Supplementary Online Material

Materials and methods

The mitochondrial model and co-sets calculated by Thiele et al used were used (Thiele, Price et al. 2005). The sampling of the steady state each solution space was performed five times by sampling 500,000 random points with 100 iterations between each point. Co-sets were defined as those sets of enzymatic fluxes which were perfectly correlated (correlation coefficient of 1).

The NCBI Entrez Gene ID (http://www.ncbi.nlm.nih.gov/entrez/) tags associated with nuclear genes encoding mitochondrial proteins were assembled and all of the genes with diseases associated MIM tags were identified. These sets of genes were then further evaluated for evidence in the literature of causal SNPs related to the corresponding diseases. MIM tags are listed only if causal SNPs have been identified for the particular enzyme deficiency. From the initial 225 unique nuclear encoded mitochondrial proteins in the model, subsequent filtering based on the 33 co-sets described by Thiele et al, resulted in 9 remaining co-sets (see Supplementary Tables 1-9). Associated diseases due to causal SNPs are described for each enzyme in the co-sets unless otherwise stated. From the 56 genes listed below, all but 4 have been identified/associated with an MIM disease tag.

Supplementary Tables

Summary charts for the set of SNP-disease associated co-sets of human mitochondrial metabolism. Charts are composed of gene abbreviations, gene-IDs, MIM reference tag, and SNP associated diseases/symptoms, respectively column-wise.

Supplementary Table 1: Heme co-set

ALAD	CPOX	FECH	HMBS	PPOX	UROD	UROS	ALAS2
210	1371	2235	3145	5498	7389	7390	212
125270	121300	177000	176000	176200	176100	606938	301300
porphyria	porphyria	porphyria	porphyria	porphyria	porphyria	porphyria	porphyria

Supplementary Table 2: Urea cycle co-set

ASL	ASS	CPS1	OTC
435	445	1373	5009
207900	603470	237300	300461
failure to thrive, neurological symptoms	vomiting, neurological symptoms	failure to thrive, neurological symptoms	visual problems, gradual blindness

Supplementary Table 3: Phospholipids II co-set

HMGCS2	HMGCL	OXCT1
3158	3155	5019
600234	246450	245050
hypoglycemia, acidosis, seizures	infantile hypoketotic hypoglycemia, acidosis, hepatomegaly, aciduria	acidosis, vomiting, polypnea

Supplementary Table 4: TCA co-set

FH	SDHA	SDHB	SDHC	SDHD
2271	6389	6390	6391	6392
136850	600857	185470	602413	602690
no symptoms	similar to Leigh syndrome			

Supplementary Table 5: Citrulline/ornithine co-set

SLC25A15	SLC25A2
10166	83884
603861	608157
HHH syndrome: hyperorn, hyperamm, momcitrullenemia, neuro sx	recovers from HHH syndrome

Supplementary Table 6: OxPhos/ROS detox co-set

lots - CYOOm3	UQCRB	SOD2
4512, 4513, 4514, 1327, 84701, 9377, 1329, 1337, 1339, 1340, 125965, 1345, 1346, 1347, 9167, 1349, 170712, 1350, 1351, 341947	7381	6648
no omim	191330	147460
	hypoglycemia, liver dysfunction	cardiomyopathy associated with hereditary hemochromatosis

Supplementary Table 7: Fatty Acid oxidation co-set

CPT2	SLC25A20	[FAO complex]
1376	788	33, 35, 1892, 51, 1962, 10449
600650	212138	606885
myoglobinuria, hypoketotic hypoglycemia and cardiomyopathy, lethargy	fasting induced coma, seizures, hypotension, hepatomegaly, cardiomyopathy	hypotonia and seizures, developmental delay

Supplementary Table 8: Citrate co-set

SLC25A1	PCK1
6576	5105
no SNP	261680
	hypoglycemia, fatty liver, liver failure

Supplementary Table 9: Malate-Aspartate shuttle co-set

SLC25A13	GOT2
10165	2806
603859	138150 - no disease descriptions
citrullenemia, cholestatic jaundice, fatty liver and fibrosis	