Data-driven Analysis of TRP Channels in Cancer: Linking Variation in Gene Expression to Clinical Significance

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Abstract. *Background: Experimental evidence has suggested that transient receptor potential (TRP) channels play a crucial role in tumor biology. However, clinical relevance and significance of TRP channels in cancer remain largely unknown. Materials and Methods: We applied a data-driven approach to dissect the expression landscape of 27 TRP channel genes in 14 types of human cancer using International Cancer Genome Consortium data. Results: TRPM2 was found overexpressed in most tumors, whereas TRPM3 was broadly down-regulated. TRPV4 and TRPA1 were found up- and down-regulated respectively in a cancer type-specific manner. TRPC4 was found to be closely associated with incidence of head and neck cancer and poor survival of patients with kidney cancer. TRPM8 was identified as a new molecular marker for lung cancer diagnosis and TRPP1 for kidney cancer prognosis. Conclusion: Our data-driven approach demonstrates that the variation in the expression of TRP channel genes is manifested across various human cancer types and genes, for certain TRP channels have strong predictive diagnostic and prognostic potential.*

Transient receptor potential (TRP) channels generate electrochemical signals in terms of membrane potential or intracellular Ca^{2+} in response to various internal and external stimuli (1, 2). In human, the TRP channel superfamily consists of 27 isotypes that are classified into six subfamilies (3): canonical (TRPC), vanilloid (TRPV), melastatin (TRPM), polycystin (TRPP), mucolipin (TRPML), and ankyrin (TRPA). Emerging evidence has shown that the aberrant functions of TRP channels are closely associated with cancer hallmarks, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, and activating invasion and metastasis (4, 5). In addition, the TRP channel network suggests that TRP channels are involved in tumor biology by interacting with oncogenes or tumor suppressors (6-8). However, the clinical relevance and significance of TRP channels in patients with cancer has not been investigated.

Recently, an alliance of computational biology with high-throughput technologies has provided useful frameworks for linking biological information to clinical significance. In particular, integration and analysis of a large volume of heterogeneous biological and clinical datasets *in silico* has expanded our epistemic scope of biomedical knowledge (9-11). With advances in genomic technologies, such as next-generation sequencing and bioinformatics, data-driven approaches have been reforming the way in which we understand tumor biology, discover tumor-associated genes, and develop anticancer therapeutic strategies (12). Consequently, data-driven cancer research can deliver the promise of early diagnosis and medical treatments of patients with cancer (12). Therefore, data-driven approaches may be useful to ascertain clinical relevance and significance of TRP channel in cancer.

In the present study, we investigated the clinical significance of 27 TRP channels in 14 human cancer types using the International Cancer Genome Consortium (ICGC) dataset. Our study provides a novel conceptual framework for translating biological knowledge on TRP channels into clinical practice.

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Key Words: Data-driven approach, TRP channel, cancer, clinical significance.

Materials and Methods

Data selection. The normalized gene-expression data of all cancer types were downloaded in data repository (ftp site) from the ICGC data portal (https://dcc.icgc.org). The downloaded ICGC data includes gene-expression data from 42 projects (Data release 15.1, February 11th, 2014). Of 42 projects, 28 projects were filtered out: 16 projects did not have gene-expression data and 12 projects did not include normal samples. Finally, 14 projects containing matched tumor and normal samples (552 pairs) were chosen to analyze gene expression data (Table I). Table II shows the clinical information of these 552 patients. Because the gene-expression data from each project use different normalization methods, the expression levels of TRP channels were determined by the ratio of the normalized gene-expression levels between normal and tumor samples.

Statistical analysis. All statistical analyses were performed using program R 3.1.2 (https://www.r-project.org/). To calculate odds ratios (ORs), the best threshold values were chosen by calculating F1 score based on receiver operating characteristic (ROC) analysis for all combinations of cancer types and TRP channel genes. ORs and their 95% confidence interval (CI) were estimated using logistic regression. Using those threshold values, the expression values of each TRP channel gene were classified into high and low expression groups. Univariate analysis was then applied to calculate *p*-values, ORs, and CI between high- and low-expression groups. Finally, multivariate logistic regression was applied for significant TRP channel genes whose *p*-values of univariate analysis were less than 0.01 and the area under the ROC curve (AUC) values of univariate analysis were greater than 0.8. The criteria of *p*-value and AUC were empirically chosen.

Survival analysis to evaluate the discriminatory power and the predictive accuracy of TRP channel gene expression were applied to only one project, such as kidney cancer [clear cell carcinoma (CCC)] among 14 projects because the CCC kidney cancer type included cancer survival data (13). The non-parametric Kaplan–Meier method was used to determine survival curves and the log-rank test was used to determine overall survival rates. Using median gene expression values as bifurcating point, the samples were divided into high- and low-expression groups and the survival rates of groups were compared. Cox proportional hazards model was applied to estimate hazard ratios (HRs) and 95% CIs. Harrell's concordance index (c-index), widely used as a surrogate for the ROC analysis (14), was calculated on the basis of HR and 95% CI.

Network visualization. The open-source program, Gephi 0.8.2-beta (http://gephi.github.io/) was used to visualize the relation between genes and cancer types.

Table I. The International Cancer Genome Consortium gene expression data used in this study. Among 4,854 tumor samples, 552 matched normal samples were used in this study.

Cancer type	Cancer	Normal
Bladder	185	16
Breast	981	108
Cervix	65	3
Colon	416	23
Head and neck	353	39
Kidney (CCC#)	496	72
Kidney (PCC#)	127	28
Liver	123	46
Lung (AC#)	443	55
Lung (SCC#)	398	44
Prostate	174	38
Rectum	143	5
Thyroid	471	22
Uterus	479	53
Total	4,854	552

CCC, Clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma.

Results

Variation in the expression of TRP channel genes in human cancer. To gain deeper insight into the roles of TRP channels in tumor biology, we dissected the expression landscape of 27 TRP channel genes in 14 human cancer types (Table I). Ubiquity and specificity of the altered expression of TRP channels was found throughout cancer types (Figure 1 and Table III). *TRPM2, TRPM3*, and *TRPM6* are a typical example of the ubiquity of altered expression: *TRPM2* was found up-regulated in most cancer types (by 1.47- to 7.56-fold), whereas *TRPM3* and *TRPM6* were broadly down-regulated (by 0.13- to 0.56-fold), suggesting the isotype-specific functions of TRP channels in cancer biology.

The altered expression of certain TRP channels was specific for cancer types (Figure 1 and Table III). Interestingly, in some cases, an opposing expression pattern was observed according to cancer type: *TRPV4* was found to be overexpressed in cervical cancer (18.65-fold), whereas its expression was reduced in liver cancer (0.21-fold); *TRPA1* was found to be up-regulated in kidney cancer (by 11.94- to 28.74-fold), whereas its expression was reduced in prostate cancer (0.15-fold). These results suggest that TRP channels have opposing roles depending on the cancer type. However, we found *TRPV1* not to be significantly changed in different cancer types.

The association between TRP channel expression and cancer incidence or clinical outcome. We then questioned the clinical relevance and significance of TRP channels in human cancer. To identify whether the altered expression of TRP channels are associated with cancer incidence, we performed univariate and multivariate logistic regression analysis. Our results are summarized in Table IV. TRP channels significantly affect the risk of cancer incidence. We found higher expression of *TRPM2* to be closely associated with an increased risk for four cancer types, namely bladder, head and neck, liver, and lung cancer (adenocarcinoma) (OR=14.260-389.563). In contrast, the higher expression of *TRPM3* was found to be associated with a decreased risk for bladder, breast, and thyroid cancer (OR=0.062-0.102). Interestingly, higher expression of *TRPC6* was associated with reduced risk for breast, colon and prostate

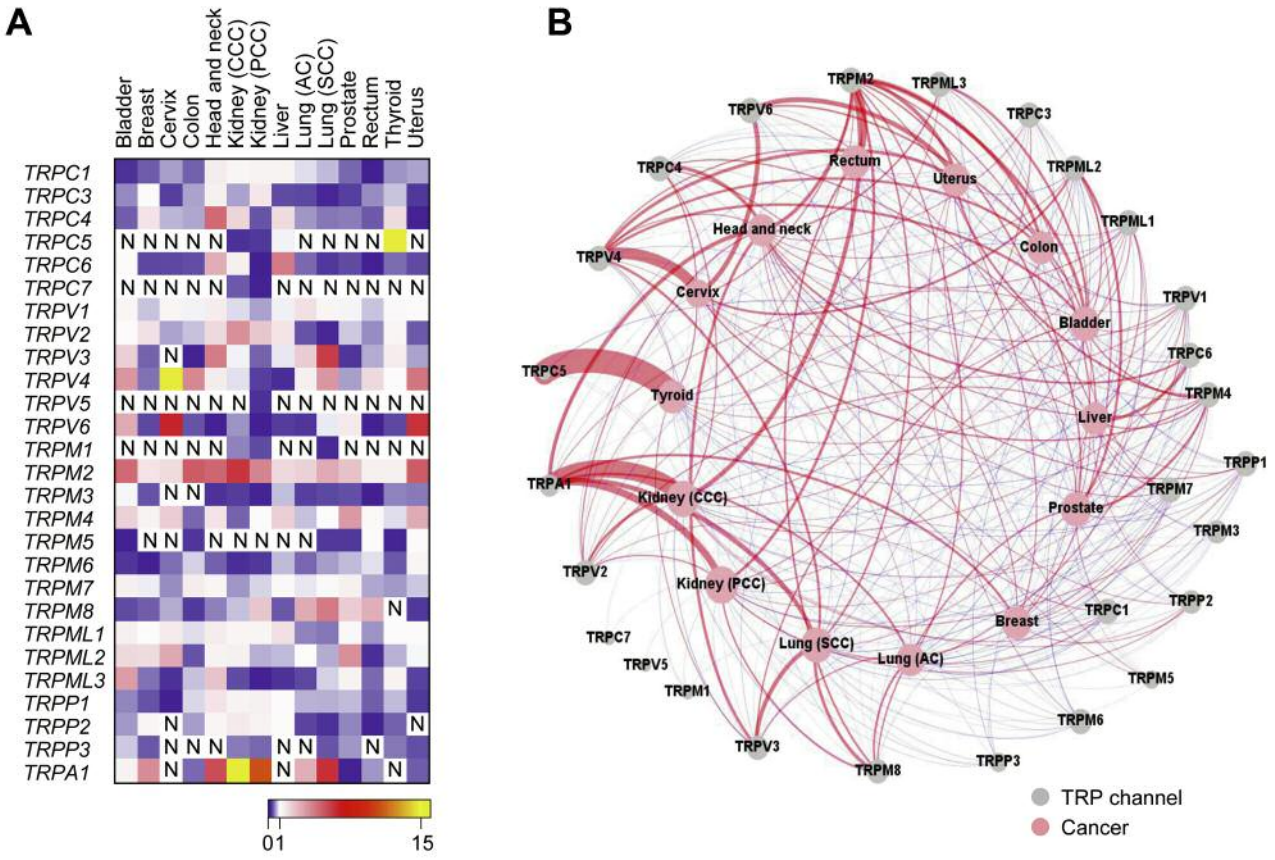

Figure 1. *Altered expression of transient receptor potential (TRP) channels in human cancer. A: Heat map representing the median values of expression of TRP channel genes (ratio of cancer to normal). N: Not available. B: Network visualizing the association between TRP channel isotypes (gray nodes) and cancer types (pale red nodes). Line colors represent up (red)- or down (blue)-regulation of TRP channel genes and line width indicates their expression levels in cancer. CCC, Clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma; TRPC, transient receptor potential channels canonical; TRPV, transient receptor potential channels vanilloid; TRPM, transient receptor potential channels melastatin; TRPML, transient receptor potential channels mucolipin; TRPP, transient receptor potential channels polycystin; TRPA, transient receptor potential channels ankyrin.*

Table II. *Clinical information of 552 tumor-normal matched samples in the International Cancer Genome Consortium data.*

Cancer type	Diagnosis (ICD-10)	Number of patients	Age (mean±SD), years	Gender		Vital status	
				F	M	A	D
Bladder	C67	16	69.5±10.51	7	9	9	7
Breast	C50	107	56.91±14.70	106	1	70	37
Cervix	C53	3	54.33±11.44	3	0	2	1
Colon	C18	23	68.65±12.86	8	15	17	6
Head and neck	C14, C02, C32, C04, C01	39	62.56±13.23	12	27	8	31
Kidney (PCC)	C64	100	62.37±12.72	30	70	72	28
Liver	C22	46	61.63±15.62	20	26	18	28
Lung (AC)	C34	54	66.14±11.04	31	23	32	22
Lung (SCC)	C34	44	68.52±8.627	11	33	20	24
Prostate	C61	38	61.78±6.669	0	38	38	0
Rectum	C20	5	75.2±13.87	4	1	5	0
Thyroid	C73	53	44.50±17.02	37	16	50	3
Uterus	C54	22	59.04±11.98	0	22	21	1

ICD-10, International Classification of Diseases 10th Edition; F, female; M, male; A, alive; D, deceased; CCC, clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma.

Table III. *Alterations in the gene expression of transient receptor potential (TRP) channels in cancer. The data are expressed as median values (cancer-to-normal ratios).*

Gene	Bladder	Breast	Cervix	Colon	Head and neck	Kidney (CCC[#])	Kidney (PCC[#])	Liver	Lung (AC[#])	Lung (SCC[#])	Prostate	Rectum	Thyroid	Uterus
TRPC1	0.237	0.423	0.664	0.444	1.573	1.318	1.388	1.446	0.888	0.758	0.461	0.129	0.619	0.685
TRPC3	0.577	1.170	0.298	0.674	1.474	0.668	1.733	0.353	0.343	0.190	0.298	0.595	0.788	0.270
TRPC4	0.425	1.835	0.742	0.694	5.896	2.278	0.392	2.169	0.629	0.520	0.539	0.412	2.178	0.161
TRPC5	N.D.	N.D.	N.D.	N.D.	N.D.	0.230	0.263	0.964	N.D.	N.D.	N.D.	N.D.	38.695	N.D.
TRPC6	1.133	0.333	0.336	0.359	3.566	1.496	0.129	5.337	0.472	0.265	0.349	0.133	0.478	0.344
TRPC7	N.D.	N.D.	N.D.	N.D.	N.D.	0.413	0.157	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
TRPV1	1.319	0.796	1.283	0.968	1.597	0.869	0.673	0.958	1.955	1.280	0.970	0.789	1.253	1.171
TRPV2	1.179	1.982	0.678	0.784	2.227	4.629	2.770	1.878	0.377	0.182	0.818	0.589	1.312	0.413
TRPV3	2.499	0.449	N.D.	0.165	5.270	0.967	0.447	0.928	2.581	7.434	0.259	0.712	1.613	0.674
TRPV4	4.296	0.498	18.654	4.888	1.623	0.897	0.297	0.212	1.483	4.339	0.665	2.192	1.119	5.475
TRPV5	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.230	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
TRPV6	3.669	0.338	8.220	0.389	0.155	0.617	0.111	0.287	0.258	0.933	1.646	0.151	0.339	7.649
TRPM1	N.D.	N.D.	N.D.	N.D.	N.D.	0.560	0.346	N.D.	N.D.	0.195	N.D.	N.D.	N.D.	N.D.
TRPM2	5.834	1.884	2.112	6.316	5.937	7.556	4.959	2.216	2.446	3.727	2.969	1.495	1.465	6.313
TRPM3	0.983	0.383	N.D.	N.D.	0.236	0.283	0.174	0.773	0.299	0.342	0.367	0.125	0.563	0.529
TRPM4	2.390	1.426	2.596	0.462	1.828	0.451	1.178	2.528	0.784	0.996	4.215	1.246	0.888	3.665
TRPM5	0.146	N.D.	N.D.	0.254	N.D.	N.D.	N.D.	N.D.	N.D.	0.272	0.266	1.136	0.181	1.175
TRPM6	0.259	0.149	0.485	0.845	0.441	0.213	0.263	0.760	0.462	0.649	0.767	0.898	0.396	1.275
TRPM7	1.525	0.945	0.592	1.557	1.322	0.632	0.854	1.267	0.923	1.269	1.545	0.688	0.644	0.799
TRPM8	0.353	0.432	0.715	0.279	0.553	0.782	2.794	0.396	3.644	5.353	2.594	3.465	N.D.	0.272
TRPML1	1.543	0.995	1.711	0.884	1.574	1.314	1.349	1.984	0.559	0.517	1.230	0.624	1.143	1.164
TRPML2	2.234	2.159	3.755	0.380	1.439	1.514	0.722	0.767	0.994	0.715	4.623	0.216	0.729	0.980
TRPML3	4.173	0.497	0.232	0.784	2.863	0.351	0.146	0.241	0.335	0.846	1.424	0.472	1.429	0.311
TRPP1	0.567	0.378	0.120	0.862	1.869	1.453	1.511	1.143	0.728	0.723	0.765	0.428	0.762	0.272
TRPP2	0.643	1.338	N.D.	0.653	1.295	1.681	1.452	1.145	0.320	0.226	0.567	0.158	0.438	N.D.
TRPP3	0.817	0.396	N.D.	N.D.	N.D.	0.527	0.462	N.D.	N.D.	0.389	0.636	N.D.	0.524	0.365
TRPA1	1.412	4.665	N.D.	0.474	6.774	28.740	11.944	N.D.	3.522	7.754	0.153	0.635	N.D.	0.419

[#]N.D., Not determined; CCC, clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma.

cancer (OR=0.572, 0.012 and 0.153, respectively) but an elevated risk for head and neck cancer (OR=1.922).

To assess the effect of the altered expression of TRP channels on clinical outcomes, we performed univariate and multivariate survival analyses for clear cell kidney cancer (survival data are available only for this cancer type) (Figure 2). We divided the patients based on the expression levels of each TRP channel gene (*i.e.* high- and low-expression groups). Kaplan–Meier analysis indicated that the patients with CCC kidney cancer with low expression of TRPC4, *TRPM3, TRPP1*, and *TRPA1* had significantly worse overall survival and higher risk of death than those with high expression (HR=3.754, 3.000, 3.355, and 2.649, respectively; log-rank test p=0.0068, 0.0229, 0.0147, and 0.0437, respectively).

Feasibility of TRP channels as diagnostic and prognostic markers. We also performed ROC analysis to assess the feasibility of TRP channels as diagnostic markers. Our results are summarized in Table V. TRP channels have a strong diagnostic potential for various cancer types, particularly in head and neck, kidney, and lung cancer, in which clinically useful diagnostic markers are not available: overexpression of *TRPC4, TRPM2*, and *TRPM8* might be used as diagnostic markers, in terms of sensitivity and specificity, for cancer of the head and neck cancer, kidney (clear cell carcinoma and papillary cell carcinoma), and lung (adenocarcinoma and squamous cell carcinoma), respectively.

We calculated Harrell's concordance index (c-index) to evaluate the usefulness of TRP channels as prognostic markers. The c-index is defined as the proportion of all patient pairs in which the predictions and outcomes are concordant (15). *TRPC4, TRPM3, TRPP1*, and *TRPA1* for kidney (CCC) cancer had c-indices of 0.636, 0.614, 0.643, and 0.598, respectively (Table VI). When four TRP channels were combined, the c-indices were elevated to 0.710. Therefore, genes for each of these TRP channels or their combination could be used as promising prognostic markers for patients with kidney cancer.

Discussion

Accumulating experimental evidence has suggested that TRP channels play crucial roles in tumor biology (16-20). However,

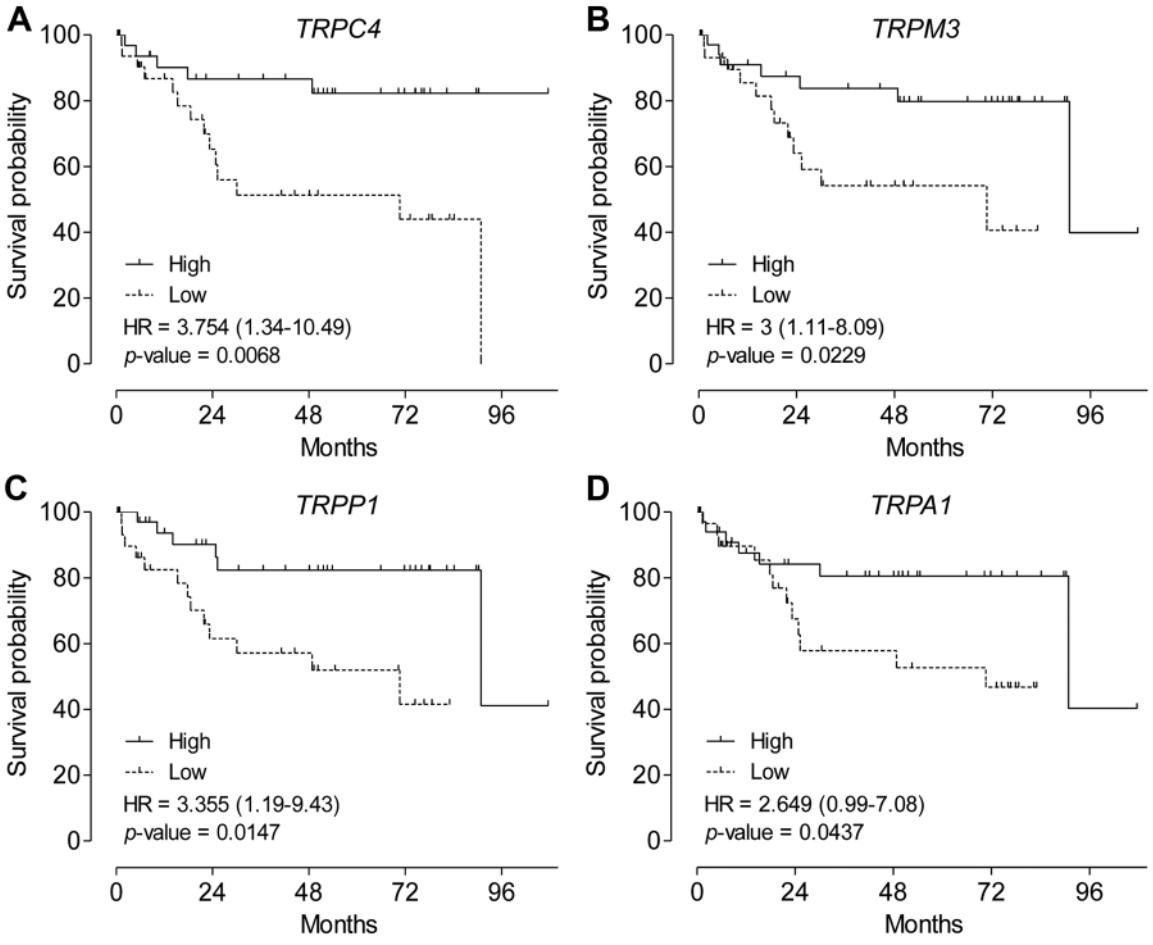

Figure 2. *Survival curve for patients with kidney cancer (clear cell carcinoma) based on the expression levels of transient receptor potential channels canonical 4 (TRPC4; A), TRPM3 (B), transient receptor potential channels polycystin 1 (TRPP1; C), and transient receptor potential channels ankyri 1 (TRPA1; D). HR, Hazard ratio (95% confidence interval).*

the clinical relevance and significance of TRP channels in cancer is poorly understood. In the present study, we applied a data-driven approach to dissecting the expression landscape of 27 TRP channels in 14 human cancer types and to assessing clinical relevance and significance of TRP channels. We found distinct features of variation in the expression of genes for TRP channels according to cancer type. We also show that TRP channels are clinically valuable for cancer diagnosis and prognosis. Our study provides a novel conceptual framework for unraveling the role of TRP channels in cancer biology and clinical oncology.

Our study provides insight into understanding of the role of TRP channels in carcinogenesis. Normal cells evolve into cancer cells through many genetic and epigenetic changes (21, 22). During such somatic evolution processes, many cancerous cells are removed by various host mechanisms and microenvironmental selection. The expression patterns of TRP channel genes in cancer suggest that cancer type-specific TRP channel-mediated Ca^{2+} remodeling mechanisms may play a crucial role in tumor cell survival under the pressure of microenvironmental selection. Changes in TRP channel expression may confer selective growth and survival advantages over internal or external threats to cancerous cells. Our data-driven study will assist future investigations to enlight the molecular mechanisms of TRP channels in tumor evolutionary processes and to develop feasible tests for cancer diagnosis and prognosis. However, TRP signatures depend not only on the level of expression but also on the subcellular localization of the channels. Therefore, the location-specific expression of TRP channels needs to be investigated in future studies.

As far as we know, this study is the first data-driven approach in TRP channel research. We showed that our focused data-driven approach effectively links biological information to clinical and epidemiological knowledge. Our results

Table IV. *Odd ratios (ORs), confidence interval (CI), and p-value between high- and low-expression groups for transient receptor potential (TRP) channel genes and cancer incidence. The table shows nine cancer types, each of which is associated with the overexpression or underexpression of at least one TRP channel at a p-value of multivariate logistic regression of less than 0.01.*

Cancer type	TRP channel	Univariate		Multivariate	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Bladder	*TRPC1*	0.071 (0.201-0.212)	5.24E-06	0.320 (0.055-1.865)	2.05E-01
	TRPC3	0.014 (0.001-0.073)	4.78E-05	0.030 (0.003-0.310)	3.24E-03
	TRPM2	22.432 (5.969-146.429)	6.03E-05	25.205 (3.852-164.935)	7.60E-04
	TRPM3	0.031 (0.005-0.118)	8.46E-06	0.102 (0.014-0.720)	2.21E-02
Breast	*TRPC1*	0.031 (0.018-0.052)	1.44E-37	0.350 (0.152-0.833)	1.52E-02
	TRPC6	0.026 (0.014-0.043)	1.35E-38	0.572 (0.245-1.375)	2.03E-01
	TRPM3	0.008 (0.002-0.019)	7.22E-21	0.062 (0.017-0.180)	2.34E-06
	TRPM6	0.018 (0.008-0.035)	1.06E-26	0.153 (0.057-0.377)	7.66E-05
	TRPP2	0.009 (0.005-0.018)	5.98E-45	0.093 (0.037-0.220)	1.17E-07
Colon	*TRPC6*	0.017 (0.001-0.084)	8.23E-05	0.012 (0.000-0.131)	1.83E-03
	TRPV3	0.017 (0.004-0.053)	2.38E-10	0.176 (0.014-1.788)	1.45E-01
	TRPV4	48.435 (10.002-872.274)	1.61E-04	132.996 (12.146-5555.018)	9.06E-04
	TRPM6	0.004 (0.001-0.014)	1.06E-16	0.038 (0.001-0.436)	1.69E-02
	TRPA1	0.032 (0.005-0.112)	4.36E-06	0.208 (0.013-2.067)	2.01E-01
Head and neck	*TRPC4*	73.479 (21.778-458.661)	5.78E-09	45.134 (4.695-1278.759)	4.91E-03
	TRPC6	24.041 (10.918-58.981)	7.72E-14	1.922 (0.284-14.073)	5.01E-01
	TRPV2	16.505 (6.841-49.198)	1.30E-08	0.384 (0.031-3.882)	4.21E-01
	TRPV6	0.034 (0.008-0.098)	3.65E-08	0.002 (0.000-0.023)	4.52E-05
	TRPM2	18.469 (7.998-50.347)	2.64E-10	42.606 (5.309-996.111)	2.55E-03
	TRPML1	11.375 (5.384-26.355)	1.30E-09	17.288 (2.128-319.562)	1.98E-02
	TRPA1	50.242 (14.978-312.763)	1.02E-07	190.578 (16.273-8781.115)	6.50E-04
Liver	*TRPC4*	10.231 (4.564-25.521)	8.75E-08	6.967 (2.066-27.285)	2.75E-03
	TRPM2	18.931 (6.449-81.063)	2.46E-06	14.260 (3.221-86.199)	1.25E-03
	TRPM4	19.059 (7.566-58.649)	9.07E-09	13.368 (3.738-59.235)	1.90E-04
	TRPML1	39.091 (13.122-169.012)	6.22E-09	27.470 (7.272-145.280)	9.22E-06
Lung (AC)	*TRPC3*	0.051 (0.024-0.098)	2.36E-17	0.030 (0.002-00.185)	1.54E-03
	TRPV2	0.004 (0.001-0.015)	1.69E-13	0.001 (0.000-0.021)	2.08E-05
	TRPM2	19.732 (8.457-57.680)	5.04E-10	389.563 (50.823-9333.400)	1.83E-06
	TRPML1	0.030 (0.013-0.060)	1.70E-20	0.899 (0.093-7.765)	9.23E-01
Lung (SCC)	*TRPC3*	0.004 (0.000-0.017)	3.98E-08	0.006 (0.000-0.103)	4.80E-03
	TRPV3	63.963 (13.735-1139.525)	4.31E-05	N.D.	N.D.
	TRPM2	48.650 (14.664-301.440)	1.11E-07	N.D.	N.D.
	TRPM8	18.321 (9.012-39.952)	1.19E-14	18.443 (2.031-447.029)	2.19E-02
	TRPML1	0.015 (0.006-0.034)	2.27E-20	0.141 (0.004-2.581)	2.00E-01
	TRPP1	0.098 (0.041-0.207)	1.07E-08	0.186 (0.016-1.759)	1.46E-01
	TRPA1	21.065 (9.266-56.865)	2.13E-11	105.116 (10.211-4011.940)	1.17E-03
Prostate	*TRPC1*	0.103 (0.045-0.221)	1.83E-08	2.522 (0.455-16.823)	3.06E-01
	TRPC3	0.060 (0.021-0.143)	3.91E-09	0.108 (0.018-0.498)	7.29E-03
	TRPC6	0.047 (0.011-0.139)	9.58E-07	0.153 (0.016-1.061)	7.31E-02
	TRPC7	0.031 (0.002-0.229)	2.62E-03	N.D.	N.D.
	TRPV3	0.076 (0.029-0.176)	1.41E-08	0.245 (0.045-1.117)	7.81E-02
	TRPM4	79.030 (29.140-250.162)	8.55E-16	28.606 (6.890-156.327)	1.74E-05
	TRPML2	31.473 (11.656-110.501)	7.38E-10	22.159 (5.103-134-669)	1.53E-04
Thyroid	*TRPC4*	51.807 (15.821-319..242)	5.69E-08	135.301 (28.484-1114.237)	6.72E-08
	TRPC5	78.013 (23.744-481.455)	2.20E-09	30.520 (4.992-303.560)	8.76E-04
	TRPM3	0.013 (0.002-0.044)	3.17E-09	0.093 (0.012-0.460)	7.48E-03
	TRPM5	0.041 (0.017-0.086)	1.79E-15	0.083 (0.018-0.315)	5.04E-04
	TRPM6	0.090 (0.036-0.191)	7.44E-09	0.151 (0.030-0.649)	1.45E-02
	TRPM7	0.084 (0.043-0.157)	4.05E-14	0.262 (0.066-0.966)	4.69E-02

CCC, Clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma; N.D., not determined.

demonstrate clinical relevance and significance of TRP channels in human cancer, supporting the previous experiment-driven findings that TRP channels play an important role in cancer development and progression (16, 17, 23, 24). These results imply that further accumulation of information-rich biological data will make substantial progress in answering biological and clinical questions on TRP channels. In addition, the data-driven approach will produce the integrated knowledge on TRP

Table V. *Diagnostic accuracy of transient receptor potential (TRP) channels for detecting cancer. Threshold values were chosen by calculating F1 score based on receiver operating characteristic (ROC) analysis for all combinations of cancer types and TRP channel genes.*

Cancer type	TRP channel	Threshold	AUC (%)	PPV (%)	NPV (%)	Specificity (%)	Sensitivity (%)
Bladder	*TRPM2* ↑	3.34E-06	80.41	98.60	24.14	62.50	69.73
	TRPM4 ↑	2.02E-05	72.23	96.72	15.19	31.25	96.22
	TRPC3 ↓	2.78E-07	93.45	99.35	31.91	50.00	79.46
	TRPM5 ↓	1.19E-08	58.95	94.53	12.33	62.50	62.16
Breast	*TRPM2* ↑	6.46E-06	79.74	98.32	23.26	59.26	71.44
	TRPA1 ↑	6.58E-08	78.75	97.92	21.30	87.96	63.55
	TRPM3 ↓	3.60E-08	95.33	99.50	38.81	77.78	49.33
	TRPM6 ↓	3.45E-07	91.29	99.12	36.59	82.41	87.23
Cervix	*TRPV4* ↑	1.80E-06	99.49	100.00	75.00	100.00	100.00
	TRPP2 ↑	9.65E-09	96.92	100.00	50.00	100.00	75.38
	TRPC4 ↓	1.71E-06	100.00	100.00	100.00	100.00	44.62
	TRPP1 ↓	2.37E-05	100.00	100.00	100.00	100.00	7.69
Colon	*TRPM2* ↑	6.56E-06	86.86	100.00	23.71	60.87	87.41
	TRPV4 ↑	5.77E-07	83.41	99.64	15.07	95.65	12.85
	TRPM6 ↓	8.17E-06	94.51	98.98	70.37	60.87	52.14
	TRPV3 ↓	5.90E-07	92.13	99.16	32.79	73.91	51.13
Head and neck	*TRPC4* ↑	1.13E-07	94.53	99.30	34.58	79.49	86.12
	TRPM2 ↑	2.41E-06	86.38	97.85	29.20	74.36	41.93
	TRPV6 ↓	6.21E-07	85.35	98.81	25.90	94.87	73.09
	TRPM6 ↓	3.33E-07	70.25	98.07	18.92	64.10	75.92
Kidney (CCC)	*TRPM2* ↑	2.02E-06	96.34	99.33	58.97	90.28	88.91
	TRPA1 ↑	2.22E-07	91.87	98.44	54.17	69.44	61.29
	TRPV6 ↓	2.02E-06	98.88	99.80	92.21	91.67	43.35
	TRPC5 ↓	2.55E-08	84.37	95.87	40.91	75.00	84.27
Kidney (PCC)	*TRPM2* ↑	1.45E-06	85.90	95.96	42.86	96.43	91.34
	TRPA1 ↑	1.25E-07	85.36	97.80	40.63	92.86	70.08
	TRPV5 ↓	9.08E-08	99.47	100.00	87.50	85.71	48.82
	TRPV6 ↓	1.74E-06	97.19	100.00	80.00	67.86	67.72
Liver	*TRPC6* ↑	5.55E-08	94.98	100.00	74.19	100.00	5.69
	TRPML1 ↑	1.47E-05	88.59	96.77	56.58	95.65	35.77
	TRPM8 ↓	3.85E-06	79.42	100.00	44.66	69.57	52.85
	TRPV4 ↓	2.13E-06	73.93	98.70	48.91	82.61	68.29
Lung (AC)	*TRPM8* ↑	1.26E-07	91.99	100.00	31.25	96.36	89.62
	TRPM2 ↑	3.82E-06	82.34	98.33	25.13	63.64	74.72
	TRPV2 ↓	2.78E-05	96.98	99.50	53.54	63.64	60.27
	TRPML1 ↓	2.87E-05	90.23	97.74	46.46	80.00	71.11
Lung (SCC)	*TRPM8* ↑	3.18E-08	87.82	96.88	37.08	93.18	89.70
	TRPM2 ↑	6.05E-06	86.26	99.29	25.93	88.64	59.30
	TRPV2 ↓	3.05E-05	99.66	100.00	75.86	100.00	10.30
	TRPC3 ↓	1.83E-07	95.59	99.71	44.33	77.27	54.02
Prostate	*TRPM4* ↑	9.12E-05	93.87	96.45	74.42	36.84	81.61
	TRPML2 ↑	9.10E-07	85.81	97.16	47.89	68.42	48.28
	TRPC6 ↓	8.25E-07	85.13	97.39	36.08	81.58	62.07
	TRPV3 ↓	4.59E-08	83.27	94.89	41.33	92.11	64.37
Rectum	*TRPV4* ↑	2.59E-07	95.52	100.00	26.32	60.00	78.32
	TRPM2 ↑	2.68E-06	91.61	100.00	22.73	100.00	9.79
	TRPM6 ↓	8.62E-06	98.46	100.00	45.45	80.00	88.81
	TRPML2 ↓	6.31E-06	91.47	100.00	14.29	100.00	88.11
Thyroid	*TRPC5* ↑	1.50E-07	85.42	99.45	30.18	88.68	64.72
	TRPC4 ↑	2.87E-07	83.84	99.38	24.52	66.04	68.68
	TRPM3 ↓	1.80E-07	88.54	99.44	29.48	96.23	67.22
	TRPM5 ↓	2.31E-07	88.45	97.98	33.33	60.38	60.96
Uterus	*TRPM2* ↑	4.01E-06	97.01	99.77	42.00	54.55	52.13
	TRPP2 ↑	1.38E-08	77.17	98.02	15.91	63.64	80.00
	TRPP1 ↓	1.88E-05	98.84	100.00	33.85	77.27	57.87
	TRPC1 ↓	4.84E-06	98.73	99.57	76.92	63.64	84.26

AUC, Area under the curve; PPV, positive predictive value; NPV, negative predictive value; CCC, clear cell carcinoma; PCC, papillary cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma; ↑, high expression; ↓, low expression.

Table VI. *Prognostic value of transient receptor potential (TRP) channels in clear cell kidney cancer.*

TRP channel used	c-Index	SE
TRPC4	0.636	0.0617
TRPM3	0.614	0.0615
TRPP1	0.642	0.0619
TRPA1	0.598	0.0617
TRPC4+TRPM3	0.668	0.0686
TRPC4+TRPP1	0.688	0.0687
TRPC4+TRPA1	0.670	0.0689
TRPM3+TRPP1	0.683	0.0690
TRPM3+TRPA1	0.648	0.068
TRPP1+TRPA1	0.678	0.069
TRPC4+TRPM3+TRPP1	0.706	0.071
TRPC4+TRPM3+TRPA1	0.685	0.071
TRPC4+TRPP1+TRPA1	0.706	0.071
TRPM3+TRPP1+TRPA1	0.698	0.071
TRPC4+TRPM3+TRPP1+TRPA1	0.710	0.071

SE, Standard error.

channels from biological and clinical data. Therefore, our efforts may facilitate a new way of future research on TRP channels for unraveling their roles in biology and disease.

Conflicts of Interest

The Authors declare no conflicts of interest.

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