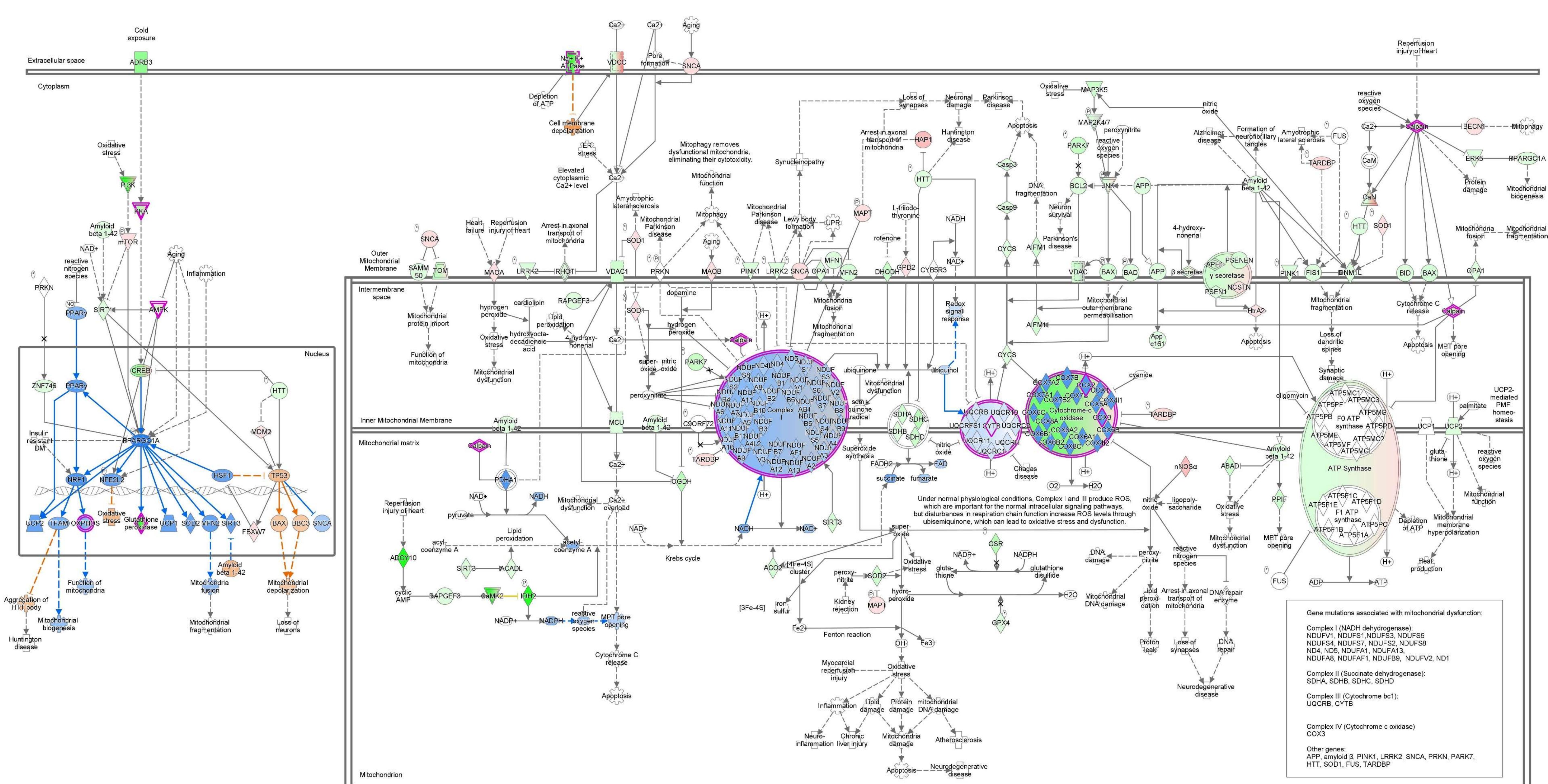
**Figure S1. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway: Chemical Carcinogenesis – DNA adducts.**

A KEGG pathway ‘Chemical Carcinogenesis – DNA adduct’ enriched liver tissues from mice fed fructose water, which was retrieved from transcriptome for KEGG pathway terms.

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes

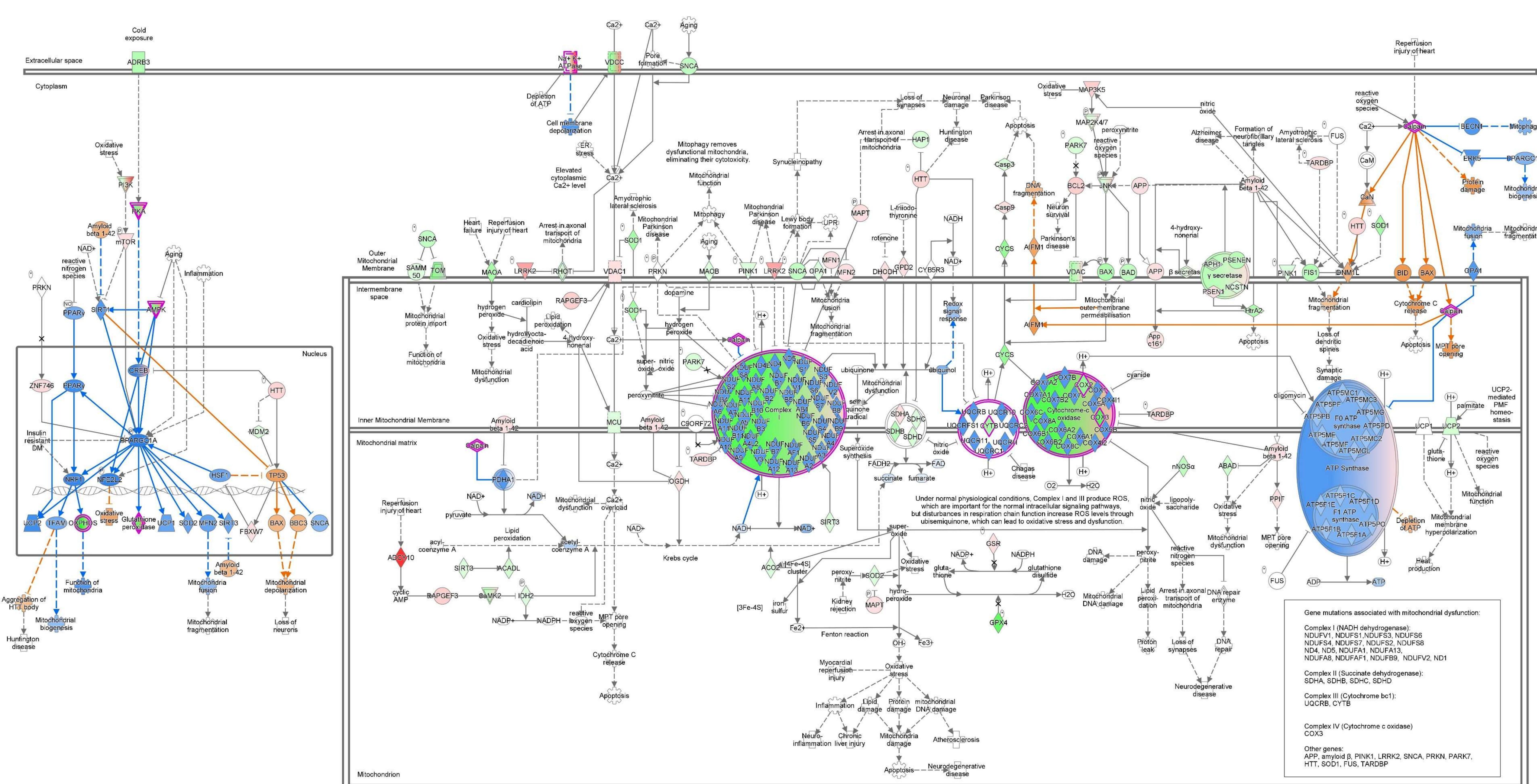


## Figure S2. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics suggests that IDH2 KO-induced mitochondrial dysfunction is linked to the suppression of Complex IV and V in comparison to WT mice.

Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

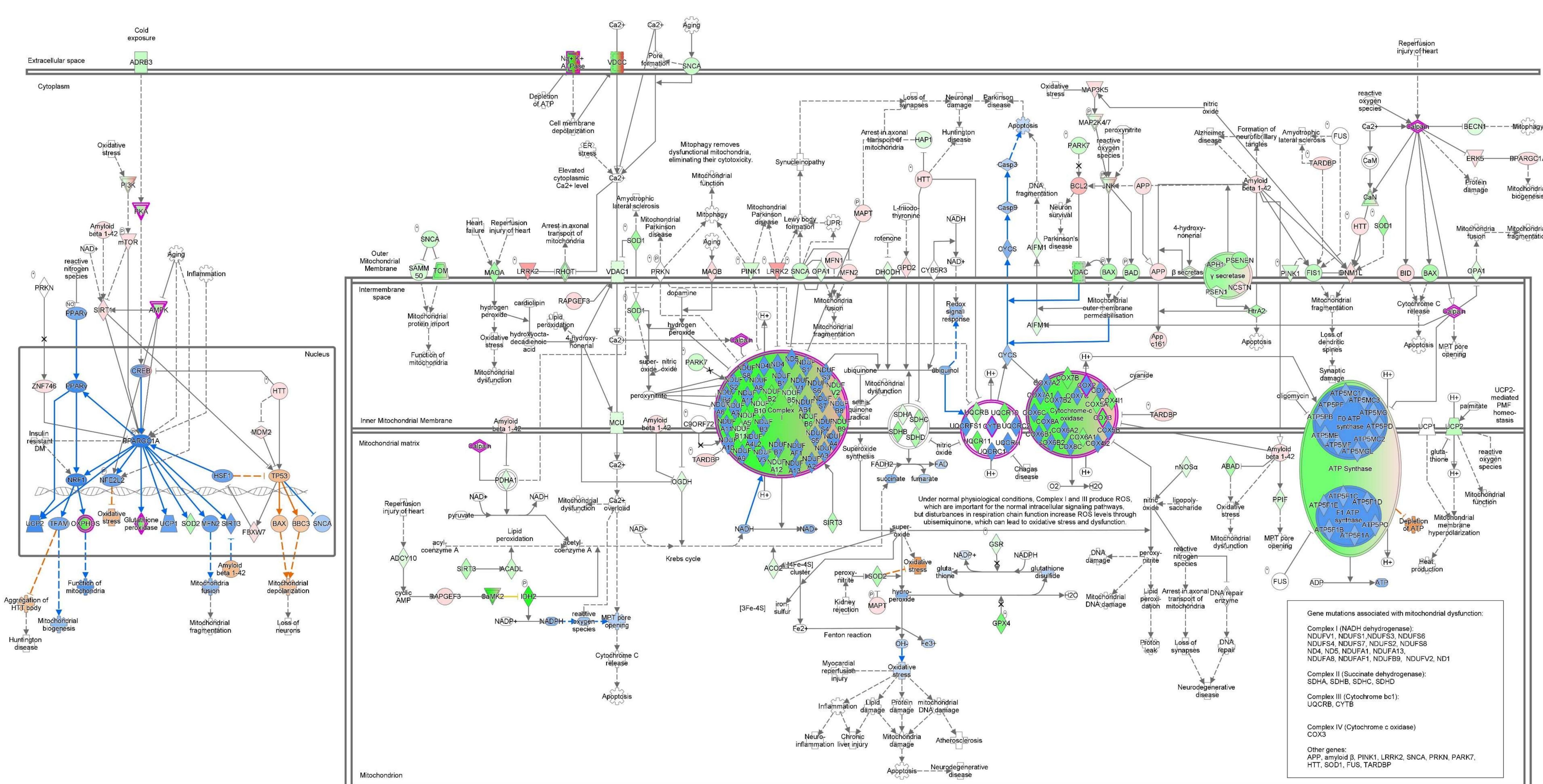
&lt;div[](Abbreviations\_IDH2\_KO\_WT.png) Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; WT, wild type



## Figure S3. Canonical Pathway: Mitochondrial dysfunction.

&lt;div Colonic transcriptomics reveals that 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP)-mediated mitochondrial dysfunction is linked to the suppression of Complex I and IV in WT mice. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

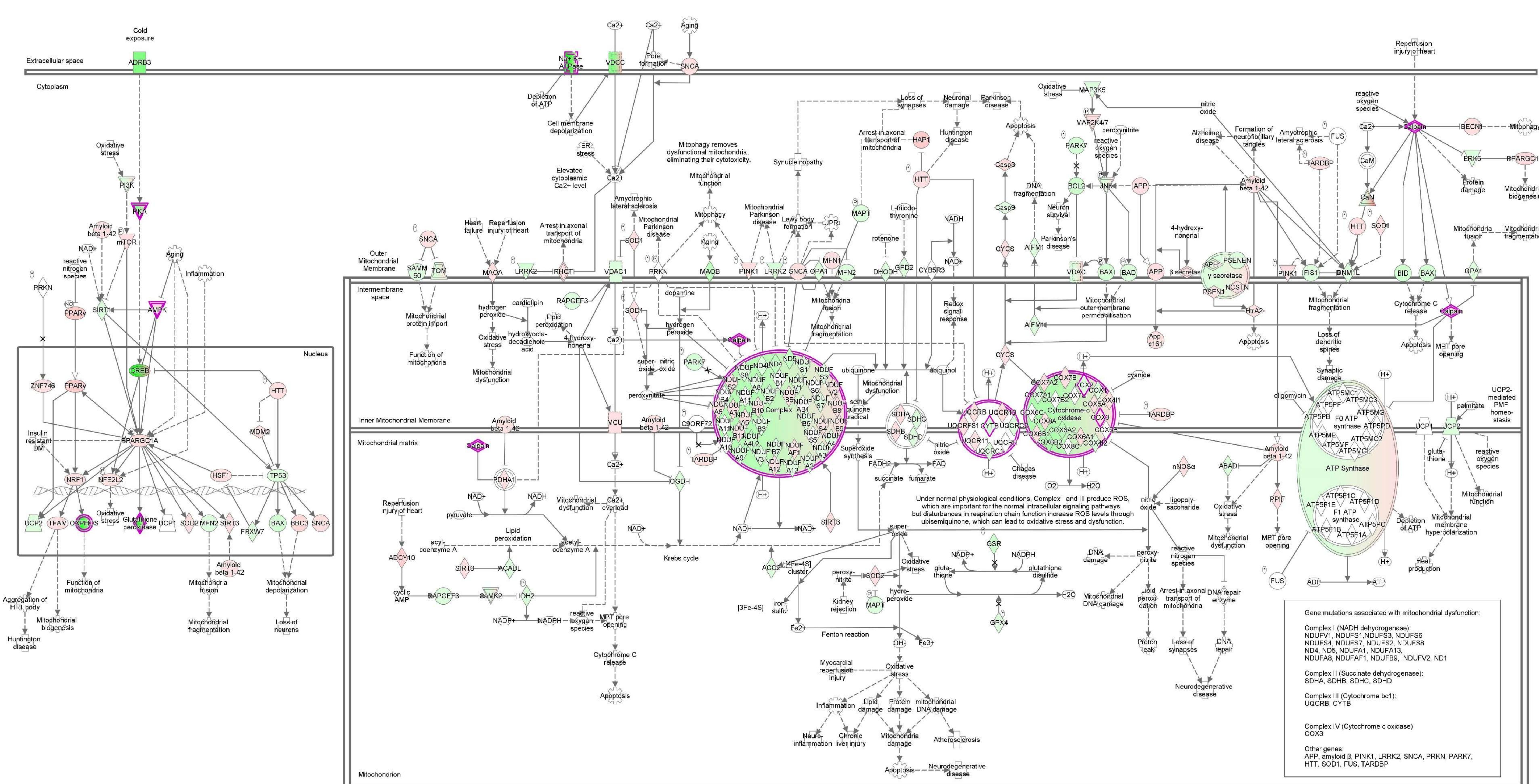
Complex I and IV in WT mice. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation. Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-*b*)pyridine; WT, wild type.



## Figure S4. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics suggests that IDH2 KO exacerbates PhIP-mediated mitochondrial dysfunction via overall suppression of the electron transport chain. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

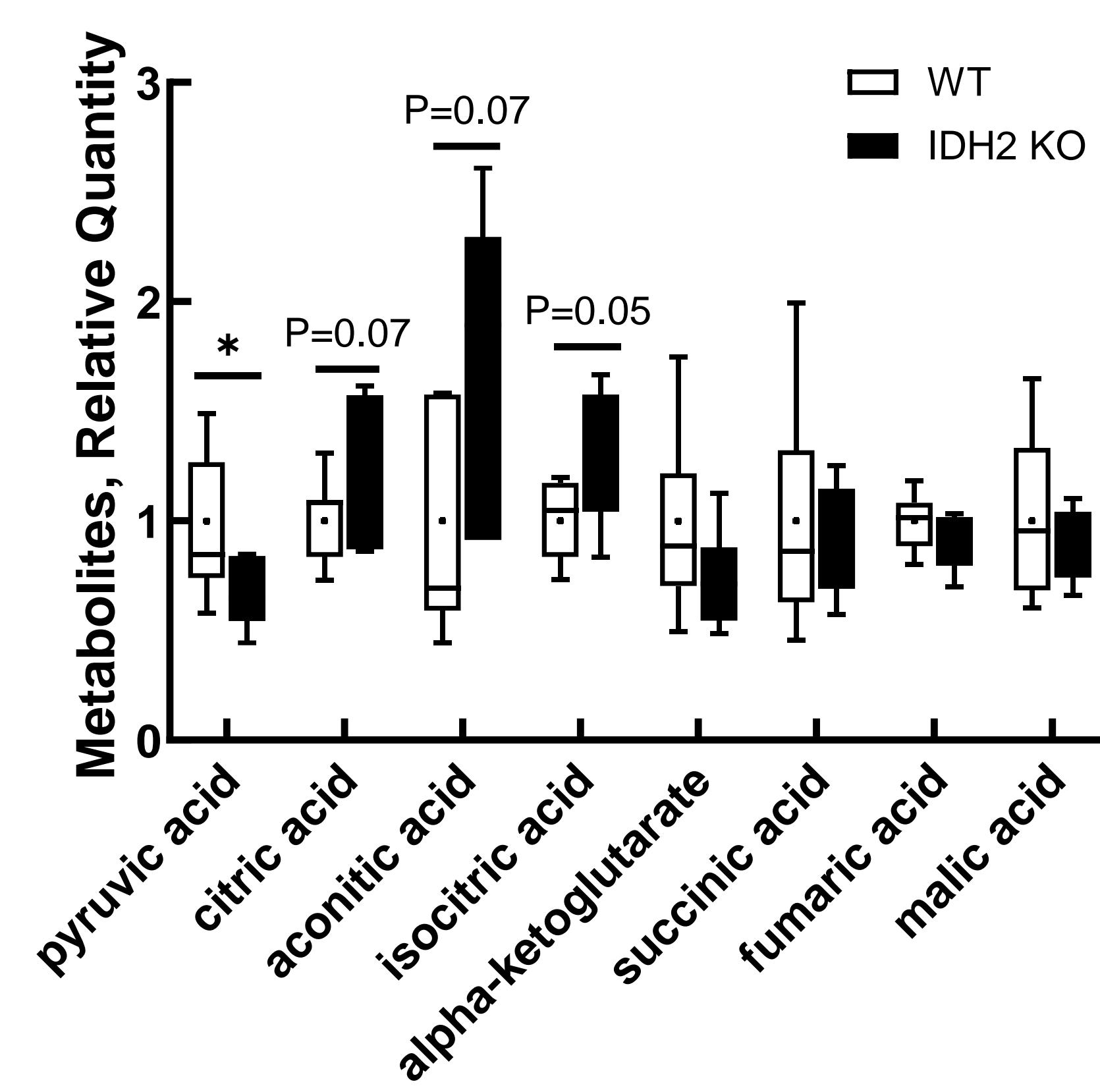
Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine



## Figure S5. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics suggests that PhIP treatment in IDH2 KO mice did not significantly alter mitochondrial dysfunction in the colon compared to IDH2 KO mice alone. Red indicates observed inhibition/activation, while green represents predicted inhibition.

Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine



**Figure S6. Plasma metabolomics revealed that isocitrate dehydrogenase 2 (IDH2) knockout (KO) may induce reductive TCA cycle.**

Key metabolites of the TCA cycle in plasma of mice to validate IDH2 KO-mediated metabolic shift. Data are present as mean  $\pm$  standard error of the mean (n=6 per group). A p-value of 0.05 or less was considered statistically significant; \*p<0.05.

Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; WT, wild type