

Supplementary Tables and Figures

Manuscript Title:

GENE EXPRESSION PROFILING OF PERINEURAL INVASION IN HEAD AND NECK CUTANEOUS SQUAMOUS CELL CARCINOMA.

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Supplementary Table 1. PNI cohort categories and nerve proportions. Green highlighted EXT specimens grouped with major focal/non-PNI cohort using fold change ± 2 stratification (refer to Figure 3).

PNI ID	% Nerve proportion*	Age, sex, primary site and additional comments
NONPNI-1	-	63yo male, scalp. Large nodal mets. CLL
NONPNI-2	-	66yo male. Scalp. Large nodal mets.
NONPNI-3	-	83yo male. Scalp. Marked inflammatory changes and desmoplasia.
NONPNI-4	-	76yo male. Ear.
NONPNI-5	-	73yo male. Preauricular.
NONPNI-6	-	73yo male. Ear
NONPNI-7	-	74yo male. Ear.
NONPNI-8	-	53yo female. Scalp.
NONPNI-9	-	59yo male. Preauricular.
FOCAL-1	1%	74yo male. Ear.
FOCAL-2	0%	92yo female. Forehead/scalp.
FOCAL-3	0.50%	65yo male. Upper lip.
FOCAL-4	0.5-1%	62yo male. Postauricular. Nodal mets.
FOCAL-5	0.5-1%	77yo male. Ear. Nodal mets.
FOCAL-6	<1%	58yo male. Neck.
FOCAL-7	<1%	65yo male. Cheek. Nodal mets.
FOCAL-8	<1%	47yo male. Cheek/parotid.
FOCAL-9	<1%	38yo male. Lip.
FOCAL-10	1%	83yo male. Preauricular.
FOCAL-11	<1%	62yo male. Temporoparietal.
EXT-1	20-30%	66 female. Nose.
EXT-2	30%	73yo female. Cheek.
EXT-3	50-60%	43 male. Preauricular.

EXT-4	20-30%	63yo male. Forehead.
EXT-5	40-50%	67yo male. Cheek.
EXT-6	1%	69yo male. Ear.
EXT-7	5%	71yo male. Cheek.
EXT-8	1%	74yo male. Forehead.
EXT-9	1-5%	82yo male. Scalp.
EXT-10	1-5%	84yo male. Postauricular.
EXT-11	1%	88yo male. Forehead.
EXT-12	1%	54yo male. Scalp.
EXT-13	1-5%	89 female. Forehead.
EXT-14	1-5%	72yo male. Ear.
EXT-15	1%	82yo male. Scalp.
EXT-16	1%	59yo male. Temporal.
EXT-17	80%	63yo male. Cheek.
EXT-18	1%	84yo male. Parotid/Cheek.
EXT-19	1%	38yo male. Lip.
EXT20	30 - 40%	68yo male. Cheek.
EXT21	1 - 2%	88yo male. Forehead.
EXT22	2 -5%	55yo male. Preauricular.
EXT23	1%	78yo male. Nose.
EXT24	20 - 30%	86yo female. Preauricular.
EXT25	60 - 70%	58yo male. Cheek.

* Nerve proportion defined as the percentage of nerve tissue contained in the cored slide undergoing expression analysis.

Supplementary Table 2. List of 144 significantly DEG between extensive (EXT) PNI versus combined focal and non PNI (FOC_NON) based on adjusted P-values <0.01, ranked by increasing P-values. Grey highlighted genes are downregulated in EXT PNI with fold change < -2. Bolded genes are DEG with fold change >3 or < -3 (n = 70). LogFC = log2 fold change. CI.L/R = confidence intervals left/right.

	HUGO	Average_EXT	Average_FOC_NON	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
1	PTGIS	8.176542	3.911408	4.265134	3.057936	5.472331	6.280926	7.109034	5.81E-09	4.3E-06	10.41069
2	THBS4	9.00886	4.012144	4.996716	3.534998	6.458434	6.788097	6.878239	1.3E-08	4.79E-06	9.646227
3	SRGN	12.18703	10.15644	2.030587	1.403969	2.657205	11.28455	6.520409	4.51E-08	1.11E-05	8.458462
4	FERMT2	8.993999	7.276204	1.717795	1.150489	2.285101	8.230535	6.092708	2E-07	2.99E-05	7.039322
5	NR4A3	8.541688	5.711376	2.830313	1.895107	3.765518	7.283772	6.089529	2.02E-07	2.99E-05	7.028792
6	TIMP1	11.85543	9.6565	2.198932	1.45043	2.947434	10.87813	5.911193	3.76E-07	4.63E-05	6.438852
7	SAMSN1	8.602073	7.071685	1.530389	1.002459	2.058318	7.921901	5.832864	4.93E-07	5.21E-05	6.180302
8	HGF	6.548982	3.692766	2.856216	1.836671	3.875761	5.279552	5.636905	9.7E-07	8.97E-05	5.535427
9	VCAN	10.04003	8.191016	1.849012	1.172124	2.5259	9.218245	5.496411	1.57E-06	0.000122	5.075177
10	C3	10.04841	6.81079	3.237621	2.049321	4.425922	8.609468	5.482214	1.65E-06	0.000122	5.028781
11	IGFBP7	13.07847	11.3441	1.734371	1.094327	2.374415	12.30764	5.45241	1.83E-06	0.000123	4.931453
12	AKAP12	8.538593	5.737349	2.801244	1.733657	3.868831	7.293595	5.279635	3.31E-06	0.000204	4.36935
13	MS4A4A	9.520656	8.025336	1.49532	0.921147	2.069492	8.85607	5.240199	3.78E-06	0.000207	4.241595
14	LHFP	8.942235	7.475332	1.466903	0.902555	2.031252	8.290278	5.230104	3.91E-06	0.000207	4.208929
15	CDH2	5.481306	2.811874	2.669432	1.63051	3.708353	4.294892	5.170022	4.8E-06	0.000224	4.014806
16	SLIT2	6.829539	4.184884	2.644655	1.614805	3.674506	5.654137	5.167152	4.85E-06	0.000224	4.005547
17	FAP	9.81836	7.676393	2.141967	1.300917	2.983016	8.866375	5.124452	5.61E-06	0.000244	3.867939
18	ITGA5	10.2619	9.106893	1.155003	0.698652	1.611353	9.748561	5.092611	6.24E-06	0.00025	3.765509
19	CDH11	10.7942	9.018946	1.775257	1.072582	2.477933	10.0052	5.083499	6.44E-06	0.00025	3.736229
20	HLA.DPB1	12.20502	10.81758	1.387442	0.836685	1.938198	11.58838	5.068873	6.77E-06	0.00025	3.689256
21	FGFR3	8.094096	10.70626	-2.61217	-3.65298	-1.57135	9.255059	-5.04989	7.21E-06	0.000254	3.628351
22	SERPING1	11.61714	10.11045	1.506696	0.902587	2.110805	10.9475	5.018415	8.02E-06	0.00027	3.527479
23	APOD	10.46412	6.511564	3.952558	2.353878	5.551238	8.70743	4.97477	9.3E-06	0.00029	3.387904
24	FGF18	4.890604	2.313239	2.577365	1.534264	3.620466	3.745109	4.971712	9.39E-06	0.00029	3.378137
25	PLXND1	9.777288	8.725009	1.052279	0.624724	1.479834	9.309608	4.952166	1E-05	0.000297	3.315751

26	MPDZ	8.066133	6.332897	1.733236	1.023495	2.442977	7.295806	4.91376	1.14E-05	0.000325	3.193372
27	JAM3	8.947986	7.407351	1.540635	0.90642	2.17485	8.26326	4.887868	1.25E-05	0.000333	3.111027
28	ZFPM2	4.633681	2.242943	2.390738	1.405794	3.375683	3.571131	4.88401	1.26E-05	0.000333	3.098769
29	SULF1	10.64963	8.627711	2.021922	1.18476	2.859083	9.751001	4.859721	1.37E-05	0.000349	3.021657
30	DDR2	8.769871	6.950236	1.819636	1.06441	2.574862	7.961144	4.848013	1.42E-05	0.000351	2.984529
31	SFRP2	11.90511	9.631576	2.273538	1.326233	3.220843	10.89465	4.829126	1.52E-05	0.000362	2.924691
32	SERPINF1	11.65157	10.09272	1.55885	0.900421	2.217279	10.95875	4.76378	1.89E-05	0.000436	2.718227
33	TBXA2R	4.736541	2.327017	2.409525	1.387441	3.431608	3.665642	4.743525	2.02E-05	0.000452	2.654413
34	MGP	10.93773	8.228106	2.709628	1.551047	3.86821	9.733455	4.705865	2.29E-05	0.000497	2.536001
35	CYP1B1	7.29957	4.774274	2.525296	1.434826	3.615765	6.177216	4.659667	2.66E-05	0.000563	2.391176
36	LY96	8.985937	7.821156	1.164781	0.657489	1.672073	8.468257	4.620008	3.04E-05	0.000624	2.267237
37	FGFR1	9.116971	7.730922	1.38605	0.778541	1.993558	8.500949	4.59074	3.34E-05	0.000669	2.17601
38	FGL2	8.677779	7.238421	1.439358	0.804511	2.074206	8.038064	4.562007	3.68E-05	0.000713	2.086652
39	FN1	13.04137	11.01434	2.027021	1.130222	2.923819	12.14047	4.54799	3.85E-05	0.000713	2.043132
40	ICAM1	9.93147	8.502919	1.42855	0.796501	2.0606	9.296559	4.547792	3.85E-05	0.000713	2.042515
41	NR4A1	9.925446	7.351176	2.57427	1.428029	3.720512	8.781326	4.518917	4.24E-05	0.000764	1.953023
42	NDNF	5.978693	3.15764	2.821053	1.557249	4.084856	4.724891	4.491464	4.63E-05	0.000817	1.868131
43	PLXNC1	9.103322	7.994631	1.108691	0.610895	1.606487	8.610571	4.48142	4.79E-05	0.000824	1.837122
44	SPARCL1	10.72327	8.756495	1.966778	1.080653	2.852904	9.84915	4.465976	5.04E-05	0.000847	1.78949
45	BNC2	5.981212	3.900942	2.080271	1.136124	3.024417	5.056647	4.433399	5.6E-05	0.000921	1.689225
46	FOXC2	6.089285	3.786533	2.302752	1.25531	3.350195	5.065839	4.423574	5.78E-05	0.000931	1.65904
47	PTX3	5.655791	2.897084	2.758707	1.500468	4.016947	4.429699	4.411625	6.01E-05	0.000947	1.622365
48	ITGB2	9.390146	8.12456	1.265586	0.682801	1.84837	8.827663	4.369582	6.89E-05	0.001043	1.493638
49	FBLN1	11.6077	9.763386	1.844315	0.994191	2.694439	10.788	4.365249	6.99E-05	0.001043	1.480399
50	OLFML2B	9.640894	8.409339	1.231555	0.663367	1.799743	9.093536	4.361322	7.08E-05	0.001043	1.468406
51	PECAM1	9.79908	8.52566	1.27342	0.685301	1.861539	9.233115	4.35675	7.19E-05	0.001043	1.454447
52	AKAP2	9.879174	8.64341	1.235764	0.663769	1.807758	9.329946	4.347104	7.42E-05	0.001055	1.425015
53	VEZF1	8.660196	7.79851	0.861687	0.460969	1.262404	8.277224	4.326805	7.92E-05	0.001106	1.363167
54	PXDN	9.676528	8.470313	1.206214	0.644464	1.767964	9.140432	4.320536	8.08E-05	0.001107	1.344091

55	OGN	8.456998	5.104503	3.352495	1.777635	4.927354	6.967	4.28334	9.11E-05	0.001226	1.231138
56	<i>WIPF1</i>	9.732064	8.7522	0.979864	0.51705	1.442678	9.296569	4.260058	9.82E-05	0.001276	1.160641
57	SLC2A1	8.811934	10.97299	-2.16105	-3.18183	-1.14028	9.772403	-4.25981	9.83E-05	0.001276	1.15989
58	<i>ZCCHC24</i>	8.871509	7.596307	1.275202	0.669988	1.880416	8.304752	4.239615	0.000105	0.001337	1.098876
59	<i>CDS1</i>	7.299836	8.845294	-1.54546	-2.27983	-0.81108	7.986706	-4.23443	0.000107	0.001337	1.08324
60	CAMK2A	4.153675	1.952525	2.20115	1.152569	3.24973	3.175386	4.223807	0.00011	0.001361	1.051203
61	<i>ENPP2</i>	8.705625	7.225327	1.480298	0.772597	2.187999	8.047715	4.208774	0.000116	0.001405	1.005936
62	<i>C3AR1</i>	8.185371	7.042688	1.142684	0.593793	1.691574	7.677512	4.188868	0.000123	0.001464	0.946101
63	ABI3BP	9.911305	7.843304	2.068002	1.073863	3.062141	8.992194	4.185623	0.000125	0.001464	0.936361
64	<i>LUM</i>	13.37394	12.04099	1.332957	0.689899	1.976016	12.78152	4.170825	0.000131	0.001501	0.891974
65	<i>DCN</i>	12.50047	11.01845	1.482021	0.766402	2.19764	11.84179	4.167048	0.000132	0.001501	0.880657
66	<i>FLI1</i>	8.568956	7.144349	1.424607	0.736083	2.113131	7.935797	4.163247	0.000134	0.001501	0.869272
67	VCAM1	8.581596	6.850553	1.731043	0.88403	2.578056	7.812244	4.112198	0.000158	0.00174	0.716817
68	<i>SERPINA1</i>	8.363761	6.955238	1.408524	0.715046	2.102001	7.737751	4.086843	0.000171	0.001858	0.641408
69	<i>BAG2</i>	8.427783	7.148475	1.279308	0.646336	1.912281	7.859202	4.066742	0.000182	0.001929	0.581776
70	<i>ZFYVE16</i>	8.548574	7.77575	0.772823	0.390357	1.15529	8.205097	4.065773	0.000182	0.001929	0.578905
71	FHL1	9.364727	7.603661	1.761065	0.884877	2.637254	8.582031	4.044214	0.000195	0.002036	0.515104
72	<i>NR3C1</i>	10.41566	9.622065	0.793593	0.397189	1.189997	10.06295	4.028246	0.000205	0.002052	0.467952
73	MS4A6A	6.772603	4.597062	2.175541	1.088538	3.262543	5.805696	4.027105	0.000206	0.002052	0.464586
74	CXADR	8.695033	10.29111	-1.59608	-2.39389	-0.79827	9.4044	-4.02542	0.000207	0.002052	0.459631
75	<i>EVI2A</i>	6.894859	5.785167	1.109692	0.554678	1.664706	6.401663	4.023046	0.000209	0.002052	0.452615
76	CX3CL1	7.403502	5.389046	2.014457	1.006175	3.022738	6.508188	4.020058	0.000211	0.002052	0.443809
77	DSC2	10.22294	11.79555	-1.57261	-2.36617	-0.77905	10.92188	-3.98747	0.000234	0.002244	0.347955
78	MEOX2	7.06517	5.010674	2.054496	0.999201	3.10979	6.15206	3.917308	0.000291	0.002759	0.142807
79	UTS2	3.977076	2.059202	1.917873	0.930207	2.90554	3.124688	3.907202	0.0003	0.002811	0.113406
80	TBX1	6.853872	8.970473	-2.1166	-3.21311	-1.02009	7.794584	-3.88402	0.000323	0.002983	0.046092
81	<i>THBS1</i>	11.45082	9.904541	1.546277	0.740957	2.351597	10.76358	3.863446	0.000344	0.003136	-0.01346
82	<i>MMP2</i>	11.75157	10.48994	1.261629	0.603549	1.919709	11.19085	3.857527	0.00035	0.003136	-0.03057
83	<i>SRPX2</i>	7.393977	5.871319	1.522658	0.727562	2.317754	6.71724	3.853355	0.000355	0.003136	-0.04262

84	GJA5	5.449455	3.84465	1.604806	0.766519	2.443093	4.736208	3.851999	0.000356	0.003136	-0.04653
85	CLU	10.58483	8.542835	2.041998	0.974311	3.109685	9.677278	3.848288	0.00036	0.003136	-0.05724
86	ADAMTS8	3.11158	1.296359	1.81522	0.862186	2.768255	2.304815	3.832454	0.000378	0.003255	-0.10289
87	PRSS8	6.037842	8.35102	-2.31318	-3.52937	-1.09699	7.065921	-3.82704	0.000385	0.003272	-0.11846
88	ASPEN	9.327385	6.732426	2.59496	1.227027	3.962892	8.17407	3.817001	0.000397	0.003337	-0.14734
89	<i>DENND5A</i>	8.312798	7.607362	0.705437	0.333016	1.077857	7.999271	3.811362	0.000404	0.003357	-0.16354
90	NRXN3	3.713998	1.723964	1.990035	0.93786	3.042209	2.829538	3.805652	0.000411	0.003378	-0.17993
91	TFPI2	6.876605	3.7028	3.173804	1.492142	4.855467	5.466025	3.797498	0.000421	0.003426	-0.20332
92	<i>C1S</i>	10.46129	9.201829	1.259463	0.591441	1.927484	9.90153	3.793594	0.000426	0.00343	-0.2145
93	<i>ITGAM</i>	6.869665	5.309823	1.559842	0.730339	2.389345	6.176402	3.783719	0.00044	0.003497	-0.24277
94	TPM2	12.82356	11.23126	1.592298	0.744544	2.440053	12.11587	3.779294	0.000446	0.003508	-0.25543
95	<i>SORD</i>	8.785962	9.743997	-0.95803	-1.47049	-0.44557	9.211755	-3.76164	0.00047	0.003664	-0.30583
96	<i>QKI</i>	11.17532	10.53903	0.636283	0.295311	0.977255	10.89252	3.754804	0.00048	0.003702	-0.32533
97	<i>PMP22</i>	9.854247	8.911144	0.943103	0.436876	1.449329	9.43509	3.748611	0.000489	0.003734	-0.34297
98	<i>CRISPLD2</i>	9.970885	8.908296	1.06259	0.490989	1.63419	9.498623	3.740496	0.000502	0.003789	-0.36606
99	<i>CCDC80</i>	11.99446	10.48601	1.508448	0.693302	2.323594	11.32404	3.723499	0.000528	0.00395	-0.41434
100	<i>HIPK1</i>	9.483144	8.865434	0.61771	0.282627	0.952793	9.208606	3.709268	0.000552	0.004084	-0.45468
101	<i>GSN</i>	11.77425	10.71099	1.063264	0.485773	1.640756	11.30169	3.70469	0.00056	0.0041	-0.46763
102	<i>PLEKHO1</i>	10.80888	9.918621	0.890255	0.404339	1.376172	10.41321	3.686457	0.000592	0.004291	-0.51916
103	FGF2	5.314698	3.389958	1.92474	0.872609	2.976871	4.459258	3.680938	0.000602	0.004321	-0.53472
104	<i>CTNNB1</i>	11.66443	10.90388	0.760555	0.340369	1.180741	11.32641	3.642045	0.000677	0.004815	-0.64408
105	<i>CTSL</i>	9.062662	7.926084	1.136578	0.504892	1.768265	8.557516	3.620378	0.000722	0.005062	-0.70473
106	<i>WWTR1</i>	10.09973	9.094521	1.005204	0.44634	1.564069	9.652968	3.619129	0.000725	0.005062	-0.70822
107	EREG	3.992915	6.156164	-2.16325	-3.37265	-0.95385	4.954359	-3.5991	0.00077	0.005325	-0.76411
108	VSIG4	9.150768	7.220556	1.930212	0.850181	3.010244	8.292896	3.596043	0.000777	0.005325	-0.77261
109	<i>NRP2</i>	10.29514	9.162454	1.132687	0.496301	1.769072	9.791724	3.581341	0.000812	0.00551	-0.8135
110	<i>VIM</i>	14.3035	13.24121	1.062294	0.464993	1.659595	13.83137	3.578554	0.000819	0.00551	-0.82124
111	<i>NFATC2</i>	9.350565	8.003056	1.347509	0.588515	2.106503	8.751672	3.572314	0.000834	0.005563	-0.83856
112	<i>PTK6</i>	6.397552	7.772476	-1.37492	-2.15078	-0.59906	7.008629	-3.56575	0.000851	0.005601	-0.85675

113	SCG2	4.170552	2.264377	1.906175	0.830019	2.982331	3.323364	3.56405	0.000855	0.005601	-0.86147
114	<i>ITGA1</i>	9.230424	8.299875	0.930548	0.404452	1.456644	8.816847	3.559018	0.000868	0.005631	-0.8754
115	<i>PTPRC</i>	7.539817	6.343455	1.196362	0.519494	1.873231	7.008101	3.556432	0.000875	0.005631	-0.88256
116	BMP5	4.338512	2.272708	2.065805	0.894832	3.236777	3.420377	3.549759	0.000893	0.005694	-0.90102
117	<i>KCNJ8</i>	7.259001	5.957911	1.30109	0.56116	2.04102	6.680739	3.538125	0.000924	0.005845	-0.93315
118	<i>FLT1</i>	7.917472	6.390603	1.526869	0.653125	2.400613	7.238863	3.516202	0.000986	0.006157	-0.99353
119	<i>PDGFRB</i>	10.36	9.206587	1.153418	0.493142	1.813694	9.847374	3.514936	0.00099	0.006157	-0.99701
120	PTPRB	4.070078	2.092443	1.977635	0.841933	3.113337	3.191129	3.50379	0.001023	0.006305	-1.02762
121	FGF9	3.854895	2.206798	1.648098	0.700982	2.595213	3.122407	3.501357	0.001031	0.006305	-1.0343
122	IL6	5.312837	2.478713	2.834124	1.196531	4.471717	4.053226	3.482323	0.001091	0.006616	-1.08642
123	NCAM1	5.286764	2.973735	2.313029	0.973443	3.652616	4.258752	3.474294	0.001117	0.006671	-1.10836
124	<i>AKT3</i>	9.34515	8.234738	1.110412	0.467264	1.753561	8.851634	3.473997	0.001118	0.006671	-1.10917
125	<i>PKN1</i>	9.4174	8.467567	0.949833	0.398245	1.501421	8.995252	3.464885	0.001148	0.006765	-1.13403
126	<i>ITGB3</i>	7.432487	5.993123	1.439364	0.603248	2.275479	6.79277	3.46386	0.001152	0.006765	-1.13683
127	ETV4	4.855539	6.580971	-1.72543	-2.72977	-0.7211	5.622398	-3.45681	0.001176	0.006852	-1.15605
128	CNN1	4.006901	1.738547	2.268354	0.943728	3.59298	2.998744	3.44567	0.001215	0.007026	-1.18634
129	<i>KIAA1462</i>	8.18355	7.222046	0.961504	0.398867	1.524141	7.756215	3.438578	0.001241	0.007078	-1.2056
130	S100A7	7.829611	11.93479	-4.10518	-6.50788	-1.70247	9.654133	-3.43786	0.001243	0.007078	-1.20756
131	CHRD1	5.909359	2.905235	3.004124	1.242924	4.765324	4.574192	3.432143	0.001265	0.007143	-1.22305
132	<i>CHRNA7</i>	5.154154	3.700685	1.453469	0.598223	2.308715	4.508168	3.419565	0.001312	0.007287	-1.25712
133	<i>CDK14</i>	8.975443	7.816931	1.158513	0.475963	1.841062	8.460549	3.415254	0.001329	0.007287	-1.26878
134	<i>NAA15</i>	7.492039	8.442593	-0.95055	-1.51071	-0.3904	7.914508	-3.41448	0.001332	0.007287	-1.27088
135	<i>ESRP1</i>	9.659245	10.81963	-1.16039	-1.84446	-0.47631	10.17497	-3.41314	0.001337	0.007287	-1.2745
136	<i>MAP2K4</i>	7.51672	8.574664	-1.05794	-1.68173	-0.43416	7.986917	-3.41257	0.001339	0.007287	-1.27602
137	PLA2G2A	8.598091	5.321259	3.276832	1.328358	5.225307	7.141721	3.383886	0.001456	0.007867	-1.35336
138	<i>CDH1</i>	8.835033	10.33455	-1.49952	-2.39273	-0.60631	9.501487	-3.37796	0.001482	0.007925	-1.36927
139	POSTN	11.85721	10.20854	1.64867	0.666155	2.631184	11.12447	3.376378	0.001489	0.007925	-1.37353
140	<i>ALB</i>	2.794902	1.350269	1.444633	0.57735	2.311915	2.152843	3.351608	0.0016	0.008457	-1.4399
141	<i>JUN</i>	10.67711	9.560218	1.11689	0.439111	1.794669	10.18071	3.315724	0.001775	0.009317	-1.53553

142	ACTG2	6.674539	3.992938	2.681601	1.046505	4.316697	5.482716	3.299949	0.001858	0.009682	-1.57737
143	<i>GPR124</i>	6.577779	5.192164	1.385616	0.537935	2.233296	5.96195	3.289022	0.001917	0.009867	-1.60628
144	<i>CEP170</i>	9.061795	8.507533	0.554262	0.215128	0.893396	8.815457	3.288517	0.00192	0.009867	-1.60762

Supplementary Table 3. Differential gene expression in EXT-PNI cohorts based on nerve proportion in the specimens showing each genes log2 fold change >1 or < -1 of extensive PNI with high (>10%, n = 9) versus low (<10%, n = 16) nerve involvement.

	HUGO	Log2 fold change	std error (log2)	Lower confidence limit (log2)	Upper confidence limit (log2)	Linear fold change	Lower confidence limit (linear)	Upper confidence limit (linear)	P-value	adj.P. Val
1	<i>TMPRSS4</i>	-4.11	0.879	-5.83	-2.39	0.0579	0.0176	0.191	0.000105	0.504
2	<i>PRSS22</i>	-2.72	0.663	-4.02	-1.42	0.152	0.0616	0.374	0.000437	0.889
3	<i>ITGB8</i>	1.71	0.428	0.875	2.55	3.28	1.83	5.86	0.000554	0.889
4	<i>EVPL</i>	-2.13	0.578	-3.27	-0.999	0.228	0.104	0.5	0.00121	1
5	<i>KRT14</i>	-1.84	0.524	-2.86	-0.809	0.28	0.137	0.571	0.00192	1
6	<i>NOTCH1</i>	-0.951	0.277	-1.49	-0.408	0.517	0.355	0.754	0.00228	1
7	<i>CLDN7</i>	-2.36	0.711	-3.76	-0.967	0.195	0.074	0.512	0.00299	1
8	<i>IL1RN</i>	-1.43	0.433	-2.27	-0.577	0.372	0.207	0.67	0.00318	1
9	<i>FGFR3</i>	-2.07	0.684	-3.41	-0.727	0.239	0.0943	0.604	0.00606	1
10	<i>DPT</i>	-2.26	0.76	-3.75	-0.774	0.208	0.0742	0.585	0.00671	1
11	<i>RAB25</i>	-2.12	0.718	-3.53	-0.714	0.23	0.0868	0.61	0.00711	1
12	<i>DSC2</i>	-1.48	0.506	-2.48	-0.493	0.357	0.18	0.71	0.00742	1
13	<i>CXADR</i>	-1.5	0.525	-2.53	-0.473	0.353	0.173	0.72	0.00884	1
14	<i>ITGA11</i>	-2.19	0.768	-3.69	-0.681	0.22	0.0774	0.624	0.00913	1
15	<i>MEG3</i>	-1.2	0.423	-2.03	-0.373	0.435	0.245	0.772	0.00924	1
16	<i>IGFBP4</i>	1.66	0.606	0.474	2.85	3.16	1.39	7.21	0.0116	1
17	<i>ALDOA</i>	-0.861	0.314	-1.48	-0.245	0.551	0.359	0.844	0.0116	1
18	<i>VWA1</i>	1.72	0.632	0.484	2.96	3.3	1.4	7.79	0.0121	1
19	<i>TWIST2</i>	-1.19	0.443	-2.06	-0.324	0.438	0.24	0.799	0.013	1
20	<i>CDK14</i>	1.11	0.412	0.299	1.91	2.15	1.23	3.77	0.0132	1

Supplementary Table 4. Top ten genes according to adjusted *P*-values with known protein, gene function and disease associations.

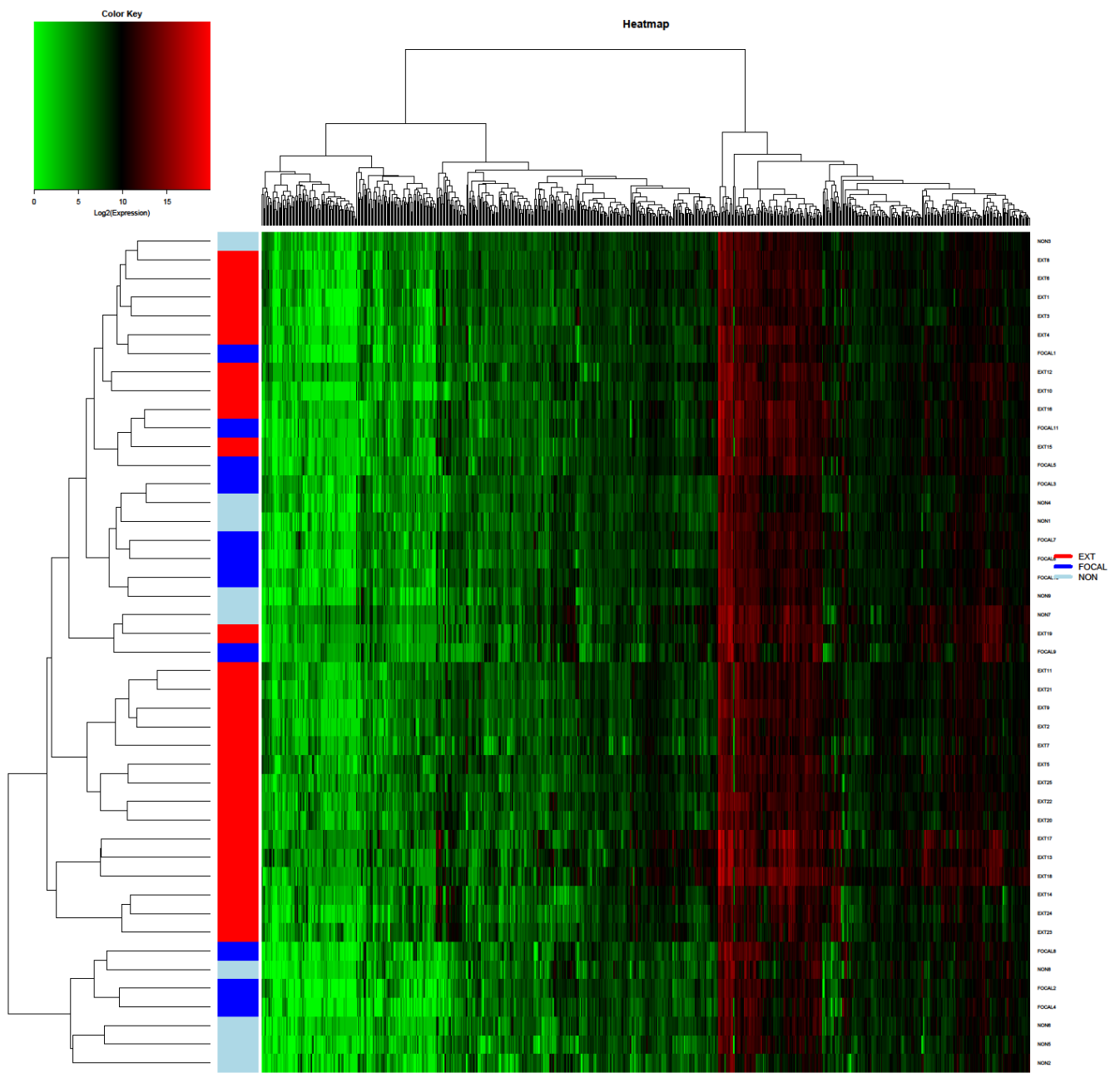
Gene Symbol¹	Protein	Function²	Associations³	Neural development	Extracellular matrix
<i>PTGIS</i>	prostaglandin I2 synthetase	Prostacyclin production. Prostacyclin is a vasodilator and inhibitor of platelet aggregation.	Hypertension. Pulmonary hypertension. Alzheimer's disease.	+	
<i>THBS4</i>	thrombospondin 4	Extracellular calcium binding. Cell proliferation, adhesion and migration.	Prostate cancer. Nephroma.	+	+
<i>SRGN</i>	serglycin	Platelet secretory granule proteoglycan. Inflammation and apoptosis.	Mucinoses.		
<i>FERMT2</i>	fermitin family member 2	Cell-ECM adhesion molecule which facilitates cell shape modulation	Kindler syndrome (epidermolysis bullosa). Leukocyte Adhesion Deficiency.	+	+
<i>NR4A3</i>	nuclear receptor subfamily 4 group A member 3	Neural development and cAMP signalling.	Chondrosarcoma.	+	
<i>TIMP1</i>	TIMP metalloproteinase inhibitor 1	Matrix metalloproteinase (MM) inhibitor. Involved in ECM degradation and stromal cell apoptosis. Growth factor.	Lung giant cell carcinoma. Oral submucous fibrosis.		+

<i>SAMSN1</i>	SAM domain, SH3 domain and nuclear localization signals 1	Cytoplasmic protein involved in signalling, cell spreading and cell polarization.	Negative regulator of B cell activation.		
<i>HGF</i>	hepatocyte growth factor	Regulates cell growth, motility and morphology. Angiogenesis, tumour development and tissue regeneration.	Deafness. Hepatocellular carcinoma.	+	+
<i>VCAN</i>	versican	Large proteoglycan ECM molecule. Cell adhesion, differentiation, proliferation and migration.	Wagner syndrome.	+	+
<i>C3</i>	complement C3	Complement activation, inflammation, immunity, neural development.	Haemolytic Uremic syndrome.		

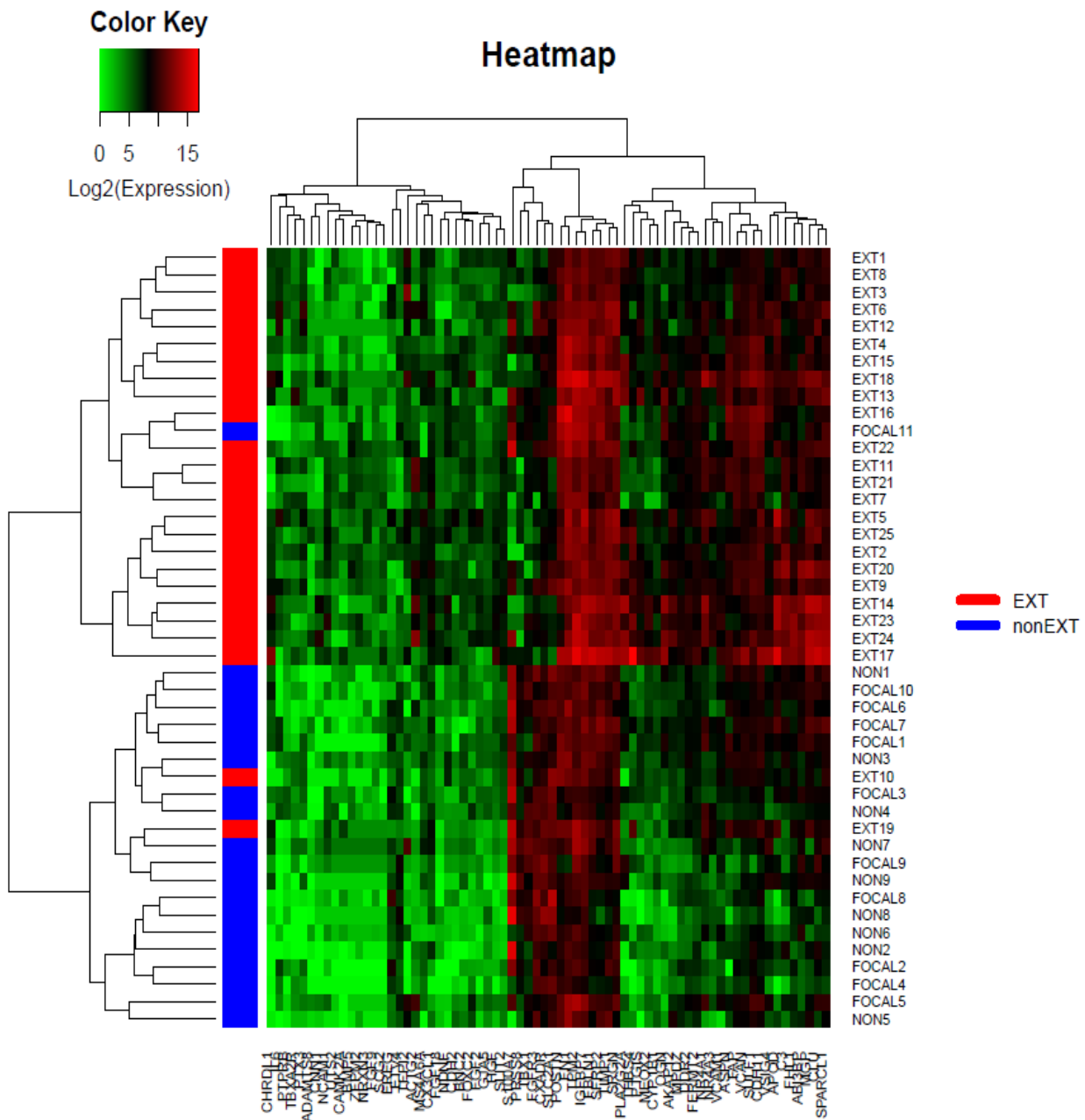
1 Gene symbol based on HUGO Gene Nomenclature Committee (HGNC), accessible at <http://www.genenames.org/>

2 Function based on OMIM gene description, accessible at <http://www.omim.org/>

3 Associations based on GeneCards human gene database, accessible at <http://genecards.org/>



Supplementary Figure 1. High level overview heatmap of the normalized data, scaled to give all genes equal variance, generated via unsupervised clustering. Shows two main clusters of EXT PNI samples (coloured red) largely grouping separately from the Focal and Non-PNI samples (colored dark and light blue). Green represents low expression, Red represents high expression.



Supplementary Figure 2. Heatmap of the normalized data, scaled to give all genes equal variance, generated via unsupervised clustering based on the highest ranking differentially expressed genes between EXT (red) and Focal/Non-PNI (blue – nonEXT) cohorts with fold change >3, < -3 and adjusted *P*-value < 0.01. Green represents low expression, Red represents high expression.