

## Supplementary Table S1: Mitochondrial gene-sets

**Citrate cycle (TCA cycle):** ACLY, ACO1, ACO2, CS, DLAT, DLD, DLST, FH, IDH1, IDH2, IDH3A, IDH3B, IDH3G, MDH1, MDH2, OGDH, OGDHL, PC, PCK2, PDHA1, PDHA2, PDHB, PDHX, SDHA, SDHB, SDHC, SDHD, SUCLA2, SUCLG1, SUCLG2

**Fatty acid biosynthesis:** ACACA, ACACB, FASN, MCAT, OXSM

**Fatty acid elongation:** ACAA2, ECHS1, HADH, HADHA, HADHB, MECR

**Fatty acid metabolism:** ACAA1, ACAA2, ACADL, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACOX3, ACSL1, ACSL4, ACSL5, ALDH1B1, ALDH2, ALDH3A2, ALDH7A1, ALDH9A1, CPT1A, CPT1B, CPT1C, CPT2, ECHS1, ECI1, ECI2, EHHADH, GCDH, HADH, HADHA, HADHB

**Synthesis and degradation of ketone bodies:** ACAT1, BDH1, HMGCL, HMGCS2, OXCT1

**Ubiquinone and other terpenoid-quinone biosynthesis:** COQ2, COQ3, COQ5, COQ6, COQ7

**Oxidative phosphorylation:** ATP5A1, ATP5B, ATP5C1, ATP5D, ATP5F1, ATP5G1, ATP5G2, ATP5G3, ATP5I, ATP5J, ATP5J2, ATP5L, ATP5O, ATP6, COX1, COX10, COX11, COX15, COX17, COX2, COX3, COX4I1, COX4I2, COX5A, COX5B, COX6A1, COX6A2, COX6B1, COX6B2, COX6C, COX7A1, COX7A2, COX7A2L, COX7B, COX7C, COX8A, CYC1, CYTB, ND1, ND2, ND3, ND4, ND4L, ND5, ND6, NDUFA1, NDUFA10, NDUFA12, NDUFA13, NDUFA2, NDUFA3, NDUFA4, NDUFA5, NDUFA6, NDUFA7, NDUFA8, NDUFA9, NDUFAB1, NDUFB10, NDUFB11, NDUFB2, NDUFB3, NDUFB5, NDUFB6, NDUFB7, NDUFB8, NDUFB9, NDUFC1, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NDUFV3, PPA2, SDHA, SDHB, SDHC, SDHD, TCIRG1, UQCR10, UQCR11, UQCRB, UQCRC1, UQCRC2, UQCRC3, UQCRH, UQCRQ

**Pyrimidine metabolism:** AK3, CTPS2, DHODH, DUT, NME1, NME1-NME2, NME2, NME3, NME4, NME6, NT5C, NT5C3, NT5M, NUDT2, PNPT1, TK2, TXNRD1, TXNRD2

**Alanine, aspartate and glutamate metabolism:** ABAT, ADSL, AGXT, AGXT2, ALDH4A1, ALDH5A1, CPS1, GLS, GLS2, GLUD1, GOT2, GPT2

**Glycine, serine and threonine metabolism:** AGXT, AGXT2, ALAS1, ALAS2, ALDH7A1, AMT, CHDH, DLD, DMGDH, GATM, GCAT, GLDC, GLYCTK, MAOA, MAOB, SARDH, SHMT1, SHMT2

**Valine, leucine and isoleucine degradation:** ABAT, ACAA1, ACAA2, ACAD8, ACADM, ACADS, ACADSB, ACAT1, ALDH1B1, ALDH2, ALDH3A2, ALDH6A1, ALDH7A1, ALDH9A1, AUH, BCAT1, BCAT2, BCKDHA, BCKDHB, DBT, DLD, ECHS1, EHHADH, HADH, HADHA, HADHB, HIBADH, HIBCH, HMGCL, HMGCS2, HSD17B10, IVD, MCCC1, MCCC2, MCEE, MUT, OXCT1, PCCA, PCCB

**Valine, leucine and isoleucine biosynthesis:** BCAT1, BCAT2, IARS2, LARS2, PDHA1, PDHA2, PDHB, VARS2

**Lysine degradation:** AADAT, AASS, ACAT1, ALDH1B1, ALDH2, ALDH3A2, ALDH7A1, ALDH9A1, BBOX1, DLST, ECHS1, EHHADH, GCDH, HADH, HADHA, OGDH, OGDHL

**Arginine and proline metabolism:** AGMAT, ALDH18A1, ALDH1B1, ALDH2, ALDH3A2, ALDH4A1, ALDH7A1, ALDH9A1, ARG2, CKMT2, CPS1, GATM, GLS, GLS2, GLUD1, GOT2, LAP3, MAOA, MAOB, NAGS, OAT, OTC, PRODH, PRODH2, PYCR1

**Tryptophan metabolism:** AADAT, ACAT1, ALDH1B1, ALDH2, ALDH3A2, ALDH7A1, ALDH9A1, CCBL2, ECHS1, EHHADH, GCDH, HADH, HADHA, KYNU, MAOA, MAOB, OGDH, OGDHL, WARS2

**beta-Alanine metabolism:** ABAT, ACADM, ALDH1B1, ALDH2, ALDH3A2, ALDH7A1, ALDH9A1, ECHS1, EHHADH, HADHA, HIBCH, MLYCD

**Pyruvate metabolism:** ACACA, ACACB, ACAT1, ACSS1, ACYP2, ALDH1B1, ALDH2, ALDH3A2, ALDH7A1, ALDH9A1, DLAT, DLD, HAGH, LDHA, LDHAL6B, LDHB, LDHD, MDH1, MDH2, ME1, ME2, ME3, PC, PCK2, PDHA1, PDHA2, PDHB, PDHX

**Glyoxylate and dicarboxylate metabolism:** ACAT1, ACO1, ACO2, CS, GLYCTK, HAO2, MCEE, MDH1, MDH2, MUT, PCCA, PCCB

**Propanoate metabolism:** ABAT, ACACA, ACACB, ACADM, ACAT1, ACSS1, ACSS3, ALDH1B1, ALDH2, ALDH3A2, ALDH6A1, ALDH7A1, ALDH9A1, ECHS1, EHHADH, HADHA, HIBCH, LDHA, LDHAL6B, LDHB, MCEE, MLYCD, MUT, PCCA, PCCB, SUCLA2, SUCLG1, SUCLG2

**Butanoate metabolism:** ABAT, ACADS, ACAT1, ACSM1, ACSM2A, ACSM3, ACSM4, ACSM5, ALDH5A1, BDH1, ECHS1, EHHADH, HADH, HADHA, HMGCL, HMGCS2, L2HGDH, OXCT1, PDHA1, PDHA2, PDHB

**One carbon pool by folate:** ALDH1L1, ALDH1L2, AMT, ATIC, MTFMT, MTHFD1, MTHFD1L, MTHFD2, MTHFD2L, SHMT1, SHMT2

**Porphyryn and chlorophyll metabolism:** ALAS1, ALAS2, COX10, COX15, CPOX, EARS2, FECH, FTH1, FTMT, HCCS, MMAB, PPOX

**Supplementary Table S2:** PARIS-derived gene P-values for the lipid metabolism mitochondrial gene-set for primary open-angle glaucoma (POAG, 3430 cases) and normal tension glaucoma (NTG, 717 cases) versus controls (3108) in the combined GLAUGEN – NEIGHBOR dataset.

Lipid metabolism mitochondrial gene	LD block count	Gene <i>P</i> -value		Other pathway?
		POAG	NTG	
<i>ACOX3</i>	21	1.00	1.00	
<i>ACACB</i>	16	0.55	0.24	Carbohydrate metabolism
<i>ALDH9A1</i>	15	0.54	0.23	Carbohydrate metabolism
<i>ACSL1</i>	15	0.11	<b>0.020</b>	
<i>MCAT</i>	13	1.00	1.00	
<i>ALDH7A1</i>	13	0.34	1.00	Carbohydrate metabolism
<i>BDH1</i>	12	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	Carbohydrate metabolism
<i>ALDH1B1</i>	12	<b>0.046</b>	0.20	Carbohydrate metabolism
<i>CPT1B</i>	10	0.19	1.00	
<i>HMGCS2</i>	9	1.00	1.00	Carbohydrate metabolism
<i>EHHADH</i>	8	<b>0.044</b>	<b>0.0009</b>	Carbohydrate metabolism
<i>ECI2</i>	8	0.24	1.00	
<i>ACADS</i>	7	1.00	1.00	Carbohydrate metabolism
<i>ACACA</i>	6	0.27	0.06	Carbohydrate metabolism
<i>CPT2</i>	5	0.09	1.00	
<i>ECHS1</i>	5	<b>0.004</b>	<b>0.002</b>	Carbohydrate metabolism
<i>CPT1A</i>	5	0.13	1.00	
<i>ACAA2</i>	5	<b>0.024</b>	<b>0.0008</b>	
<i>CPT1P</i>	5	<b>0.037</b>	1.00	

Nb: Only genes with at least 5 LD blocks are presented.

**Supplementary Table S3:** PARIS-derived gene P-values for the carbohydrate metabolism mitochondrial gene-set for primary open-angle glaucoma (POAG, 3430 cases) and normal tension glaucoma (NTG, 717 cases) versus controls (3108) in the combined GLAUGEN – NEIGHBOR dataset .

Carbohydrate metabolism mitochondrial gene	LD block count	Gene P-value		Other pathway?
		POAG	NTG	
ME3	43	<b>0.0003</b>	0.30	
ABAT	31	<b>0.047</b>	0.31	
SUCLG2	26	0.77	1.00	
PCCA	25	1.00	0.45	
ACSS3	17	1.00	0.09	
ACACB	16	0.55	0.23	Lipid metabolism
MLYCD	16	0.27	0.25	
ALDH9A1	15	0.55	0.24	Lipid metabolism
ACYP2	14	<b>0.001</b>	0.43	
ACO1	14	1.00	1.00	
ACSM5	13	1.00	1.00	
ALDH7A1	13	0.36	1.00	Lipid metabolism
ALDH5A1	13	0.13	<b>0.024</b>	
IDH3A	12	0.27	1.00	
BDH1	12	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	Lipid metabolism
ALDH1B1	12	<b>0.046</b>	0.20	Lipid metabolism
ACSM2A	11	0.12	1.00	
ACSS1	11	1.00	0.00	
PCHC	10	1.00	1.00	
HMGCS2	9	1.00	1.00	Lipid metabolism
HUMNDME	9	0.28	0.26	
SDHC	8	1.00	1.00	
PCK2	8	1.00	1.00	
HIBCH	8	1.00	<b>0.025</b>	
IDH1	8	0.14	0.12	
EHHADH	8	0.05	0.00	Lipid metabolism
HAOX2	7	1.00	1.00	
ACADS	7	1.00	1.00	Lipid metabolism
GLOD2	7	1.00	1.00	
IDH3B	7	1.00	1.00	
SDHA	7	<b>0.013</b>	<b>0.012</b>	
LDHAL6B	6	1.00	<b>0.001</b>	
IDH2	6	0.12	1.00	
LDHD	6	1.00	<b>0.004</b>	
ACACA	6	0.27	0.06	Lipid metabolism
PDHA2	6	1.00	1.00	
OGDHL	5	0.11	1.00	
ECHS1	5	<b>0.004</b>	<b>0.003</b>	Lipid metabolism
PCB	5	0.02	1.00	
LDHB	5	1.00	<b>0.003</b>	
L2HGDH	5	1.00	1.00	
DLTS	5	<b>0.037</b>	1.00	
ACSM1	5	1.00	1.00	
HAGH	5	1.00	1.00	

NB: Only genes with at least 5 LD blocks are presented.