Integrated Multiomics Analysis Identifies Defective CoQ10 Interactome in Human Kidney Cancers

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Gregory M. Miller[1], Nischal Mahaveer Chand[1], Catarina M. Quinzii[2], Brian Berman[1, 4], Vijay Modur[1], Vivek K. Vishnudas[1], Viatcheslav Akmaev[1], Niven R. Narain[1, 3,4], Stephane Gesta[1], Michael A. Kiebish[1]

[1]BPGbio, Waltham, MA USA, [2]Columbia University, New York, NY USA, [3]Department of Molecular Biology, University of Miami Miller School of Medicine, Miami, FL USA

[4]Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL USA

INTRODUCTION

Defective energy metabolism has been established as a hallmark of cancer, however, the specific genetic basis underlying this relationship across cancers remains unclear. Ubiquinone (CoQ10) plays an essential role in generation of mitochondrial ATP and regulating synthesis of reactive oxygen species levels along with regulating several other enzyme activities (Figure 1). Multi-omics assessment of the CoQ10 biosynthesis pathway genes in The Cancer Genome Atlas Program (TCGA) revealed Kidney Clear Cell Carcinoma (KIRC) and Kidney Papillary renal cell carcinoma (KIRP) as cancers that demonstrated a significant relationship between poor prognosis and low expression or copy number deletions in the CoQ10 biosynthesis genes. However, the link between deletions and low expression in enzymes known to interact with CoQ10 and poor outcomes remains unknown. Towards this aim, we defined the CoQ10 interactome as a set of 37 protein encoding genes that bind with CoQ10, along with enzymes involved in downstream pathways impacted by CoQ10 homeostasis, based on literature review (Figure 1 and 2). We then investigated this CoQ10 interactome for their association with outcomes for KIRC and KIRP patients in TCGA datasets.

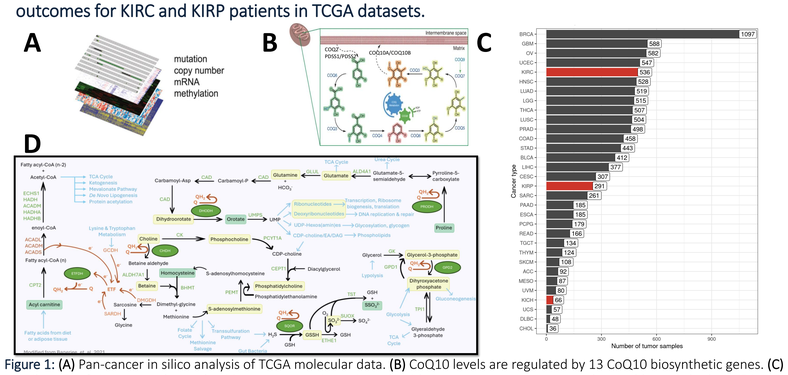

Figure 1: (A) Pan-cancer in silico analysis of TCGA molecular data. (B) CoQ10 levels are regulated by 13 CoQ10 biosynthetic genes. (C) Distribution of tissue samples in the 33 cancer types investigated. Kidney cancer tissue types are denoted by red shading. (D) CoQ Interactome Map. This has been modified from [1]

COQ10 BIOSYNTHESIS GENE DELETIONS IN KIRC AND KIRP AND INTERACTOME GENES

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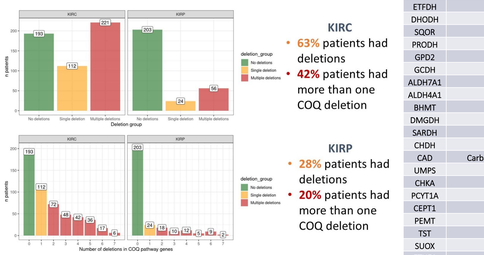
Indication	Gene	Overall Survival HR	Overall Survival q	Progression Free Interval HR	Progression Free Interval q
KIRC					
KIRC	COQ6	1.69 (1.25 - 2.28)	0.01728	1.66 (1.21 - 2.26)	0.03070
KIRC	COQ4	1.76 (1.29 - 2.38)	0.00986	2.66 (1.95 - 3.65)	0.00000
KIRC	COQ2	2.35 (1.64 - 3.37)	0.00034	2.99 (2.08 - 4.31)	0.00000
KIRP					
KIRP	COQ6	3.49 (1.83 - 6.65)	0.00713	3.27 (1.86 - 5.75)	0.00166
KIRP	COQ4	3.27 (1.64 - 6.51)	0.01894	3.68 (1.99 - 6.8)	0.00166
KIRP	COQ2	5.86 (2.97 - 11.58)	0.00005	5.46 (2.95 - 10.1)	0.00000



- **KIRC**
  - **63%** patients had deletions
  - **42%** patients had more than one COQ deletion
- **KIRP**
  - **28%** patients had deletions
  - **20%** patients had more than one COQ deletion

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Symbol	Full Name
ECHS1	Enoyl-CoA Hydratase Short Chain 1
HADH	Hydroxyacyl-CoA Dehydrogenase
ACADM	Acyl-CoA Dehydrogenase Medium Chain
HADHA	Hydroxyacyl-CoA Dehydrogenase Alpha Subunit
HADHB	Hydroxyacyl-CoA Dehydrogenase Beta Subunit
ACADL	Acyl-CoA Dehydrogenase Long Chain
ACADS	Acyl-CoA Dehydrogenase Short Chain
CPT2	Carnitine Palmitoyltransferase 2
ETFDH	Electron Transfer Flavoprotein Dehydrogenase
DHODH	Dihydroorotate Dehydrogenase
SQOR	Sulfide Quinone Oxidoreductase
PRODH	Proline Dehydrogenase
GPD2	Glycerol-3-Phosphate Dehydrogenase 2
GCDH	Glutaryl-CoA Dehydrogenase
ALDH7A1	Aldehyde Dehydrogenase 7 Family Member A1
ALDH4A1	Aldehyde Dehydrogenase 4 Family Member A1
BHMT	Betaine-Homocysteine S-Methyltransferase
DMGDH	Dimethylglycine Dehydrogenase
SARDH	Sarcosine Dehydrogenase
CHDH	Choline Dehydrogenase
CAD	Carbamoyl-Phosphate Synthetase 2 Aspartate Transcarbamylase and Dihydroorotase
UMPS	Uridine 5'-Monophosphate Synthase
CHKA	Choline Kinase
PCYT1A	Phosphate Cytidylyltransferase 1A
CEPT1	Choline/Ethanolamine Phosphotransferase 1
PEMT	Phosphatidylethanolamine N-Methyltransferase
TST	Thiosulfate Sulfurtransferase
SUOX	Sulfite Oxidase
ETHE1	ETHE1 Persulfide Dioxygenase
GK	Glycerol Kinase
GPD1	Glycerol-3-Phosphate Dehydrogenase 1
TPI1	Triosephosphate Isomerase 1
GLUL	Glutamine Synthetase
ETFA	Electron Transfer Flavoprotein Alpha Subunit
ETFB	Electron Transfer Flavoprotein Beta Subunit
PAPSS1	3'-Phosphoadenosine 5'-Phosphosulfate Synthase 1
PAPSS2	3'-Phosphoadenosine 5'-Phosphosulfate Synthase 2

Figure 2: (A) Hazard ratios (HR) and q-values associated with copy number deletion (homozygous or heterozygous) of COQ2, COQ4, or COQ6, in KIRC or KIRP and either overall survival or progression-free interval. (B) 37 genes involved in the interactome were investigated in this work due to their association with CoQ.

COQ10 INTERACTOME GENE EXPRESSION ASSOCIATED WITH PATIENT OUTCOME IN KIRC AND KIRP

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Indication	Gene	Description	Overall Survival HR	Overall Survival q	Progression Free Interval HR	Progression Free Interval q
KIRC						
KIRC	ETFDH	Electron Transfer Flavoprotein Dehydrogenase	0.51 (0.41 - 0.64)	<0.00001	0.42 (0.33 - 0.54)	<0.00001
KIRC	HADH	Hydroxyacyl-CoA Dehydrogenase	0.46 (0.36 - 0.58)	<0.00001	0.48 (0.38 - 0.61)	<0.00001
KIRC	GCDH	Glutaryl-CoA Dehydrogenase	0.55 (0.39 - 0.76)	0.00478	0.45 (0.32 - 0.63)	0.00007
KIRC	CPT2	Carnitine Palmitoyltransferase 2	0.52 (0.44 - 0.62)	<0.00001	0.5 (0.42 - 0.6)	<0.00001
KIRC	ETFA	Electron Transfer Flavoprotein Alpha Subunit	0.56 (0.45 - 0.7)	<0.00001	0.51 (0.41 - 0.64)	<0.00001
KIRC	HADHB	Hydroxyacyl-CoA Dehydrogenase Beta Subunit	0.56 (0.45 - 0.68)	<0.00001	0.57 (0.47 - 0.71)	<0.00001
KIRC	HADHA	Hydroxyacyl-CoA Dehydrogenase Alpha Subunit	0.55 (0.44 - 0.69)	<0.00001	0.61 (0.49 - 0.77)	0.00062
KIRC	DHODH	Dihydroorotate Dehydrogenase	0.6 (0.45 - 0.79)	0.00391	0.58 (0.42 - 0.74)	0.00107
KIRC	SUOX	Sulfite Oxidase	0.62 (0.48 - 0.79)	0.00257	0.58 (0.45 - 0.74)	0.00049
KIRC	ALDH7A1	Aldehyde Dehydrogenase 7 Family Member A1	0.58 (0.47 - 0.71)	<0.00001	0.63 (0.51 - 0.77)	0.00025
KIRC	GK	Glycerol Kinase	0.64 (0.55 - 0.75)	<0.00001	0.59 (0.5 - 0.7)	<0.00001
KIRC	ACADM	Acyl-CoA Dehydrogenase Medium Chain	0.64 (0.57 - 0.72)	<0.00001	0.65 (0.57 - 0.73)	<0.00001
KIRC	ECHS1	Enoyl-CoA Hydratase Short Chain 1	0.66 (0.51 - 0.85)	0.01272	0.64 (0.49 - 0.83)	0.00917
KIRC	GPD2	Glycerol-3-Phosphate Dehydrogenase 2	0.64 (0.53 - 0.78)	0.00010	0.67 (0.55 - 0.82)	0.00115
KIRC	ACADS	Acyl-CoA Dehydrogenase Short Chain	0.66 (0.55 - 0.8)	0.00046	0.66 (0.54 - 0.81)	0.00107
KIRC	CHDH	Choline Dehydrogenase	0.66 (0.58 - 0.76)	<0.00001	0.68 (0.59 - 0.78)	<0.00001
KIRC	CEPT1	Choline/Ethanolamine Phosphotransferase 1	0.68 (0.58 - 0.81)	0.00018	0.66 (0.56 - 0.79)	0.00006
KIRC	ACADL	Acyl-CoA Dehydrogenase Long Chain	0.72 (0.65 - 0.79)	<0.00001	0.67 (0.6 - 0.74)	<0.00001
KIRC	DMGDH	Dimethylglycine Dehydrogenase	0.72 (0.65 - 0.79)	<0.00001	0.74 (0.67 - 0.83)	<0.00001
KIRC	PRODH	Proline Dehydrogenase	0.87 (0.8 - 0.95)	0.01386	0.85 (0.78 - 0.93)	0.00351
KIRC	BHMT	Betaine-Homocysteine S-Methyltransferase	0.86 (0.8 - 0.91)	0.00002	0.88 (0.82 - 0.94)	0.00142
KIRP						
KIRP	GCDH	Glutaryl-CoA Dehydrogenase	0.26 (0.14 - 0.49)	0.00041	0.43 (0.25 - 0.73)	0.01869
KIRP	SUOX	Sulfite Oxidase	0.41 (0.24 - 0.68)	0.00802	0.42 (0.27 - 0.64)	0.00107
KIRP	CHDH	Choline Dehydrogenase	0.62 (0.49 - 0.79)	0.00123	0.68 (0.55 - 0.84)	0.00410

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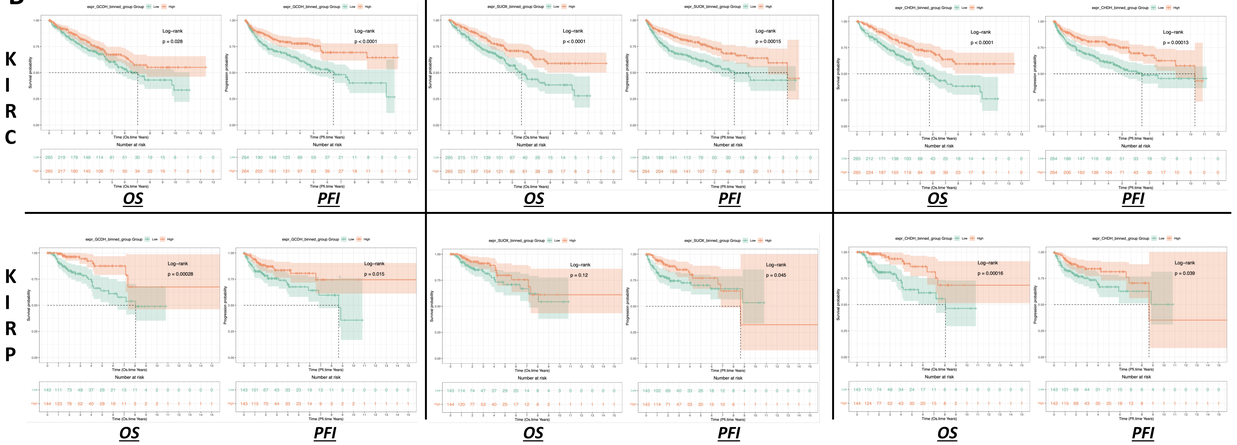

Figure 3: (A) Low expression of CoQ10 Interactome genes associated with worse patient outcome in KIRC and KIRP. Patients with low expression of 21 and 3 CoQ10 Interactome genes were found to have worse outcome in KIRC and KIRP, respectively. (B) Kaplan-Meir curves illustrating the OS and PFI differences between three genes that were found to be low in KIRC and KIRP: *GCDH*, *SUOX*, and *CHDH*.

COQ10 INTERACTOME COPY NUMBER DELETION ASSOCIATED WITH PATIENT OUTCOME IN KIRC AND KIRP

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Indication	Gene	Description	Overall Survival HR	Overall Survival q	Progression Free Interval HR	Progression Free Interval q
KIRC						
KIRC	GCDH	Glutaryl-CoA Dehydrogenase	4.16 (2.19 - 7.91)	0.00053	3.6 (1.83 - 7.08)	0.00279
KIRC	SQOR	Sulfide Quinone Oxidoreductase	2.26 (1.41 - 3.62)	0.01055	3 (1.88 - 4.77)	0.00008
KIRC	PAPSS1	3'-Phosphoadenosine 5'-Phosphosulfate Synthase 1	2.23 (1.57 - 3.17)	0.00042	2.79 (1.96 - 3.98)	<0.00001
KIRC	ETFA	Electron Transfer Flavoprotein Alpha Subunit	2.13 (1.3 - 3.48)	0.02702	2.87 (1.77 - 4.65)	0.00036
KIRC	HADH	Hydroxyacyl-CoA Dehydrogenase	2.18 (1.53 - 3.09)	0.00053	2.72 (1.91 - 3.87)	<0.00001
KIRC	ETFDH	Electron Transfer Flavoprotein Dehydrogenase	1.95 (1.37 - 2.78)	0.00458	2.62 (1.84 - 3.73)	<0.00001
KIRC	TST	Thiosulfate Sulfurtransferase	1.95 (1.25 - 3.06)	0.03370	2.32 (1.47 - 3.68)	0.00425
KIRC	PRODH	Proline Dehydrogenase	2.06 (1.34 - 3.18)	0.01448	2.2 (1.38 - 3.48)	0.00818
KIRC	SARDH	Sarcosine Dehydrogenase	1.64 (1.2 - 2.22)	0.01904	2.55 (1.86 - 3.5)	<0.00001
KIRP						
KIRP	PEMT	Phosphatidylethanolamine N-Methyltransferase	5.69 (2.5 - 12.93)	0.00107	8.21 (4.18 - 16.1)	<0.00001
KIRP	HADH	Hydroxyacyl-CoA Dehydrogenase	5.82 (2.95 - 11.5)	0.00004	5.53 (2.98 - 10.24)	<0.00001
KIRP	PAPSS1	3'-Phosphoadenosine 5'-Phosphosulfate Synthase 1	5.82 (2.95 - 11.5)	0.00004	5.53 (2.98 - 10.24)	<0.00001
KIRP	BHMT	Betaine-Homocysteine S-Methyltransferase	5.79 (2.26 - 14.8)	0.00458	4.91 (1.94 - 12.42)	0.00818
KIRP	DMGDH	Dimethylglycine Dehydrogenase	5.79 (2.26 - 14.8)	0.00458	4.91 (1.94 - 12.42)	0.00818
KIRP	ETFDH	Electron Transfer Flavoprotein Dehydrogenase	5.42 (2.74 - 10.71)	0.00008	4.86 (2.62 - 8.99)	0.00001
KIRP	CHDH	Choline Dehydrogenase	4.18 (2.05 - 8.52)	0.00210	5.03 (2.71 - 9.33)	<0.00001
KIRP	ECHS1	Enoyl-CoA Hydratase Short Chain 1	3.33 (1.48 - 7.49)	0.03411	3.73 (1.82 - 7.68)	0.00425
KIRP	SARDH	Sarcosine Dehydrogenase	3.27 (1.64 - 6.52)	0.01129	3.76 (2.03 - 6.96)	0.00044
KIRP	GK	Glycerol Kinase	3.24 (1.66 - 6.31)	0.00989	3.77 (2.06 - 6.88)	0.00033
KIRP	ALDH4A1	Aldehyde Dehydrogenase 4 Family Member A1	3.47 (1.89 - 6.38)	0.00177	3.14 (1.81 - 5.45)	0.00076
KIRP	PRODH	Proline Dehydrogenase	2.71 (1.46 - 5.02)	0.01866	2.36 (1.35 - 4.11)	0.02385

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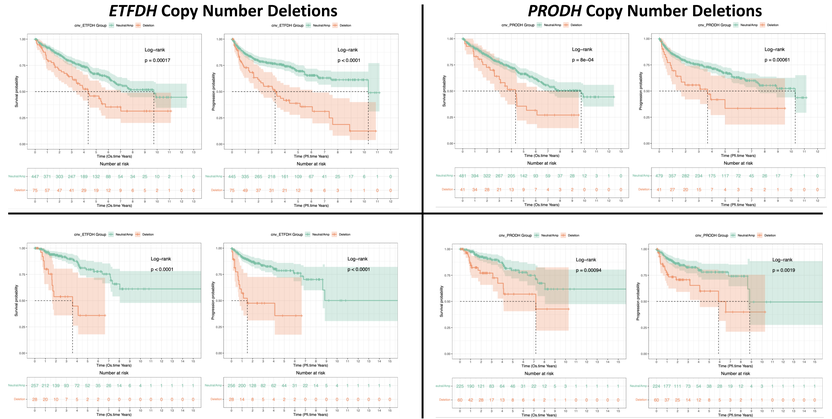

Figure 4: (A) Copy number deletions of CoQ10 interactome genes associated with worse patient outcome in KIRC and KIRP. Patients with copy number deletions in 9, and 12 CoQ interactome genes were found to have worse outcome in KIRC and KIRP, respectively. (B). Kaplan-Meir curves illustrating the OS and PFI differences between two genes that were found have a significant relationship between patient outcome and deletion status in KIRC and KIRP: *ETFDH* and *PRODH*.

RESULTS

- Previous investigation of the 33 indications in the TCGA found KIRC and KIRP as primary cancers that demonstrated poor prognosis for patients with deletions in CoQ10 biosynthesis genes, suggesting that activity of enzymes dependent on CoQ levels might also be impacted.
- By extending this analysis to a broader set of 37 CoQ10 interactome genes, we found that low gene expression in 21 of 37 CoQ10 interactome genes in KIRC, and 3 of 37 CoQ10 interactome genes in KIRP were associated with significantly worse OS and PFI.
- Furthermore, analysis of copy number deletions and their associations with patient outcomes in KIRC and KIRP revealed that deletions in 9 of 37 CoQ10 interactome genes, and 12 of 37 CoQ10 interactome genes were associated with significantly worse OS and PFI in KIRC and KIRP, respectively.
- An overlapping relationship between low expression of three genes (*GCDH*, *SUOX*, and *CHDH*) and worse patient outcomes in both KIRC and KIRP were found; as well as a consistent relationship between copy number deletion of two CoQ10 interactome genes (*ETFDH* and *PRODH*) and worse patient outcomes in these indications.

CONCLUSIONS AND FUTURE DIRECTIONS

- These results demonstrate that CoQ10 and its interactome are significantly impacted in kidney cancer subtypes and deletions or low expression in these key genes are associated with poorer survival outcomes for patients.
- BPM31510 has been shown to deliver supraphysiological concentrations of oxidized CoQ10 to tumors, tumor mitochondria, as well as kidney suggesting that this approach may mitigate the altered metabolic state of cancers that harbor deletions.
- We are actively investigating KIRC and KIRP cell lines that might harbor deletions or alterations in the CoQ biosynthetic pathway or interacting enzymes to further evaluate potential therapeutic benefit of BPM31510 due to these genetic abnormalities.

REFERENCES

1. Banerjee, R., Purhonen, J. and Kallijärvi, J. (2022), The mitochondrial coenzyme Q junction and complex III: biochemistry and pathophysiology. *FEBS J*, 289: 6936-6958. https://doi.org/10.1111/febs.16164