

Online Resource 2

DiffCorr Post-Hoc Validation of the 18 Conserved Lost Interactions: Fisher’s Z-Transformation Results per Subdataset

A multi-cohort computational framework for detection and prognostic validation
of conserved gene co-expression network dissolution in solid tumors

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Overview

This Online Resource provides the complete per-subdataset results of the DiffCorr post-hoc validation of the 18 conserved lost interactions identified in the main manuscript. For each interaction, Fisher’s z-transformation was applied to test whether the Pearson correlation between the two genes differed significantly between normal and tumor tissue, using the correlation matrices generated by the main pipeline as input. The analysis was performed using the DiffCorr package (DiffCorr::compcorr; Fukushima 2013).

For each gene pair (g_1, g_2) and each subdataset, let r_N and r_T denote the Pearson correlation coefficients in normal and tumor tissue, and let n_1 and n_2 denote the corresponding sample sizes. The test statistic is:

$$z_{\text{diff}} = \frac{\text{atanh}(r_N) - \text{atanh}(r_T)}{\sqrt{1/(n_1 - 3) + 1/(n_2 - 3)}}$$

with two-tailed p -value $= 2\Phi(-|z_{\text{diff}}|)$. Benjamini–Hochberg (BH) correction was applied per cancer pair across all tests. An interaction was classified as *DiffCorr-supported* if BH-adjusted $p < 0.05$ and $r_N > r_T$ in all subdatasets of both cancer types. Empty cells (—) in the tables below indicate that one or both genes were absent from the subdataset DEG list.

Table S1. DiffCorr Results — BRCA–LUAD Interactions

The two BRCA–LUAD interactions were tested across all four BRCA subtypes and both LUAD anatomical regions. Both interactions are DiffCorr-supported in all subdatasets of both cancer types.

DiffCorr validation results for BRCA–LUAD interactions (threshold 0.7/0.3, FC2). r_N : Pearson correlation in normal tissue; r_T : Pearson correlation in tumor tissue; FDR: BH-adjusted p -value.

Interaction	Subdataset	r_N	r_T	Δr	FDR
CST1–MMP11	BRCA Basal	0.829	0.058	0.771	<0.001
	BRCA Her2	0.792	0.128	0.664	<0.001
	BRCA LumA	0.841	0.170	0.671	<0.001
	BRCA LumB	0.792	0.111	0.681	<0.001
	LUAD Upper lobe	0.984	0.052	0.932	<0.001
	LUAD Lower lobe	0.984	0.112	0.872	<0.001
COL10A1–CST1	BRCA Basal	0.773	0.104	0.669	<0.001
	BRCA Her2	0.735	0.111	0.624	<0.001
	BRCA LumA	0.780	0.135	0.645	<0.001
	BRCA LumB	0.735	0.119	0.616	<0.001
	LUAD Upper lobe	0.924	0.002	0.922	<0.001
	LUAD Lower lobe	0.924	0.075	0.849	<0.001

Table S2. DiffCorr Results — LUAD–STAD Interactions

The nine LUAD–STAD interactions were tested across both LUAD anatomical regions and both STAD molecular subtypes. All nine interactions are DiffCorr-supported in all four subdatasets.

DiffCorr validation results for LUAD–STAD interactions (threshold 0.7/0.3, FC2). Column pairs show (r_N / r_T) for each subdataset. FDR: minimum BH-adjusted p -value across the four subdatasets. —: gene not present in subdataset DEG list.

Gene 1	Gene 2	LUAD Upper	LUAD Lower	STAD CIN	STAD MSI	Min FDR
		(r_N / r_T)	(r_N / r_T)	(r_N / r_T)	(r_N / r_T)	
IGHV5-78	TNFSF11	0.857 / −0.013	0.855 / 0.002	0.807 / 0.095	0.829 / 0.117	<0.001
IGKV3-11	JSRP1	0.707 / 0.161	0.709 / 0.071	0.789 / 0.086	0.835 / 0.164	<0.001
FCRL4	TNFSF11	0.796 / −0.007	0.794 / 0.064	0.830 / 0.086	0.842 / 0.106	<0.001
IGHV1OR15-2	IGHV4-4	0.701 / 0.167	0.702 / 0.180	0.759 / 0.093	0.776 / 0.189	<0.001
B4GALNT4	TMEM59L	0.733 / 0.146	0.735 / 0.118	0.900 / −0.092	0.793 / 0.244	<0.001
IGHV5-51	JSRP1	0.719 / 0.283	0.720 / 0.049	0.874 / 0.103	0.882 / 0.095	<0.001
IGKV1-9	JSRP1	0.711 / 0.122	0.712 / 0.030	0.868 / 0.111	0.893 / 0.274	<0.001
IGHV1OR15-2	IGHV3-20	0.758 / 0.082	0.759 / 0.041	0.770 / 0.147	0.770 / 0.250	<0.001
IGHV4-55	JSRP1	0.731 / 0.196	0.733 / 0.073	0.716 / 0.218	0.726 / 0.181	0.001

Table S3. DiffCorr Results — HNSC–STAD Interactions

The seven HNSC–STAD interactions were tested across three HNSC anatomical subsites (Larynx, Oral Cavity, Oropharynx) and two STAD molecular subtypes (CIN, MSI). All seven interactions are DiffCorr-supported in all five subdatasets.

DiffCorr validation results for HNSC–STAD interactions (threshold 0.7/0.3, FC2). Column pairs show (r_N / r_T) for each subdataset. FDR: minimum BH-adjusted p -value across the five subdatasets.

Gene 1	Gene 2	HNSC Larynx (r_N/r_T)	HNSC Oral (r_N/r_T)	HNSC Oro- pharynx (r_N/r_T)	STAD CIN (r_N/r_T)	STAD MSI (r_N/r_T)	Min FDR
HOXC11	ZIC2	0.865 / 0.125	0.730 / −0.065	0.731 / −0.162	0.902 / −0.127	0.884 / −0.175	<0.001
TNXB	WNT2	0.910 / −0.049	0.902 / 0.132	0.898 / 0.005	0.817 / 0.031	0.766 / −0.113	<0.001
GRIN2D	ZIC2	0.770 / 0.086	0.823 / 0.188	0.827 / −0.239	0.762 / 0.028	0.755 / 0.007	<0.001
AC010789.1	AL162413.1	0.704 / 0.195	0.870 / 0.093	0.872 / −0.013	0.823 / 0.096	0.826 / 0.046	<0.001
AL162413.1	GRIN2D	0.744 / 0.031	0.863 / −0.058	0.868 / 0.296	0.769 / 0.047	0.789 / 0.225	<0.001
GRIN2D	TRPM2-AS	0.819 / 0.245	0.743 / 0.219	0.747 / 0.114	0.849 / 0.126	0.862 / 0.065	<0.001
ADAMTS2	TNXB	0.717 / 0.009	0.915 / 0.276	0.913 / 0.109	0.823 / 0.058	0.838 / 0.098	<0.001

Table S4. Overall DiffCorr Validation Summary by Cancer Pair

Summary of DiffCorr support across all 18 conserved lost interactions by cancer pair.

Cancer pair	Interactions	Supported	Subdatasets tested	Min FDR (range)
BRCA–LUAD	2	2/2 (100%)	4 BRCA + 2 LUAD	< 0.001
LUAD–STAD	9	9/9 (100%)	2 LUAD + 2 STAD	< 0.001–0.001
HNSC–STAD	7	7/7 (100%)	3 HNSC + 2 STAD	< 0.001
Total	18	18/18 (100%)	11 subdatasets	

Table S5. Percentage of DiffCorr-Significant Tests per Cohort

Proportion of gene pairs with significant differential co-expression (BH-adjusted $p < 0.05$, $r_N > r_T$) per subdataset, among all testable pairs (i.e., pairs where both genes were present in the subdataset DEG list).

Cancer type	Subdataset	Pairs tested	Significant	% Significant
BRCA	Basal	5	2	40.0%
	Her2	6	2	33.3%
	LumA	3	2	66.7%
	LumB	3	2	66.7%
LUAD	Upper lobe	14	12	85.7%
	Lower lobe	13	11	84.6%
HNSC	Larynx	10	8	80.0%
	Oral Cavity	9	7	77.8%
	Oropharynx	13	9	69.2%
STAD	CIN	18	16	88.9%
	MSI	18	16	88.9%
Overall		112	87	77.7%

Note: The lower percentages in BRCA subdatasets reflect the expected design constraint: most LUAD–STAD and HNSC–STAD interactions involve genes that are not differentially expressed in BRCA, and are therefore absent from BRCA DEG lists. Among the 5 pairs testable in BRCA (those involving CST1, MMP11, COL10A1, GRIN2D, HOXC11, ZIC2), all 2 BRCA–LUAD interactions showed significant differential co-expression across all four BRCA subtypes.

Reference

Fukushima A. DiffCorr: an R package to analyze and visualize differential correlations in biological networks. *Gene*. 2013;518(1):209–214. doi:10.1016/j.gene.2012.11.028