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ORIGINAL ARTICLE

CFTR interactome may impact gastric cancer: an *in silico* system-level co-expression analysis

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ABSTRACT

Background: The cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction is linked to gastrointestinal inflammation and has been implicated in early-onset malignancies. However, its role in gastric cancer remains poorly understood.

Aims: To investigate the *CFTR* interactome and assess its potential functional involvement across different subtypes of gastric cancer.

Methods: We conducted a system-level in silico analysis using data from the Cancer Genome Atlas Stomach Adenocarcinoma (TCGA-STAD). *CFTR* expression and co-expression profiles were examined across molecular and histological subtypes of gastric cancer, including signet-ring cell carcinoma (Lauren's classification). Differential gene expression (DGE) and co-expression analyses were integrated with protein-protein interaction networks, pathway enrichment, and gene ontology (GO) analysis to delineate *CFTR's* functional associations.

Results: *CFTR* did not exhibit significant differential expression across gastric cancer subtypes. However, co-expression analysis identified *CFTR* as a key hub gene with a distinct interaction network, especially prominent in the signet-ring cell carcinoma subtype. Enrichment analyses revealed that *CFTR's* interactome is involved in regulatory pathways related to cellular homeostasis, ion transport, and immune modulation, suggesting a noncanonical yet critical role in tumor biology.

Conclusion: While *CFTR* expression remains stable across gastric cancer subtypes, its interactome reveals significant regulatory roles, particularly in signet-ring cell carcinoma. These findings highlight the potential contribution of *CFTR* to gastric cancer pathogenesis through its involvement in broader molecular networks rather than through expression changes alone.

Keywords: Gene co-expression network, CFTR, gastric cancer subtypes, signet-ring cell carcinoma.

Introduction

In 2022, gastric cancer (GC) held the fifth position globally in terms of incidence and mortality [1]. Early detection and treatment of GC remains limited by our understanding of the molecular mechanisms that drives its heterogeneity [2,3]. Emerging evidence suggests a potential role for the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, in the development of various cancers, including GC [4-8]. Moreover, the precise biological role of *CFTR* in GC remains unclear. *CFTR* mutations, particularly the ΔF508 mutation, have been associated with an increased risk of developing GC [9,10]. Than et al. experimentally identified *CFTR* as a tumor suppressor gene in the intestinal tract; otherwise, its knockout caused high rates of tumors in both colon and small intestine in human and murine models [11]. Collobert et al. emphasize the importance

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of understanding the cis-regulatory elements that control the expression of the *CFTR* gene, as this knowledge could lead to novel therapeutic strategies aimed at modulating the activity of *CFTR* in GC [12].

Previous research has predominantly explored the effects of the *CFTR* gene in isolation, with limited attention to its system-level co-expression patterns or interactome in the context of GC subtypes. Here, we investigated

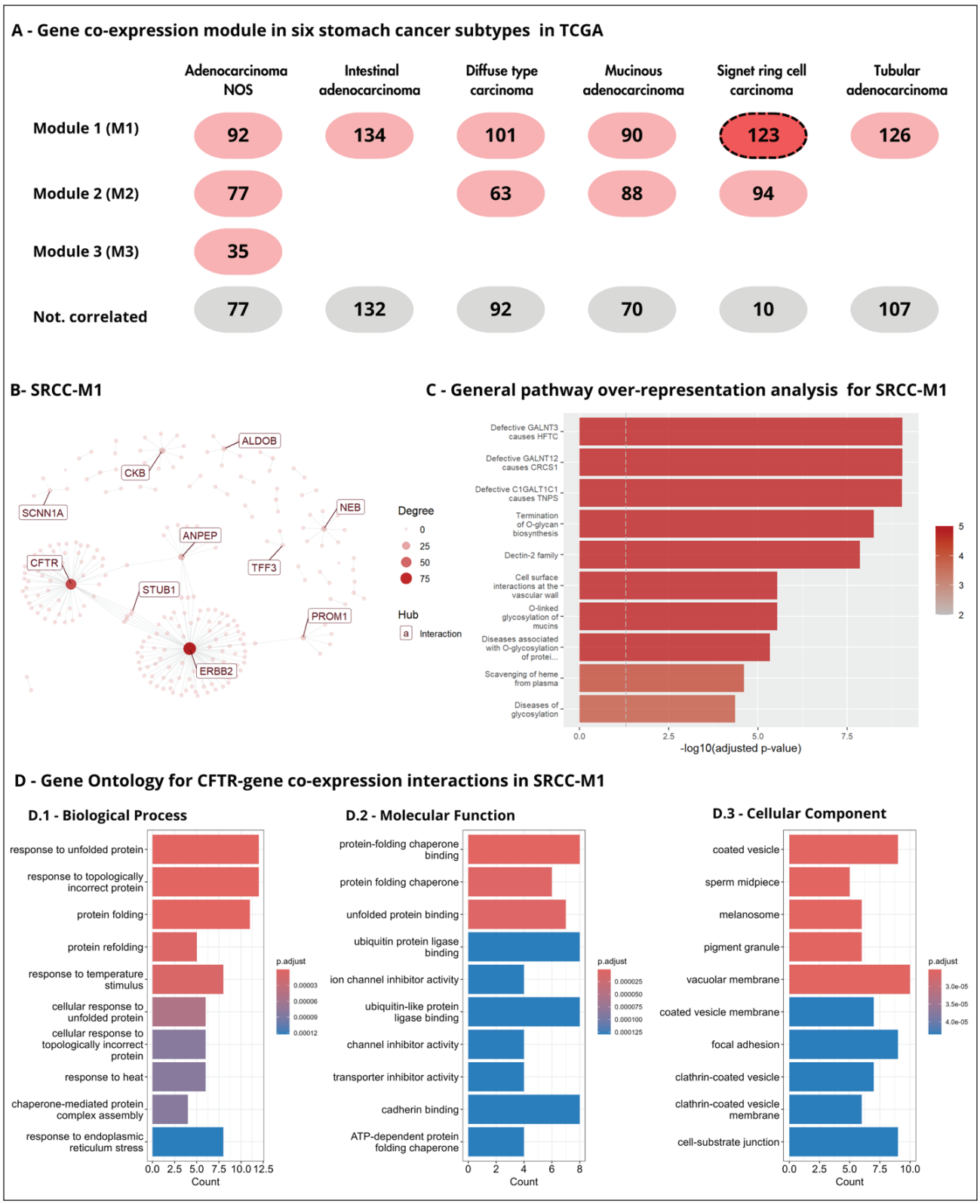

Figure 1. *CEMiTool gene co-expression results. A) Gene co-expression module detection for each TCGA-STAD subtype. The red circle with dot lines represents the module where the CFTR was found. B) Visualization of Module 1 in the signet ring cell carcinoma (SRCC-M1) subtype. C) Over-representation pathway in Module 1. D) Gene Ontology enrichment analysis of CFTR co-expressed genes in Module 1 for the SRCC subtype.*

the differential expression of *CFTR* across distinct GC subtypes, as well as its co-expression profiles and interaction networks within clinical classifications. Using systems biology approaches and comprehensive co-expression analysis, we identified distinct gene modules where *CFTR* emerges as a central interactor, providing novel insights into its functional relevance within the molecular architecture of GC.

Methods and Results

Molecular heterogeneity in TCGA-STAD subtypes

We analyzed the differential expression of 19,932 transcripts across the six TCGA-STAD subtypes, and in Lauren's clinical classification (Material and Methods in Supplementary Material and Supplementary Tables 1, 2). We observed that *CFTR* is not differentially expressed between the TCGA-STAD subtypes or even in Lauren subtypes (Supplementary Table 3).

CFTR-interactome is co-expressed in signet ring cell carcinoma in the TCGA-STAD classification

Co-expressed gene modules were identified for each TCGA-STAD subtype comparison (Figure 1). Notably, *CFTR* was identified as being co-expressed exclusively in Module 1 of the SRCC subtype (SRCC-M1), which comprises 123 genes (Figure 1A). *CFTR* is also classified as a hub gene and is co-expressed with 58 genes in the interaction network, supported by experimental studies cataloged for constructing the PPI network (Figure 1B). Over-representation pathway results for the SRCC-M1 module revealed statistical enrichment for pathways associated with glycosylation and protein modification defects, including the termination of O-glycan biosynthesis, dectin-2 family signaling, O-linked glycosylation of mucins, and diseases associated with protein glycosylation (Figure 1C). Biological processes enriched in the SRCC-M1 module are strongly linked to protein quality control, including responses to unfolded and topologically incorrect proteins. Molecular functions enriched in this module include protein-folding chaperone

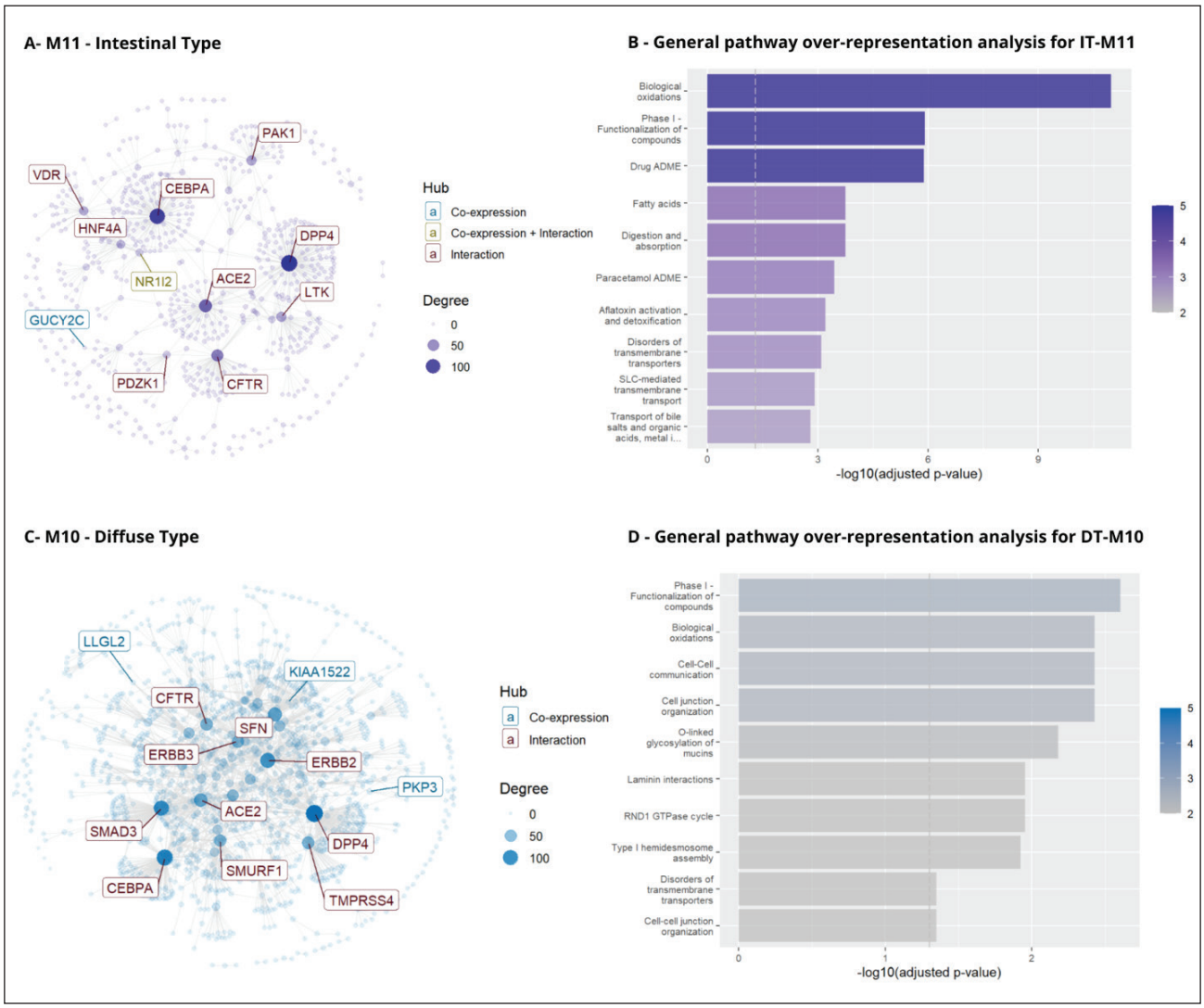

Figure 2*. CEMiTool gene co-expression results for Lauren's clinical classification. A) Module 11 in the intestinal type. B) Over-representation pathway analysis in Module 11 from Intestinal Type (IT). C) Module 10 in the Diffuse Type (DT). D) Over-representation pathway analysis in Module 10 from Diffuse Type (DT).*

binding, unfolded protein binding, ion channel, and transporter inhibition. Furthermore, cellular component analysis identified enrichment in structures involved in vesicular trafficking (Figure 1D.1-D.3).

CFTR-interactome in Lauren's classification for gastric cancer

CFTR is found co-expressed in module 11 of the intestinal type (IT-M11), which hosts 328 genes (Figure 2A). In the diffuse type, *CFTR* is found in module 10 (DT-M10) that comprises 557 genes (Figure 2C). The *CFTR* is co-expressed with 58 genes in both IT-M11 and DT-M10, similar to SRCC-M1 (Supplementary Table 4). As a result, the findings from the gene ontology analyses showed the same pathways (Figure 2B and 2D). ORA results for the DT-M10 module include cell signaling, cell-cell communication, junction and organization, and glycosylation processes.

Discussions

Single mutations and protein dysfunction of *CFTR* have been pointed to be a risk factor for gastrointestinal cancers [6-8, 10]. At the system level, we examined the differential expression and co-expression profiles of *CFTR* across TCGA-STAD subtypes and based on Lauren's classification for GC. We identified a distinct gene module associated with CFTR in SRCC samples, which are largely encompassed within the DT type in Lauren's classification. The CFTR-interactome includes 58 co-expressed genes with experimentally validated interactions. Notably, these genes exhibit consistent co-expression with *CFTR* across both the IT and DT subtypes. While IT and DT differ histologically, the convergence of *CFTR*-associated gene activity in both suggests a potential role of shared regulatory mechanisms rather than merely overlapping interactors. This convergence may contribute to reduced transcriptomic heterogeneity and positions *CFTR* as a promising therapeutic target across subtypes. However, we note that while Lauren's classification supports this distinction, such subtype-specific observations were not conclusively established in the STAD-TCGA dataset, underscoring the need for further validation.

Pathway analysis and gene ontology revealed several pathways enrichment, biological processes, and molecular functions for SRCC-M1. Functional enrichment was prominent for glycosylation-related processes in GC. Glycosylation is essential for the proper CFTR protein maturation and localization, stabilizing it on the plasma membrane, regulating endocytosis rates, and is vital for preserving channel function over time [13]. Aberrant glycosylation contributes to tumor development by disrupting cell signaling, enabling immune evasion, and causing atypical glycan expression in normal tissues [14-16].

Biological processes related to the response to misfolded proteins and the regulation of protein folding are closely linked to cancer. When CFTR fails to fold correctly, as in the case of the common ΔF508 mutation, it accumulates in the endoplasmic reticulum, causing stress to this cellular compartment. This condition activates the unfolded protein response (UPR), a mechanism to restore cellular homeostasis. In cancer cells, the UPR can support cell survival under stress but may also trigger apoptosis if the stress becomes excessive [17]. Cancer cells often exploit this pathway to evade programmed cell death, enabling uncontrolled proliferation. Additionally, cancer cells frequently exhibit alterations in various signaling pathways that regulate the cell cycle and apoptosis, such as the PI3K-Akt pathway [18, 19]. *CFTR* dysfunction can modulate the activity of signaling pathways such as PI3K-Akt and MAPK, which are involved in cell proliferation and survival [9, 19] and may interact in cell cycle regulation and apoptosis [8].

Cellular component enrichment analysis showed an enrichment of structures involved in vesicular trafficking in the SRCC. This finding is consistent with the single-cell analysis by Zhao et al., which showed that SRCC cells exhibit decreased cell adhesion, which may facilitate metastasis [3]. A key feature of DT is the loss of cell adhesion, facilitating the migration and invasion of cancer cells into adjacent tissues [20]. Cell signaling pathways were prominent in the DT-M11 module, reflecting uncontrolled proliferation and apoptosis evasion, which drive oncogenesis through hyperactivation of pro-tumor signaling [21].

Although *CFTR* expression remains stable across GC subtypes, its interactome demonstrates significant regulatory activity, particularly in SRCC. These findings indicate that *CFTR* may influence tumor behavior through its integration in key molecular pathways, independent of expression levels. This suggests a potential role for *CFTR* as a functional biomarker or therapeutic target, especially in subtypes with limited prognostic or treatment options, supporting its clinical relevance in GC stratification and management.

Our study is based entirely on in silico analyses, which, while powerful for generating hypotheses, cannot fully capture the complexity of in vivo biological systems. TCGA datasets may introduce potential biases due to sample representation across cancer subtypes. These factors may affect robustness of our findings. Additionally, we acknowledge the experimental validation to confirm the functional significance of the predicted *CFTR* interactions and their downstream effects.

Conclusion

We found that CFTR-interactome may play a pivotal role in tumor biology by influencing the activity of co-expressed genes in signet ring cell carcinoma, and in Lauren's subtype classification, DT and IT types. These findings suggest that *CFTR* and its interactions contributes to cancer progression at the system level, highlighting its potential as a key modulator of pathway dynamics in GC.

List of abbreviations

AC-NOS	Adenocarcinoma not otherwise specified
DC	Diffuse type carcinoma
DT	Diffuse type
GC	Gastric cancer
GCN	Gene co-expression network

IA	Intestinal adenocarcinoma
IT	Intestinal type
MA	Mucinous adenocarcinoma
SRCC	Signet ring cell carcinoma
TA	Tubular adenocarcinoma
UPR	Unfolded protein response

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Conflict of interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for participation
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Ethical approval
Not applicable.

Author contributions
All authors have read and agreed to the published version of the manuscript. Camila Sinimbú Forte: Software, Formal analysis, Investigation, Methodology, Writing - Original draft preparation; Amanda Ferreira Vidal: Writing - Review and Editing; Pablo Diego do Carmo Pinto: Writing - Review and Editing; Gilderlanio Santana de Araújo: Conceptualization, Formal analysis, Methodology, Writing - Original draft, Writing - Review and Editing, Supervision and Project administration.

Data availability
All next-generation sequencing data can be downloaded TCGABiolink (https://bioconductor.org/packages/release/bioc/html/TCGAbiolinks.html).

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Supplementary Material

Supplementary Table 1. *Sample distribution by gastric cancer subtype, gender, and therapy.*

Samples (N)		
	AC-NOS	154
	IA	79
Stomach Adenocarcinoma Subtype	TA	73
	DC	66
	MA	17
	SRCC	13
Gender	Female	146
	Male	264
Pharmaceutic therapy	No	180
	Not reported	43
Radiation therapy	Yes	187
	No	293
	Not reported	39
	Yes	78

Supplementary Table 2. *Number of differential expressed genes between gastric cancer subtypes.*

GC subtypes	Downregulated	Upregulated
IA x AC-NOS	269	323
IA x MA	803	1503
IA x SRCC	28	274
IA x TA	66	52
AC-NOS x MA	181	621
AC-NOS x SRCC	5	65
AC-NOS x TA	1941	1221
DC x IA	2449	2754
DC x AC-NOS	742	1097
DC x MA	1	23
DC x SRCC	0	9
DC x TA	2715	3040
SRCC x MA	0	0
SRCC x TA	347	20
TA x MA	1535	1035

Supplementary Table 3. *CFTR differential expression across cancer subtypes.*

GC subtype comparison	logFC	logCPM	LR	PValue	FDR
IA x AC-NOS	−0.409398844	5.897554506	2.659509444	0.102932475	0.395321944
IA x MA	−0.630251909	6.093556777	1.657396598	0.197955197	0.448318444
IA x SRCC	−0.839613295	6.120387237	2.113141998	0.1460392	0.536723791
IA x TA	0.157495399	6.22094543	0.282459633	0.595093599	0.910663028
AC-NOS x MA	−0.047149198	5.695396682	0.009438367	0.922606275	0.982430555
AC-NOS x SRCC	−0.533033943	5.708331706	0.947719736	0.330300399	0.866940061
AC-NOS x TA	0.678384281	5.913692851	6.918452271	0.008531078	0.052643123
DC x IA	−0.369814438	5.994617951	1.403934055	0.236065991	0.413052745
DC x AC-NOS	0.176246766	5.711767194	0.405116084	0.524458856	0.751540233
DC x MA	−0.113897304	5.684288315	0.045212479	0.831613805	0.999160178
DC x SRCC	−0.388583245	5.697880848	0.388989139	0.532831232	1
DC x TA	0.541209778	6.020233795	3.079380275	0.079290733	0.186264388
SRCC x MA	−0.248120812	5.563251832	0.083362685	0.772791088	0.999985068
SRCC x TA	0.681746318	6.175103141	1.456056929	0.227558548	0.698077473
TA x MA	0.780575159	6.137801685	2.315979099	0.128050649	0.353607609
IT x DT	−0.4210756	6.028201	1.924078	0.1654078	0.3249337

Supplementary Table 4. *CFTR gene network by CEMiTool.*

#	GENE 1	GENE 2
1	CFTR	COMMD1
2	CFTR	HSPA8
3	CFTR	MARCH2
4	CFTR	PDZK1
5	CFTR	PRKAA1
6	CFTR	SLC9A3R1
7	CFTR	STUB1
8	CFTR	STX1A
9	CFTR	VIMP
10	CFTR	EZR
11	CFTR	HSP90AA1
12	CFTR	ABCC11
13	CFTR	AHSA1
14	CFTR	AMFR
15	CFTR	CALM2
16	CFTR	CAC-NOSX
17	CFTR	CAP1
18	CFTR	CAPZB
19	CFTR	CLIC1
20	CFTR	COPG1
21	CFTR	DAB2
22	CFTR	DERL1
23	CFTR	DNAJA1
24	CFTR	DNAJB1
25	CFTR	DNAJC5
26	CFTR	DRG1
27	CFTR	DSTN
28	CFTR	FHL2
29	CFTR	GLTSCR2
30	CFTR	GNAS
31	CFTR	GNB2
32	CFTR	GOPC
33	CFTR	HSPA4
34	CFTR	HSPB1
35	CFTR	HSPD1
36	CFTR	KRT13
37	CFTR	KRT31
38	CFTR	MCCC2
39	CFTR	MYO6
40	CFTR	NRIP3
41	CFTR	PDIA3
42	CFTR	PSMD4
43	CFTR	RAB5A
44	CFTR	SDHA
45	CFTR	SLC9A3R2
46	CFTR	SNAP23
47	CFTR	SQSTM1
48	CFTR	STAU1
49	CFTR	TFG
50	CFTR	TMEM40
51	CFTR	TRAFD1
52	CFTR	TRIM5
53	CFTR	USP10
54	CFTR	VAPA
55	CFTR	VAPB
56	CFTR	VCP
57	CFTR	VDAC2
58	CFTR	VPS4A