

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

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

55	<b>OGN</b>	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	<b>SLC2A1</b>	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	<b>CDS1</b>	7.299836	8.845294	-1.54546	-2.27983	-0.81108	7.986706	-4.23443	0.000107	0.001337	1.08324
60	<b>CAMK2A</b>	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	<b>ABI3BP</b>	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	<b>VCAM1</b>	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	<b>FHL1</b>	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	<b>MS4A6A</b>	6.772603	4.597062	2.175541	1.088538	3.262543	5.805696	4.027105	0.000206	0.002052	0.464586
74	<b>CXADR</b>	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	<b>CX3CL1</b>	7.403502	5.389046	2.014457	1.006175	3.022738	6.508188	4.020058	0.000211	0.002052	0.443809
77	<b>DSC2</b>	10.22294	11.79555	-1.57261	-2.36617	-0.77905	10.92188	-3.98747	0.000234	0.002244	0.347955
78	<b>MEOX2</b>	7.06517	5.010674	2.054496	0.999201	3.10979	6.15206	3.917308	0.000291	0.002759	0.142807
79	<b>UTS2</b>	3.977076	2.059202	1.917873	0.930207	2.90554	3.124688	3.907202	0.0003	0.002811	0.113406
80	<b>TBX1</b>	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	<b>GJA5</b>	5.449455	3.84465	1.604806	0.766519	2.443093	4.736208	3.851999	0.000356	0.003136	-0.04653
85	<b>CLU</b>	10.58483	8.542835	2.041998	0.974311	3.109685	9.677278	3.848288	0.00036	0.003136	-0.05724
86	<b>ADAMTS8</b>	3.11158	1.296359	1.81522	0.862186	2.768255	2.304815	3.832454	0.000378	0.003255	-0.10289
87	<b>PRSS8</b>	6.037842	8.35102	-2.31318	-3.52937	-1.09699	7.065921	-3.82704	0.000385	0.003272	-0.11846
88	<b>ASPEN</b>	9.327385	6.732426	2.59496	1.227027	3.962892	8.17407	3.817001	0.000397	0.003337	-0.14734
89	<b>DENND5A</b>	8.312798	7.607362	0.705437	0.333016	1.077857	7.999271	3.811362	0.000404	0.003357	-0.16354
90	<b>NRXN3</b>	3.713998	1.723964	1.990035	0.93786	3.042209	2.829538	3.805652	0.000411	0.003378	-0.17993
91	<b>TFPI2</b>	6.876605	3.7028	3.173804	1.492142	4.855467	5.466025	3.797498	0.000421	0.003426	-0.20332
92	<b>C1S</b>	10.46129	9.201829	1.259463	0.591441	1.927484	9.90153	3.793594	0.000426	0.00343	-0.2145
93	<b>ITGAM</b>	6.869665	5.309823	1.559842	0.730339	2.389345	6.176402	3.783719	0.00044	0.003497	-0.24277
94	<b>TPM2</b>	12.82356	11.23126	1.592298	0.744544	2.440053	12.11587	3.779294	0.000446	0.003508	-0.25543
95	<b>SORD</b>	8.785962	9.743997	-0.95803	-1.47049	-0.44557	9.211755	-3.76164	0.00047	0.003664	-0.30583
96	<b>QKI</b>	11.17532	10.53903	0.636283	0.295311	0.977255	10.89252	3.754804	0.00048	0.003702	-0.32533
97	<b>PMP22</b>	9.854247	8.911144	0.943103	0.436876	1.449329	9.43509	3.748611	0.000489	0.003734	-0.34297
98	<b>CRISPLD2</b>	9.970885	8.908296	1.06259	0.490989	1.63419	9.498623	3.740496	0.000502	0.003789	-0.36606
99	<b>CCDC80</b>	11.99446	10.48601	1.508448	0.693302	2.323594	11.32404	3.723499	0.000528	0.00395	-0.41434
100	<b>HIPK1</b>	9.483144	8.865434	0.61771	0.282627	0.952793	9.208606	3.709268	0.000552	0.004084	-0.45468
101	<b>GSN</b>	11.77425	10.71099	1.063264	0.485773	1.640756	11.30169	3.70469	0.00056	0.0041	-0.46763
102	<b>PLEKHO1</b>	10.80888	9.918621	0.890255	0.404339	1.376172	10.41321	3.686457	0.000592	0.004291	-0.51916
103	<b>FGF2</b>	5.314698	3.389958	1.92474	0.872609	2.976871	4.459258	3.680938	0.000602	0.004321	-0.53472
104	<b>CTNNB1</b>	11.66443	10.90388	0.760555	0.340369	1.180741	11.32641	3.642045	0.000677	0.004815	-0.64408
105	<b>CTSL</b>	9.062662	7.926084	1.136578	0.504892	1.768265	8.557516	3.620378	0.000722	0.005062	-0.70473
106	<b>WWTR1</b>	10.09973	9.094521	1.005204	0.44634	1.564069	9.652968	3.619129	0.000725	0.005062	-0.70822
107	<b>EREG</b>	3.992915	6.156164	-2.16325	-3.37265	-0.95385	4.954359	-3.5991	0.00077	0.005325	-0.76411
108	<b>VSIG4</b>	9.150768	7.220556	1.930212	0.850181	3.010244	8.292896	3.596043	0.000777	0.005325	-0.77261
109	<b>NRP2</b>	10.29514	9.162454	1.132687	0.496301	1.769072	9.791724	3.581341	0.000812	0.00551	-0.8135
110	<b>VIM</b>	14.3035	13.24121	1.062294	0.464993	1.659595	13.83137	3.578554	0.000819	0.00551	-0.82124
111	<b>NFATC2</b>	9.350565	8.003056	1.347509	0.588515	2.106503	8.751672	3.572314	0.000834	0.005563	-0.83856
112	<b>PTK6</b>	6.397552	7.772476	-1.37492	-2.15078	-0.59906	7.008629	-3.56575	0.000851	0.005601	-0.85675

113	<b>SCG2</b>	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	<b>BMP5</b>	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	<b>PTPRB</b>	4.070078	2.092443	1.977635	0.841933	3.113337	3.191129	3.50379	0.001023	0.006305	-1.02762
121	<b>FGF9</b>	3.854895	2.206798	1.648098	0.700982	2.595213	3.122407	3.501357	0.001031	0.006305	-1.0343
122	<b>IL6</b>	5.312837	2.478713	2.834124	1.196531	4.471717	4.053226	3.482323	0.001091	0.006616	-1.08642
123	<b>NCAM1</b>	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	<b>ETV4</b>	4.855539	6.580971	-1.72543	-2.72977	-0.7211	5.622398	-3.45681	0.001176	0.006852	-1.15605
128	<b>CNN1</b>	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	<b>S100A7</b>	7.829611	11.93479	-4.10518	-6.50788	-1.70247	9.654133	-3.43786	0.001243	0.007078	-1.20756
131	<b>CHRD1</b>	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	<b>PLA2G2A</b>	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	<b>POSTN</b>	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	<b>ACTG2</b>	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 2. PNI cohort categories and nerve proportions.** Green highlighted EXT specimens grouped with major focal/non-PNI cohort using fold change  $\pm 2$  stratification (refer to Figure 3).

<b>PNI ID</b>	<b>% Nerve proportion*</b>	<b>Age, sex, primary site and additional comments</b>
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 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.

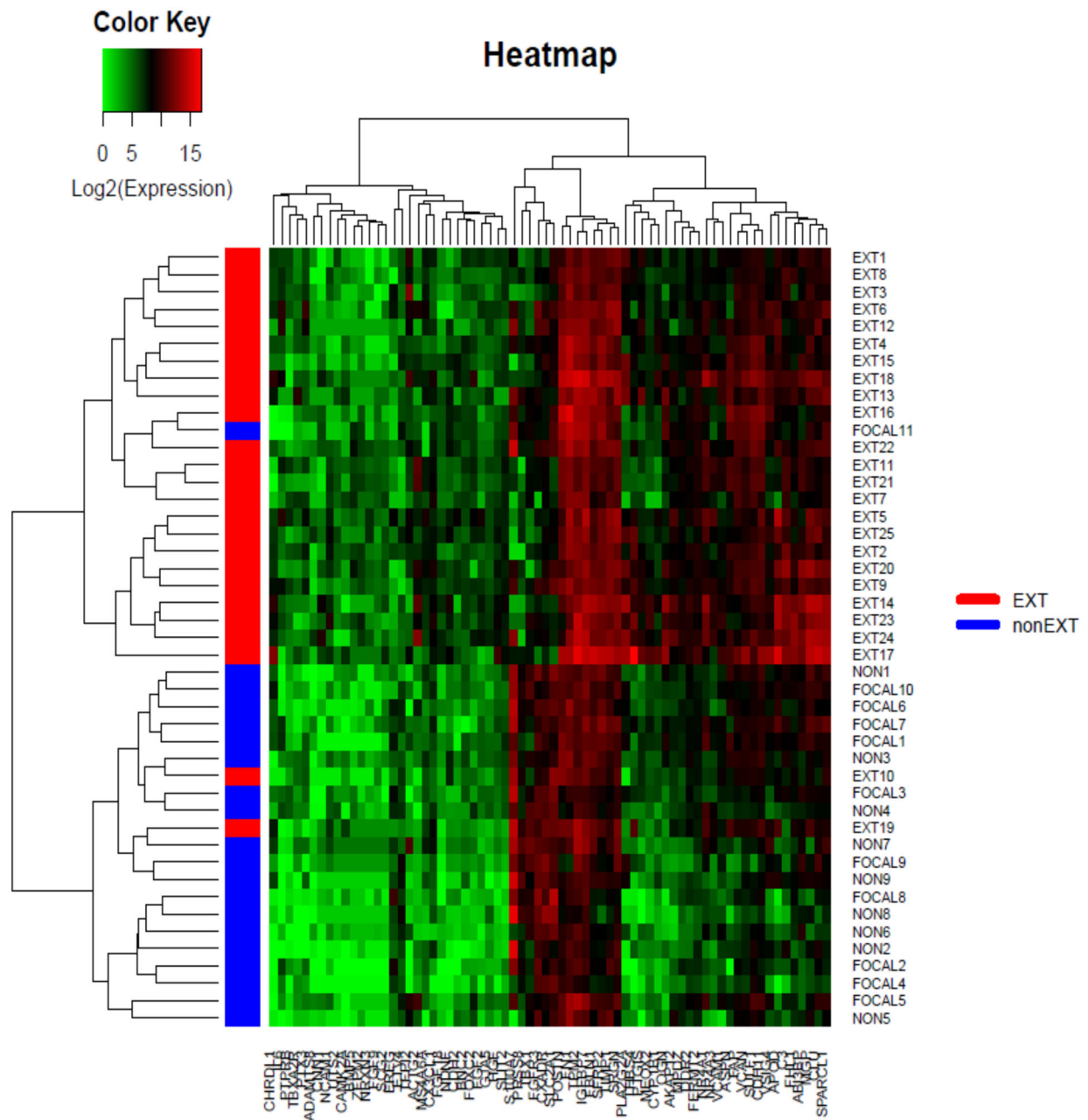
<b>Gene Symbol<sup>1</sup></b>	<b>Protein</b>	<b>Function<sup>2</sup></b>	<b>Associations<sup>3</sup></b>	<b>Neural development</b>	<b>Extracellular matrix</b>
<i>PTGIS</i>	prostaglandin I2 synthetase	Prostacyclin production. Prostacyclin is a vasodilator and inhibitor of platelet aggregation.	Hypertension. 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.** 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.