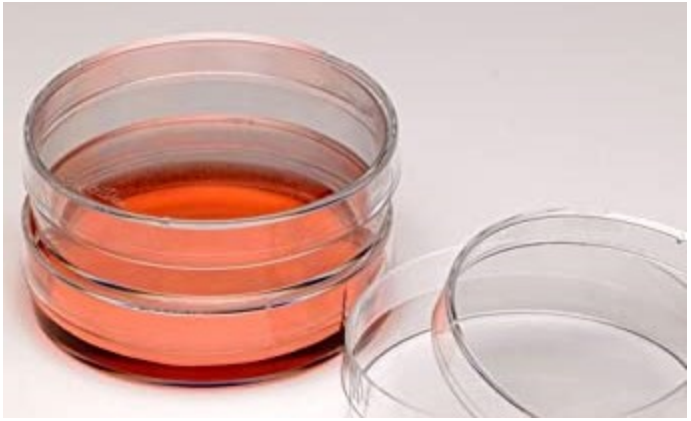
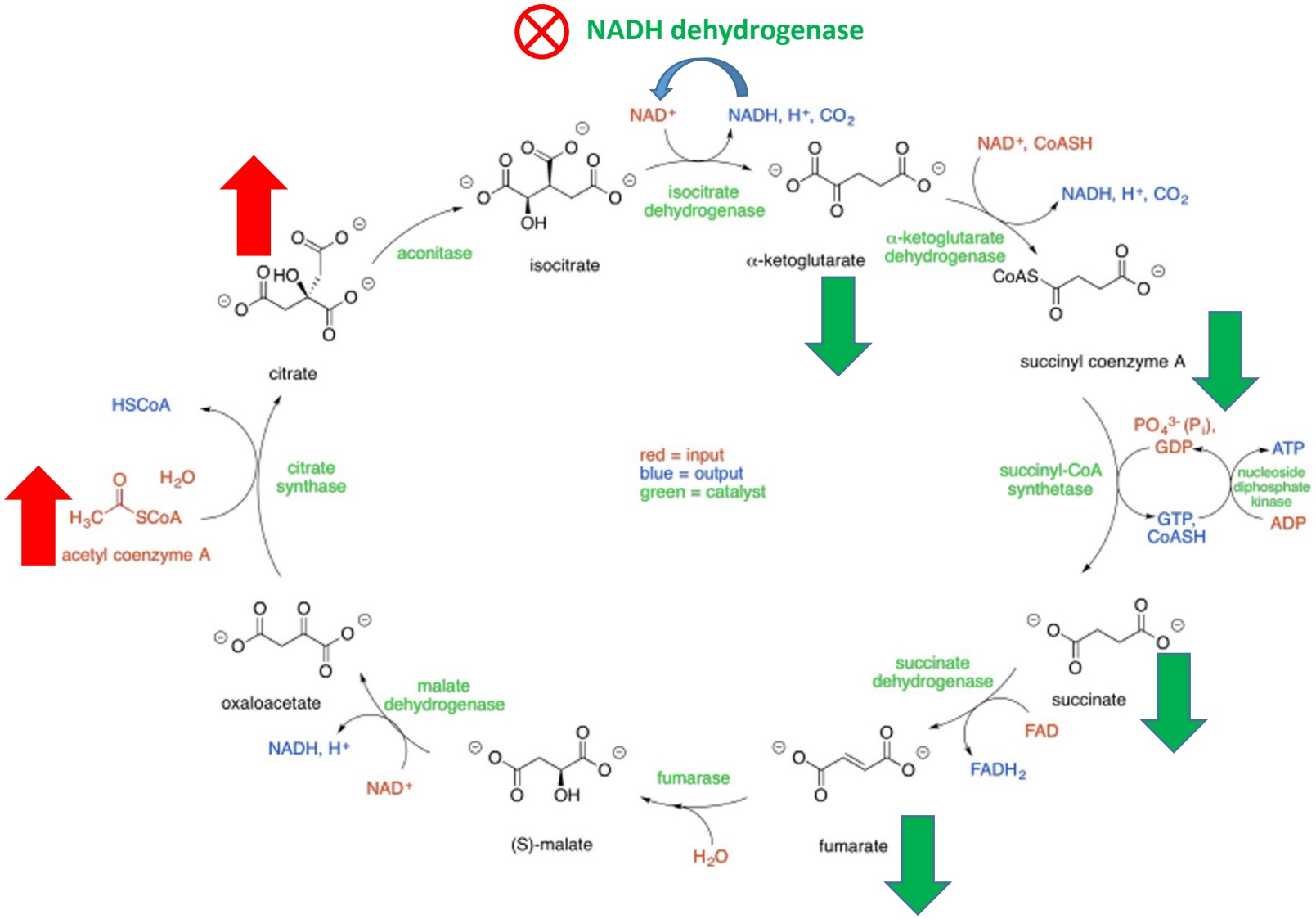
Supplemental Figure 1. Outline of experimental groups of HEK293 Tet-on cell lines

Treatment	Genotype			
	Empty Vector	APOL1	APOL1	APOL1
	EV	G0	G1	G2
Dox (-)	N=3	N=3	N=3	N=3
Dox (+)	N=3	N=3	N=3	N=3

*Cells were grown in 150 mm cell culture dishes. Experiments were done in triplicate.



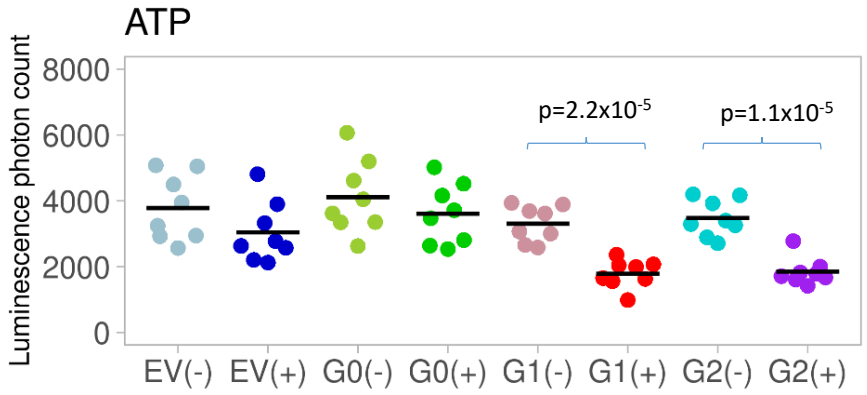


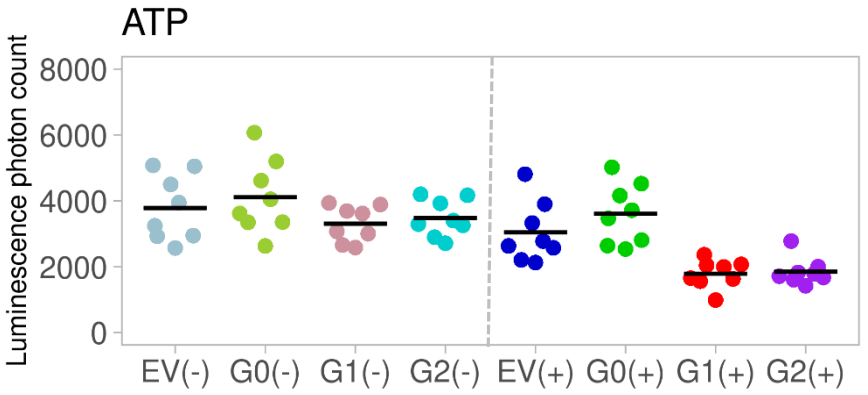
Supplemental Figure 2

Supplemental Figure 2. *APOL1* KRVs alter the TCA cycle. Mild overexpression of *APOL1* G1 and G2 variants altered the pattern of metabolites in the TCA cycle. The altered pattern of metabolites matched deficiency of type I NADH dehydrogenase or mitochondrial complex I. Red arrows refer to increased metabolites and green arrows reflect reduced metabolites, corresponding to those in Figure 1.

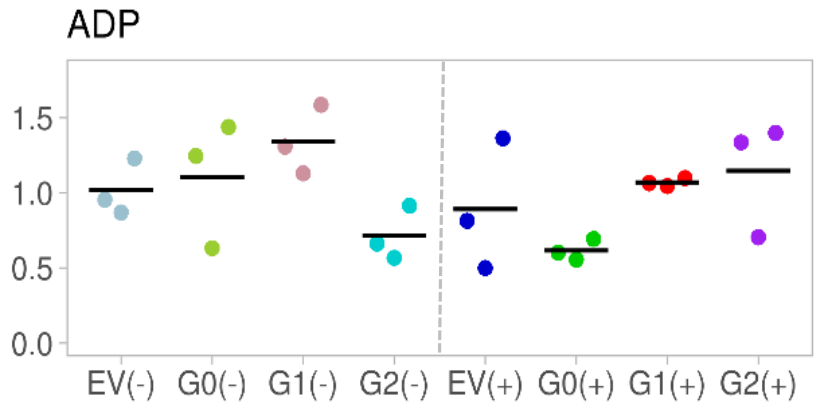
The TCA cycle backbone image is adopted from https://employees.csbsju.edu/cschaller/Reactivity/tcacycle/TCAoverview.html

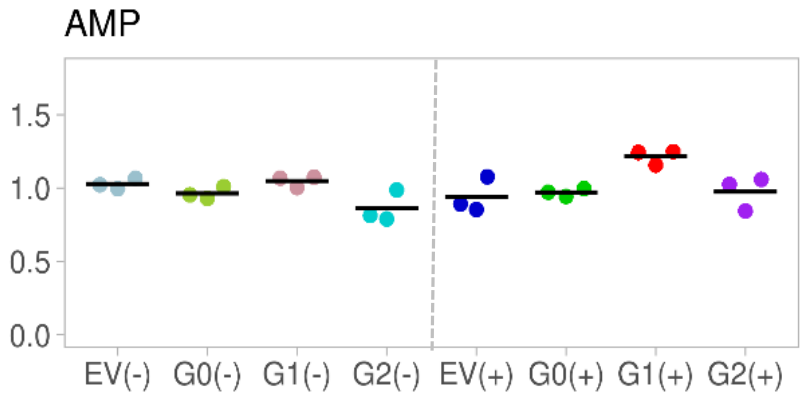
a





b

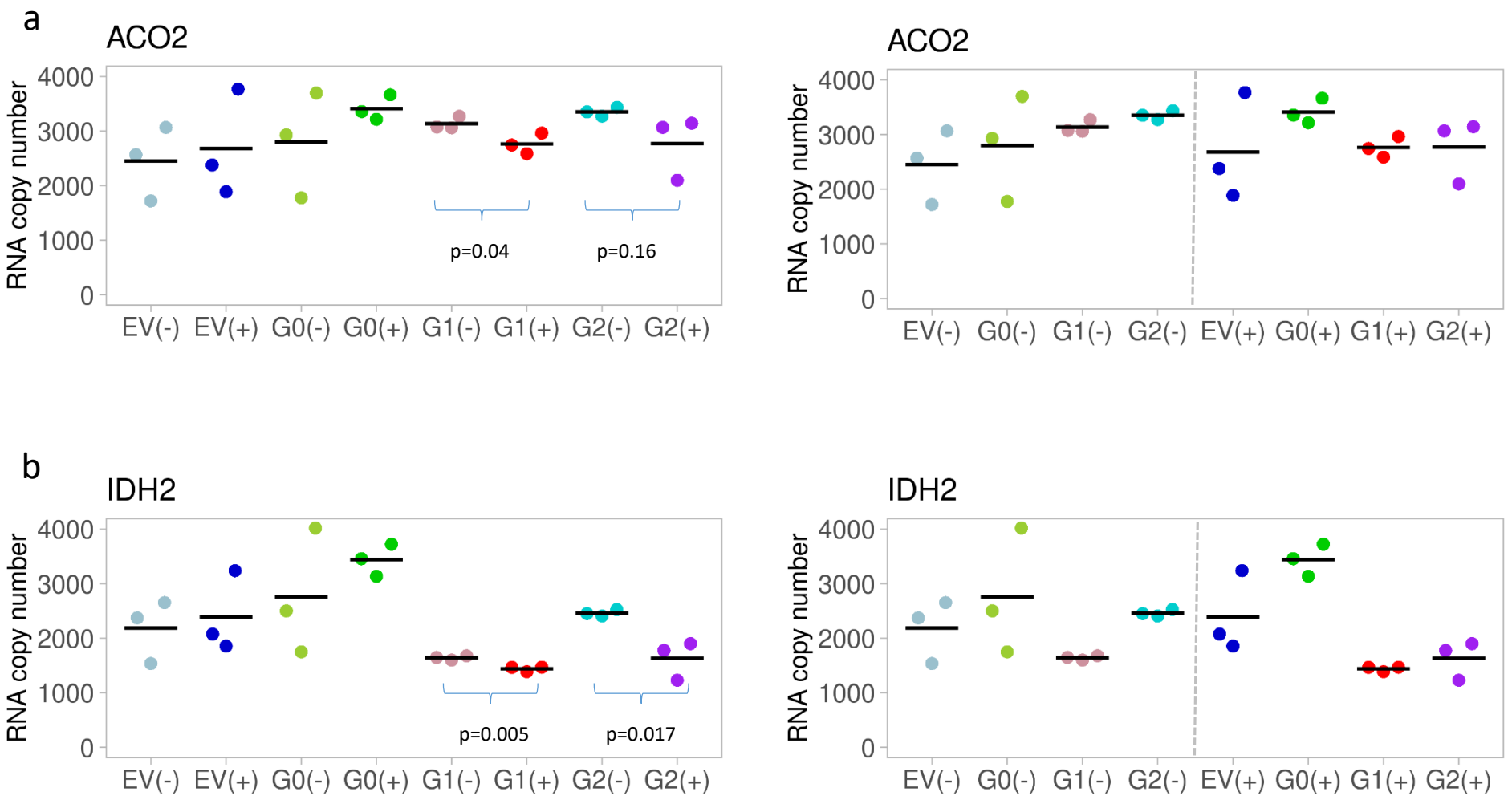




Biochemical Name	Fold of Change (with DOX)	
	G1 WT	G2 WT
adenosine 5'-diphosphate (ADP)	1.73	1.86
adenosine 5'-monophosphate (AMP)	1.25	1.01

Supplemental Figure 3

Supplemental Figure 3. *APOL1* kidney risk variants cause energy depletion. Mild overexpression of *APOL1* G1 and G2 variants a) reduced intracellular ATP content measured by a luminescent ATP detection assay (Abcam, Cat # ab113849) after controlling for the total number of cells in each well (10,000 cells/well when seeded) on a lumox 96-well plate (Sarstedt, Germany), using a BioTek Synergy HTX multi-mode plate reader (BioTek, Winooski, VT); and
b) increased ADP levels in G1 and G2 cells and increased AMP levels in G1 cells. Red indicates significant between-group differences ($p \leq 0.05$), metabolite ratio ≥1.00 (original data from Supplementary Table 3).



Supplemental Figure 4

Supplemental Figure 4. *APOL1* kidney risk variants reduced the transcript levels of *ACO2* and *IDH2.* Mild overexpression of *APOL1* G1 and G2 variants a) reduced *ACO2* (the mitochondrial form of aconitase) by RNA sequencing; b) reduced *IDH2* (the mitochondrial form of isocitrate dehydrogenase) via RNA sequencing.