK1
Spindle pole	5.260	<0.001	<0.001	10.000	AUNIP, CCNB1, CDC20, CDC6, CENPF, CKAP2L, FAM110C, NEK2, PLK1, TPX2
Anchored component of plasma membrane	5.940	<0.001	<0.001	5.000	PRSS22, PRSS27, TEX101, ULBP1, ULBP2
Condensed chromosome kinetochores	4.920	<0.001	<0.001	8.000	BIRC5, BUB1, BUB1B, ERCC6L, HJURP, KIF2C, NEK2, ZWINT
Mitotic spindle midzone	5.610	<0.001	<0.001	3.000	AURKB, KIF18A, KIF18B
Spindle pole centrosome	5.360	<0.001	0.001	3.000	AURKA, AURKB, DLGAP5
Centrosome	4.080	<0.001	0.001	21.000	ASPM, AUNIP, AURKA, CAMK2N2, CCNB1, CCNB2, CCNE1, CDC20, CDC45, CDKL5, CENPF, CEP55, CKAP2L, ESPL1, HMMR, IVL, KIF23, KIF2C, NEK2, PLK1, STIL
Specific granule lumen	4.510	<0.001	0.001	6.000	ARG1, CXCL1, HPSE, LCN2, LRG1, TCN1
Cyclin-dependent protein kinase holoenzyme complex	4.710	<0.001	0.001	4.000	CCNA2, CCNB1, CCNB2, CCNE1

Supplementary Table S5. Continued

Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Extracellular space	3.610	<0.001	0.001	53.000	A2ML1, ACPP, ARG1, C10orf99, CCL20, CCL7, CHI3L2, CLEC3A, CSTA, CXCL1, DEFB4A, ENDOU, EREG, FGFBP1, IFNE, IGFL1, IL17A, IL17C, IL17F, IL20, IL36A, IL36G, IL36RN, INA, KLK13, KLK8, LCN2, LRG1, OAS3, PCSK6, PCSK9, PGLYRP2, PGLYRP3, PGLYRP4, PLBD1, RAET1E, RAET1G, RAET1L, S100A7, S100A8, S100A9, SAA2, SAA4, SEMG2, SERPINB10, SERPINB13, SERPINB3, SERPINB4, TCN1, ULBP1, ULBP2, WNT5A, XDH
Microtubule cytoskeleton	3.780	<0.001	0.002	9.000	AURKA, CCNB2, HMMR, KIF18A, KIF2C, PLK1, SKA1, TPX2, TUBA1C
Intercellular bridge	3.720	0.001	0.003	5.000	CEP55, KIF20A, KIF23, KIF4A, TPX2
Extrinsic component of plasma membrane	3.520	0.002	0.006	3.000	NLRP10, PRSS22, PRSS27
Condensed chromosome	3.520	0.002	0.006	3.000	MKI67, NCAPG, TOP2A
Azurophil granule lumen	3.300	0.002	0.006	6.000	ARG1, FABP5, GM2A, HRNR, S100A7, SERPINB3
Flemming body	3.430	0.002	0.006	3.000	CEP55, KIF14, KIF23
Microtubule	3.030	0.002	0.008	13.000	CDK5R1, FAM110C, KIF14, KIF18A, KIF18B, KIF20A, KIF23, KIF24, KIF2C, KIF4A, NEK2, TPX2, TUBA1C
Chromosome, centromeric region	2.930	0.004	0.012	4.000	BIRC5, CENPF, HJURP, KIF2C
Secretory granule	2.670	0.006	0.017	5.000	KLK10, KLK13, KLK8, KLK9, TMPRSS4
Integral component of presynaptic membrane	2.680	0.006	0.017	4.000	EPHB2, HTR3A, SCN2A, SLC6A11
Secretory granule membrane	2.360	0.010	0.027	5.000	CD177, CXCR1, CXCR2, FABP5, SERPINB10
Mitotic spindle	2.350	0.010	0.027	4.000	CKAP2L, ESPL1, KIF23, TPX2
Integral component of postsynaptic membrane	2.350	0.010	0.027	3.000	EPHB2, HTR3A, SLC6A11
Microtubule organizing center	2.350	0.011	0.027	7.000	BUB1B, CEP55, DLGAP5, FAM110C, KIF18A, TCTEX1D4, TPX2
Anchored component of membrane	2.260	0.012	0.031	5.000	CD177, RAET1G, RAET1L, VNN1, VNN3
Centriole	2.180	0.014	0.035	6.000	AURKA, CEP55, KIF24, PLK1, STIL, TOP2A
Cleavage furrow	1.940	0.020	0.047	3.000	CEP55, HTR3A, KIF20A
Tertiary granule lumen	1.940	0.020	0.047	3.000	CXCL1, LRG1, TCN1
Photoreceptor outer segment	1.870	0.023	0.051	3.000	CNGB1, GNAT1, GNAT2
Voltage-gated potassium channel complex	1.860	0.025	0.054	4.000	CNTNAP2, KCNG3, KCNK6, LRRC55
Rough endoplasmic reticulum	1.800	0.025	0.055	3.000	PCSK9, SLC7A11, ZC3H12A
Axoneme	1.730	0.030	0.064	4.000	CCDC63, CENPF, TCTEX1D4, WDR66
Apical plasma membrane	1.360	0.067	0.140	9.000	ASPM, GJB6, GM2A, GNAT1, P2RY1, RHCG, SLC22A13, SLC5A1, SLC7A5
Basolateral plasma membrane	1.270	0.072	0.140	6.000	ABCC1, ATP12A, GM2A, NDRG4, P2RY1, RHCG
Postsynapse	1.130	0.075	0.150	3.000	EPHB2, INA, WNT5A
Neuron projection	1.260	0.079	0.150	9.000	ARG1, CDK5R1, CHRNA5, CHRNA9, EPHB2, FOSL1, HTR3A, HTR3B, SLC6A11
Intracellular membrane-bounded organelle	1.290	0.080	0.150	17.000	AASS, ABCA12, B3GAT1, CDK5R1, CLEC7A, CYP2S1, GPR1, HPSE, LRG1, NEU2, OAS2, OAS3, RDH16, SAMD9, SLC7A5, UGT1A10, UGT1A7
Integral component of plasma membrane	1.250	0.091	0.160	32.000	ABCC1, CHRNA5, CHRNA9, CXCR2, CXCR6, EPHB2, EREG, GPR1, GPR15, HAS3, HRH3, HTR3A, HTR3B, KCNJ15, KCNK10, KCNK6, LRRC55, MFSD2B, MTNR1B, NPR3, P2RY1, RHCG, SCN2A, SLC16A6, SLC22A13, SLC5A1, SLC7A1, TMPRSS11A, TMPRSS11D, TNFRSF21, TNFRSF9, TPBG

(continued)

Supplementary Table S5. Continued
Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Perinuclear region of cytoplasm	1.210	0.092	0.160	17.000	AURKA, BUB1B, CDC20, CDK5R1, CDKL5, CDKN3, CENPF, GDPD3, GJB2, HRNR, OAS2, OFCC1, PCSK9, SERINC5, SPRR3, SYT5, ZDHHC20
Golgi cisterna membrane	0.985	0.094	0.160	3.000	FUT2, FUT3, FUT6
Axon	1.120	0.096	0.160	8.000	CDK5R1, CNTNAP2, EPHB2, HTR3A, LRP8, SCN2A, SYT5, TNFRSF21
Cell surface	1.170	0.097	0.160	15.000	CDH26, CNTNAP2, CXCR2, FGFBP1, HMMR, HTR3B, HYAL4, P2RY1, PCSK6, PCSK9, SLC7A11, TPBG, TREML1, ULBP2, WNT5A
Lysosomal lumen	0.965	0.097	0.160	3.000	GM2A, HPSE, SERPINB13
Golgi lumen	0.779	0.130	0.210	3.000	DEFB4A, PCSK6, WNT5A
External side of plasma membrane	0.897	0.140	0.220	9.000	CXCR1, CXCR2, CXCR6, RAET1E, RAET1G, RAET1L, TNFRSF9, ULBP1, ULBP2
Nuclear matrix	0.676	0.150	0.230	3.000	CENPF, KIF4A, UHRF1
Nuclear body	0.761	0.160	0.250	7.000	EXO1, IVL, KIF18B, MCIDAS, MKI67, ZIC2, ZWINT
Chromatin	0.580	0.170	0.260	3.000	CENPF, ESCO2, PLK1
Secretory granule lumen	0.564	0.170	0.260	3.000	S100A12, S100A8, S100A9
Mitochondrial outer membrane	0.553	0.190	0.280	4.000	ARG1, CYP24A1, IFI27, NLRX1
Chromosome	0.489	0.190	0.280	3.000	CDA2, ESCO2, KIF4A
Membrane	0.728	0.210	0.290	42.000	ABCC1, BUB1, CCNB1, CCNB2, CDK5R1, CEP55, CNTNAP2, CXCR2, EN2, ERCC6L, FUT3, GLTP, GNAT1, GTSE1, HMMR, KIF14, KIF2C, KIF4A, KPNA2, LRG1, LRP8, MCTP2, MELK, MKI67, NCAPG, NCAPH, NEU2, OAS2, OASL, PCSK6, PGLYRP2, PGLYRP3, PGLYRP4, PLA2G4D, PRR11, RGS20, SLC16A6, SLC7A1, SLC7A5, TMEM86A, TTK, ZDHHC20
Neuronal cell body	0.423	0.260	0.360	8.000	ARG1, CDK5R1, CNTNAP2, EPHB2, GNAT1, HTR3A, LRP8, SYT5
Vesicle	0.205	0.280	0.380	3.000	SERPINB3, SLC6A14, TUBA1C
Collagen-containing ECM	0.314	0.290	0.390	7.000	HRNR, LMAN1L, PCSK6, S100A7, S100A8, S100A9, WNT5A
Postsynaptic membrane	0.142	0.320	0.420	4.000	CHRNA5, FABP5, HTR3B, P2RY1
Glutamatergic synapse	0.186	0.330	0.430	7.000	CDKL5, EPHB2, HTR3A, KPNA2, P2RY1, SCN2A, WNT5A
Synapse	0.035	0.370	0.470	5.000	CHRNA5, CHRNA9, FABP5, HTR3A, HTR3B
Trans-Golgi network	-0.039	0.370	0.470	3.000	CHAC1, MICALL1, RGS20
Lysosome	-0.286	0.490	0.610	4.000	AKR1B10, HPSE, PCSK9, PLBD1
Postsynaptic density	-0.294	0.490	0.610	4.000	CDK5R1, FABP5, LRP8, P2RY1
Dendrite	-0.261	0.510	0.620	7.000	CDK5R1, CNTNAP2, EPHB2, HRH3, LRP8, P2RY1, ZWINT
Transcription factor complex	-0.393	0.520	0.630	3.000	ARNTL2, HNF1B, PITX1
Cytoskeleton	-0.327	0.530	0.630	6.000	MPZL2, S100A12, S100A8, S100A9, SLC7A11, ZC3H12A
Cell junction	-0.354	0.560	0.650	9.000	CHRNA5, CHRNA9, ESCO2, FABP5, GJB6, HTR3A, NLRX1, S100A9, SYT5
Protein-containing complex	-0.406	0.580	0.670	10.000	FOXP3, KIF24, NEK2, NPR3, PGLYRP3, PGLYRP4, RAD54L, SLC7A1, TOP2A, ZC3H12A
Lysosomal membrane	-0.620	0.630	0.720	4.000	ACPP, HPSE, PCSK9, PLA2G4E
Nuclear chromatin	-0.661	0.640	0.720	3.000	MXD1, POLR3G, UHRF1
Endoplasmic reticulum	-0.542	0.650	0.730	16.000	ATP10B, CRABP2, CYP2S1, DUOXA2, KCNG3, PCSK6, PCSK9, RAET1G, RAET1L, S100A7, TPBG, UGT1A10, UGT1A7, ULBP1, ULBP2, ZDHHC20
Early endosome	-0.804	0.700	0.770	3.000	CNTNAP2, MICALL1, PCSK9
Golgi membrane	-0.758	0.720	0.780	9.000	B3GAT1, B4GALNT2, CNGB1, FUT3, GCNT4, HS3ST3A1, LMAN1L, RAB1C, ST6GALNAC1

Supplementary Table S5. Continued
 Canonical/KEGG/Reactome/BioCarta Pathways

Term Name	Z-Score	P-Value	FDR	Number of Genes Overlapped	Genes
Cellular_component	-0.914	0.760	0.820	6.000	<i>CDRT1, CHAC2, MAP3K9, S100A2, TTC39A, VNN3</i>
Endoplasmic reticulum lumen	-1.150	0.820	0.870	3.000	<i>ARSF, PCSK9, WNT5A</i>
Endoplasmic reticulum membrane	-1.100	0.830	0.870	13.000	<i>ATP10B, B3GAT1, CYP2S1, DUOXA1, DUOXA2, GDPD3, IFI27, LMAN1L, NDRG4, RDH16, SLC37A2, UGT1A10, UGT1A7</i>
Golgi apparatus	-1.500	0.920	0.950	12.000	<i>CLSPN, CNTNAP2, EHF, ESCO2, FUT2, FUT6, KBTBD8, KIF20A, PCSK9, SERINC5, SPRR3, ZDHHC20</i>
Nuclear speck	-1.680	0.940	0.960	3.000	<i>E2F7, SERPINB13, SMC4</i>
Nucleolus	-1.710	0.950	0.960	17.000	<i>ARNTL2, CDC6, E2F8, EMX1, EN2, ETV4, HJURP, MCIDAS, MCM10, MKI67, NEK2, OASL, PITX1, SDR9C7, SERPINB13, SNORD101, TOP2A</i>
Mitochondrion	-2.210	0.990	0.990	13.000	<i>AASS, AKR1B10, CASP14, CYP24A1, DLGAP5, HJURP, IFI27, KYNU, MXD1, NDRG4, NLRX1, P2RY1, PIF1</i>

Abbreviations: ECM, extracellular matrix; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes; MHC major histocompatibility complex.

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Transcriptomic Analysis of the Major Ichthyosis Subtypes

Supplementary Table S6. RT-PCR Primers

RT-PCR Primers

18S-Hs99999901_s1
CAMP-Hs00189038_m1
CCL17-Hs00171074_m1
CCL18-Hs00268113_m1
CCL20-Hs01011368_m1
CCL22-Hs01574247_m1
CCL26-Hs00171146_m1
CXCL1-Hs00236937_m1
CXCL10-Hs00171042_m1
CXCL8-Hs00174103_m1
DEFB4B_DEFEB4A-Hs00823638_m1
EREG-Hs00914313_m1
FLG-Hs00856927_g1
IFNG-Hs00989291_m1
IL12B-Hs01011518_m1
IL13-Hs00174379_m1
IL15-Hs01003716_m1
IL17A-Hs00174383_m1
IL17C-Hs00171163_m1
IL17F-Hs01028648_m1
IL19-Hs00604657_m1
IL1B-Hs01555410_m1
IL1RN-Hs00893626_m1
IL2-Hs00174114_m1
IL20-Hs00218888_m1
IL22-Hs01574154_m1
IL23A-Hs00372324_m1
IL23R-Hs00332759_m1
IL31-Hs01098710_m1
IL36A-Hs00205367_m1
IL36B-Hs00758166_m1
IL36G-Hs00219742_m1
IL36RN-Hs01104220_g1
KLK13-Hs01087305_g1
KYNU-Hs01114105_m1
LCN2-Hs01008571_m1
LOR-Hs01894962_s1
MMP12-Hs00899662_m1
MX1-Hs00895608_m1
PI3-Hs00160066_m1
PPL-Hs01011417_m1
RPLP0-Hs99999902_m1
S100A12-Hs00942835_g1
S100A7-Hs01923188_u1
S100A9-Hs00610058_m1
VNN1-Hs01546812_m1
VNN3-Hs01125168_m1
