Supplementary Information

Inborn errors of metabolism: Lessons from iPSC models

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Table Supplementary 1. Summary of induced pluripotent stem cell models for inborn errors of metabolism

Disease	OMIM number	Gene (Mutation)	Differentiated cell type	Disease phenotype described	Reference
1. Disorders of amino acid and peptide metabolism					
1.1. Urea cycle disorders and inherited hyperammonaemias					
1.1.1. Ornithine transcarbamylase deficiency	311250	**OTC** c.663+2T>G c.386G>A, r.299_386del and r.386_387ins386+1_384+4	Hepatic organoids	Deregulated urea cycle activity. Ureagenesis is decreased.	[1, 2]
1.1.2. Citrullinaemia type1	215700	**ASS1** Exon 6, c.364-2 A>G, p. G259*; Exon 13, c.910 C>T, p.R304W; c.1168G>A	Hepatocyte, hepatic organoids	Ureagenesis is decreased. Tricarboxylic acid (TCA) cycle metabolites are accumulated. Response to arginine treatment	[3, 4]
1.1.3. Argininosuccinic aciduria	207900	**ASL** c.557 G>A, p.R186Q; c.857 A>G, p. Q286R; c.655+1 G>A; c.857 A>G, p.Q286R	Endothelial cells	Decreased nitric oxide (NO) signalling. Increased oxidative stress. Impaired angiogenesis *in vitro* and *in vivo*	[5]
1.1.4. Citrullinemia Type 2	603859	**SLC25A13** 851del4, p.R284fs (286X); IVS1ins3kb, p.A84fsc (585X)	Hepatocyte	Lack of urea production. Increased triglyceride levels. Peroxisome proliferator-activated receptors-α downregulated. Aberrant mitochondrial β-oxidation and abnormal mitochondrial structure	[6]

1.2. Organic acidurias					
1.2.1. Propionic aciduria	232000	**PCCA** c.1899+4_1899+7delAGTA; p.C616_V633del; p.G477Efs*9	Cardiomyocytes	Reduced oxygen consumption. Accumulation of lipid droplets. Endoplasmic reticulum stress. Calcium perturbations	[7, 8]
		PCCB c.1218_1231del14ins12 (p.G407 fs)	Not performed	Not performed	[9, 10]
1.2.2. Methylglutaconic aciduria					
1.2.2.1. Methylglutaconic aciduria type II, Barth syndrome	302060	**TAZ** c.517delG; c.328 T>C, c.590 G>T; p.G197V, c.110-1; c.AG>AC; p.r.spl Ex2del?; c.170 G>T; p.R57L	Cardiomyocytes	Abnormal cardiolipids biogenesis and mitochondrial function. Metabolic alterations and energy production. Rearrangements of respiratory chain complexes. Increased ROS production. Abnormal sarcomerogenesis. Severe defect in contractility	[11-16]
1.2.2.2. Methylglutaconic aciduria type V	610198	**DNAJC19** IVS3-1G>C	Cardiomyocytes	Abnormal mitochondrial morphology. Mitochondrial dynamics imbalance	[17]
1.2.3. Aminoacylase deficiency					
1.2.3.1. Aminoacylase 2 deficiency (Canavan disease)	271900	**ASPA**	Neural precursor cells (NPCs)	Phenotype rescued after corrected NPCs transplantation into mouse model	[18]

1.3. Disorders of the metabolism of branched-chain amino acids not classified as organic acidurias					
1.3.1. Maple syrup urine disease					
1.3.1.1. BCKD E1 alpha subunit of deficiency	248600	**BCKDHA** c.1280_1282 delTGG and c.632C>T)	Not performed	Not performed	[19]
1.3.1.2. BCKD E1 beta subunit of deficiency	248600	**BCKDHB** c.502C>T/p.R168C, c.965C>T/p.T322I	Not performed	Not performed	[20]
1.4. Disorders of phenylalanine or tyrosine metabolism					
1.4.1. Phenylalanine hydroxylase deficiency	261600	**PAH** c.331 C>T; c.975 C>G	Not performed	Not performed	[21]
1.5. Disorders of ornithine or proline metabolism					
1.5.1. Ornithine aminotransferase deficiency	258870	**OAT** c.677 C>T; p.A226V	Retinal pigment epithelium	Very low OAT activity	[22, 23]
1.6. Disorders of serine, glycine or glycerate metabolism					
1.6.1. P protein deficiency	238300	**GLDC** c.1742C > G (p.Pro581Arg) and c.2368C > T (p.Arg790Trp)	Not performed	Not performed	[24]
1.7. Disorders of amino acid transport					
1.7.1. Lowe syndrome	309000	**OCRL** c.2582-1 G>T, c.2470-2 A>G; 2179delC, c.2626dupA	Neurons, kidney cells, neural progenitor cells	F-actin and WAVE-1 expression altered. Cytoskeletal disorganization	[25-28]

2. Disorders of carbohydrate metabolism

2.1. Disorders of glyoxylate metabolism

2.1.1.	Primary hyperoxaluria type I	260000	**AGXT** c.731 T>C; p.I244T c.508G>A (G170R) and c.364C>T (R122*)	Hepatocytes	Not performed	[29-32]

2.2. Glycogen storage disorders

2.2.1.	Glycogen storage disease type 1a, von Gierke	232200	**G6PC** c.648G > T; p.Leu216	Hepatocyte	Intracellular glycogen accumulation, lipid accumulation and excessive production of lactic acid	[33, 34]
2.2.2.	Glycogen storage disease type 1b, von Gierke	232220	**G6PT**	Hepatocytes and neutrophils	Glycogen, lactate, pyruvate and lipid accumulation. Superoxide anion production. Increased annexin V binding. Activation of caspases 3 and 9	[35]
2.2.3.	Glycogen storage disease type II, Pompe	232300	**GAA** del ex18/del ex18; c.1935 C>A; c.1935 C>A/c.2040 +1 G>T; p.D645E/c.1935 C>A; del Ex18/del525T; c.1062 C>G; p.Y354X/c.1935 C>A; IVS1-13 T>G/ del Ex18; 1441delT/2237 G>A; c.796 C>T/c.1316 T>A; IVS1-13 T>G/ del525T; IVS1-13 T>G/ c.923 A>T c.2560C > T (p.R854X); c.1822C>T, p.R608X; c.2662G>T, p.E888X	Cardiomyocytes, skeletal muscle cells, neural progenitors cells, neurons, hepatocytes	Increased lysosomal glycogen accumulation, mitochondrial dysfunction, multiple ultrastructure aberrances, large glycogen-containing vacuoles, glycan processing abnormality, increased oxidative stress, suppressed mTORC1 activation	[36-51]

2.2.4. Glycogen storage disease type V, McArdle	232600	**PYGM** c.148 C>T; p.R50Ter	Not performed	Not performed	[52]
2.2.5. Glycogen storage disease type IX					
2.2.5.1. Cardiac muscle phosphorylase kinase deficiency	261740	**PRKAG2** c.905 G>A; p.R302Q; p.R531Q; p.N488I	Cardiomyocytes	Cellular enlargement. Electrophysiological irregularities. Glycogen accumulation. AMPK activity increased. Arrhythmic calcium handling. Increased twitch force	[53-55]
3. Disorders of fatty acid and ketone body metabolism					
3.1. Disorders of carnitine transport and the carnitine cycle					
3.1.1. Carnitine palmitoyltransferase II (CPTII) deficiency	255110	**CPT2** 1223delCT/c.1891 C>T; p.R631C	Myocytes	Palmitoylcarnitine accumulation	[56]
3.2. Disorders of mitochondrial fatty acid oxidation					
3.2.1. Very long-chain acyl-CoA dehydrogenase deficiency	201475	**ACADVL** c. 848T >C (p.Val283Ala) c.1141_1143delGAG (p.Glu381del); c.104delC (p.Pro35Leufs*26)	Cardiomyocytes	Electrophysiological alterations	[57, 58]
3.2.2. Mitochondrial trifunctional protein deficiency	143450	**HADHA** c.1528 G>C; p.E510Q	Retinal pigment epithelium, cardiomyocytes	Lipid accumulation. Inefficient pigmentation. Defect in tight junctions. Defective calcium dynamics and repolarization kinetics. Mitochondrial alterations	[59, 60]
4. Disorders of energy metabolism					
4.1. Disorders of pyruvate metabolism					

4.1.1. Pyruvate kinase deficiency	266200	**PKLR** c.359 C>T/1168 G>A; IVS9(+1) G>C	Erythrocytes	Energetic imbalance (ATP production impaired)	[61]
4.2. Mitochondrial respiratory chain disorders					
4.2.1. Respiratory chain disorders caused by mutations of mtDNA					
4.2.1.1. Large-scale single deletion of mtDNA					
4.2.1.1.1. Pearson Syndrome	557000		Hematopoietic progenitors	Iron granule deposition. Differences in growth, mitochondrial function *vs* control	[62]
4.2.1.1.2. Kearns Sayre Syndrome	530000		Neural progenitor cells, cardiomyocytes	Not phenotype	[62-65]
4.2.1.2. Point mutations of mtDNA					
4.2.1.2.1. Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, MELAS	540000	**MT-TL1** m.3243 A>G **MT-TW** m.5541 C>T **mtDNA** m.13513 G>A	Neurons, myoblasts, myocytes, cardiomyocytes, neural progenitor cells, spinal cord organoids, retinal pigment epithelium	Oxidative stress. Enhanced autophagy flux. Low mitophagy. ROS and intracellular calcium increased. Depolarization of mitochondrial membrane potential and reduction of mitochondrial ATP production. Small fragmented mitochondria. Neuronal maturation impaired. Lower synaptic density. Neuronal network activity and synchronicity impaired	[66-76]

4.2.1.2.2. Myoclonic epilepsy associated with ragged red fibres, MERRF	545000	**MT-TK** m.8344 A>G	Inner ear hair cells (HCs), cardiomyocytes, neural progenitor cells	Elevated ROS production. Fragmented mitochondria and impaired functionality. Altered antioxidant gene expression. Failed to acquire mature stereociliary bundles, more single cilia with a shorter length and fewer stereociliary bundle-like protrusions	[77-81]
4.2.1.2.3. Leber Hereditary Optic Neuropathy, LHON	535000	**MT-ND4** m.11778 G>A, m.11778 G>C, m.14484 T>C; m.4160 T>C; m.3460G > A/MT-ND1	Retinal ganglion cells	Defective neurite growth. Oxidative stress. Increased level of apoptosis. Mitochondrial dysfunction	[82-87]
4.2.1.2.4. Maternally inherited Mitochondrial Cardiomyopathy	n/a	**MT-RNR2** m.2336 T>C	Cardiomyocytes	Mitochondrial dysfunction and ultrastructure defects. ATP/ADP ratio and mitochondrial membrane potential reduced. Abnormal Ca^{2+} homeostasis	[88]
4.2.2. Respiratory chain disorders caused by mutations of nuclear DNA					
4.2.2.1. Mitochondrial DNA Depletion Syndromes					
4.2.2.1.1. Alpers-Huttenlocher Syndrome	203700	**POLG** c.1251-2 A>T	Hepatocyte	Valproic acid (VPA) hepatotoxicity increased, higher VPA sensitivity. Abnormal mitochondrial ultrastructure. Mitochondrial dysfunction	[89]

4.2.2.1.2. Hepatocerebral (*DGUOK*, *MPV17*, *PEO1*)	251880	**DGOUK** DGUOK$^{\Delta 14/\Delta 5}$: p.W166Ter; H167L fsTer213	Hepatocyte	Reduction in mtDNA copy number. Mitochondria with decreased matrix density and abnormal cristae. Decrease in mitochondrial membrane potential and electron transport chain deficiencies. Attenuated capacity for energy production. Increase in ROS and lactate levels	[90]
4.2.2.1.3. Childhood-onset autosomal dominant optic atrophy		**OPA1** c.2496+1 G>T	Retinal ganglion cells (RGCs)	Increased apoptosis. Inefficient differentiation into RGCs	[91-93]
4.2.2.1.3.1. Behr syndrome	210000	**OPA1** c.610+364 G>A/c.1311 A>G	Not performed	Not performed	[91]
4.2.2.1.3.2. Optic atrophy 'plus' phenotype		**OPA1** c.1861 C>T; p.Q621Ter	Not performed	Not performed	[92]
4.2.2.1.4. Mitochondrial Neurogastrointestinal Encephalopathy, MNGIE	603041	**TYMP**	Cerebral organoids	Not performed	[94]
4.2.2.2. Multiple mtDNA Deletion Syndromes					
4.2.2.2.1. Progressive External Ophthalmoplegia Autosomal Dominant (PEOA)					

4.2.2.2.1.1. PEOA1	157640	**POLG** c.2243 G>C; p.W748S	Not performed	Not performed	[95]
4.2.2.3. Leigh Syndrome (LS)	256000	**MT-ATP6** c.8993 T>G; p.L156R **MT-ND5** c.13513 G>A; p.D393N **SURF1** c.530T>G p.(V177G) c.769G>A p.(G257R)	Cardiomyocytes, skeletal muscle cells and neural progenitor cells, neurons, brain organoids	Impaired oxygen consumption and ATP production. Mitochondrial dysfunction. High cytoplasmic calcium concentration. Cardiac differentiation impaired. Compromised neuronal morphogenesis	[70, 96-101]
4.2.2.4. Ubiquinone (CoQ10) deficiency (Non-LS)	607426	**COQ4** c.483 G>C; p.E161D	Skeletal muscle, dopaminergic neuron, motor neuron	Impaired mitochondrial function and metabolic defects. Impaired differentiation into skeletal muscle cells	[102, 103]
5. Disorders in the metabolism of purines, pyrimidines and nucleotides					
5.1. Disorders of purine metabolism					
5.1.1. Adenosine deaminase deficiency	102700	**ADA** GGG>AGGEx7/ GAAGAdelEx10	Not performed	Not performed	[104]
5.1.2. Deoxyguanosine kinase deficiency	251880	**DGUOK** p.W166X/H167fs	Hepatocytes	mtDNA depletion, reduced oxidative phosphorylation and energetic capacity	[90]
5.1.3. Lesch-Nyhan syndrome	308000	**HPRT1** Inv/del, ex6-9; IVS7 + 5 G>A; delEx1; c.151 C>T; c.508 C>T; c.371insTT	Neurons	Impaired neural differentiation. Shorter neurites.	[104-110]
5.1.4. Purine nucleoside phosphorylase deficiency	164050	**PNP**	Neurons	Reduced levels of hypoxanthine	[111]

5.1.5. Mitochondrial ribonucleotide reductase subunit 2 deficiency	604712	**RRM2B** 10delEx2	Hepatocytes	mtDNA depletion, reduced oxidative phosphorylation and energetic capacity	[90]
5.2. Disorders of pyrimidine metabolism					
5.2.1. Thymidine phosphorylase deficiency	131222	**TYMP**	Cerebral organoids	Not performed	[94]
5.3. Disorders of nucleotide metabolism					
5.3.1. Aicardi-Goutières syndrome (AGS)					
5.3.1.1. AGS1	225750	**TREX1** c.260insAG/S88fs*22	Not performed	Not performed	[112, 113]
5.3.1.2. AGS2	610181	**RNASEH2B** c.529 G>A	Not performed	Not performed	[112, 114]
5.3.1.3. AGS5	612952	**SAMHD1** Ex14-15del	Not performed	Not performed	[115]
5.3.1.4. AGS7	615846	**IFIH1** c.2471 G>A	Not performed	Not performed	[112, 116]

6. Disorders of the metabolism of sterols

6.1. Disorders of sterol biosynthesis

6.1.1. Smith-Lemli-Opitz syndrome	270400	**DHCR7** c.964-1 G>C; p.T93M	Neural progenitors, retinal pigmented epithelium cells	7-dehydrocholesterol accumulation and decreased cholesterol levels. Defective phagosome maturation. Accumulation of ubiquitinated proteins. Aberrant neural differentiation	[117, 118]
6.1.2 Antley-Bixler syndrome with disordered steroidogenesis	201750	**POR** c.1370G>A	Not performed	Not performed	[119]

6.2. Disorders of bile acid biosynthesis

6.2.1. Oxysterol 7-alpha-hydroxylase deficiency	613812	**CYP7B1** p.Y275X; p.R486C	Not performed	Not performed	[120, 121]
6.2.2. Cerebrotendinous xanthomatosis	213700	**CYP27A1** c.1183 C>A; p.R395S	Not performed	Not performed	[122]

6.3. Disorders of bile acid metabolism and transport

6.3.1. Bilirubin UDP-glucuronosyltransferase 1 deficiency	218800	**UGT1A1** 13bp-del Ex2	Not performed	Not performed	[33]
6.3.2. Progressive familial intrahepatic cholestasis type 2	601847	**ABCB11** c.-24 C>A; c.2417 G>A c.2782 C>A (R928X) c.3268 C>T (R1090X)	Hepatocyte	Abnormal protein localization, defects in bile acids excretion, suppression of *de novo* bile acid synthesis	[123, 124]

7. Disorders of porphyrin and haem metabolism					
7.1. Congenital erythropoietic porphyria	263700	**UROS** c.217 T>C c.683 C>T	Hematopoietic progenitors	Not performed	[125]
7.2. X-linked sideroblastic anaemia (XLSA)	300751	**ALAS2** c.1737 T>C (V562A)	Erythrocytes	Presence of ring sideroblasts, abnormal mitochondrial iron deposition	[126]
8. Disorders of lipid and lipoprotein metabolism					
8.1. Inherited hypercholesterolaemias					
8.1.1. Disorder of low density lipoprotein receptor	143890	**LDLR** c.2108_2114dup (A705fsX14); c.654_656delTGG (G219del); c.901 G>T c.97 C>T	Hepatocytes	Impaired transport from endoplasmic reticulum, LDL uptake deficiency, high ApoB and cholesterol secretion	[33, 127-135]
8.2. Inherited hypertriglyceridaemias					
8.2.1.1. Familial lipoprotein lipase deficiency	238600	**LPL** c.928 T>C (C310R)	Not performed	Not performed	[136]
8.3. Disorders of high density lipoprotein metabolism					
8.3.1. Tangier disease	205400	**ABCA1** E1005X; S2046R/K531N	Hepatocytes	Impaired cholesterol efflux, loss of HDL formation, enhance trygliceride secretion and ANGPL3 expression	[137]
8.4. Inherited hypolipidaemias					

8.4.1.	Familial abetalipoproteinaemia	200100	**MTTP** R46G	Hepatocytes, cardiomyocytes	Absent ApoB protein, excess intracelular cholesterol and triglycerides storage, cardiac sensitization to stress	[138]
8.4.2.	Familial hypobetalipoproteinaemia	144010	**APOB** c.10579 C>T (R3527W)	Not performed	Not performed	[139]
9.	**Congenital disorders of glycosylation and other disorders of protein modification**					
9.1.	**Disorders of protein N-glycosylation**					
9.1.1.	Phosphomannomutase 2 deficiency	601785	**PMM2** R141H/F119L	Hepatocytes	Diminished mannose incorporation into proteins, protein hypoglycosylation. Increased cell surface LDLR expression	[140, 141]
9.1.2.	Glucosyltransferase 1 deficiency	603147	**ALG6**	Hepatocytes	Increased cell surface LDLR expression	[141]
9.2.	**Disorders of protein O-glycosylation**					
9.2.1.	Multiple exostoses type I	133700	**EXT1** c.1883+1G>T	Not performed	Not performed	[142]
9.2.2.	Fukutin-related protein deficiency	606596	**FKRP** c.826 C>A (L276I) c.1364 C>A (A455D)	Cardiomyocytes, cortical neurons	Abnormal action potentials, reduced expression of channel currents, reduced intracellular Ca^{2+} concentrations. Absence of glycosylation in neurons	[143, 144]

10. Lysosomal disorders

10.1. Mucopolysaccharidoses

10.1.1.	MPS I, Hurler, Scheie disease	252800	**IDUA** IVS5AS-7 G>A/ W402X; Y167X/W402X; H358-T364del c.266 G>A	Neural progenitor cells, hematopoietic progenitors	Accumulation of GAG, enlarged lysosomes, dysregulated autophagy pathway. Migration defects	[145-148]
10.1.2.	MPS II, Hunter disease	309900	**IDS** c.182 C>T (S61F); c.1181-1 G>A; c.1403 G>A (R468Q); c.85C>T; c.208insC	β3-Tubulin^{+} neurons, astrocytes, CNPase^{+} oligodendrocytes	Glial and neuronal GAG accumulation, decreased neuronal self-renewal capacity, structural alterations in Golgi and endoplasmatic reticulum, vacuoles accumulation	[149-156]
10.1.3.	MPS IIIA, Sanfilippo A disease	252900	**SGSH** E447K/R245H	Not performed	Not performed	[157]
10.1.4.	MPS IIIB, Sanfilippo B disease	252920	**NAGLU** c.531+1G.C; R482W; P358L; c.457 G>A	Neural precursors, β3-Tubulin^{+} neurons	HS proteoglycans accumulation, disorganized Golgi structure, increased LAMP1 and GM130	[158-160]
10.1.5.	MPS IIIC, Sanfilippo C disease	252930	**HGSNAT** c.633+1 G>A/ c.1334 T>C (L445P); c.372-2 A>G	MAP2^{+} neurons, astrocytes	GAG accumulation, large vacuoles with an empty-like appearance, impaired neuronal network activity and connectivity. Increased in lysosomes in heparin sulfate	[161-163]
10.1.6.	MPS IVA, Morquio A disease	253000	**GALNS** R61W/WT405del	Not performed	Not performed	[164]

10.1.7.	MPS VII, Sly disease	253220	**GUSB** L176F	Neural progenitor cells, β3-Tubulin^{+} neurons	GAG accumulation, expanded endocytic compartments, accumulation of lipofuscin granules, increased number of autophagosomes, reduced neuronal activity and altered network connectivity	[165, 166]
10.2.	**Oligosaccharidoses**					
10.2.1.	Sialidosis	256550	**NEU1** A544G/c.667_679 del c.649 G>A/644 T>C; c.1109 A>G; c.1195_12000dup/c.679 G>A G227R and V275A/R347Q	Oligodendrocytes, astrocytes and neurons	Impaired lysosomal and autophagic function. Defects in neural differentiation. Glycolitic impairment. Presynaptic dysfunction. Deregulation of Ca^{2+} dynamics	[167-170]
10.3.	**Sphingolipidoses**					
10.3.1.	GM1-gangliosidosis	230500	**GLB1** R201C I51T	Neural progenitor cells	Defective GLB1 activity, increased lysosomes, activation of inflammasome. Impaired neurotransmitter release, accumulation of GMS1 ganglioside	[171, 172]
10.3.2.	GM2-gangliosidosis 0-variant, Sandhoff disease	268800	**HEXB** 16kb-del/ IVS10- 2A>G	Cerebral organoids	GM2 accumulation mainly in β3-Tubulin^{+} neurons, alterations in neuronal differentiation	[173]
10.3.3.	GM2-gangliosidosis B-variant, Tay-Sachs disease	272800	**HEXA** c.1278insTATC; c.1278insTATC/W392X 1278insTATC/IVS12+ 1G>C	Neural progenitor cells, β3-Tubulin^{+} neurons	Accumulation of lipids in NPC lysosomes, GM2 accumulation. Enlarged lysosomes, increased oxidative stress, decreased exocytotic activity	[174-176]

10.3.4.	Gaucher disease	230800	**GBA** N370S/c.84GG; c.1448 T>C (L483P); c.667 T>C (W223R); L444P; N370S; L444P/G202R; W184R/D409H; IVS2+1 G>A/L444P; L444P/P415R; G325R/C342G P213I	Dopaminergic neurons, β3-Tubulin^{+} neurons, neural progenitor cells, macrophages, hematopoietic progenitor cells, osteoblasts, astrocytes	Compromised lysosomal protein degradation, accumulation of α-synuclein, aggregation-dependent neurotoxicity, abnormal electrophysiological properties, differentiation defect in neurons, accumulation of glucosylsphingolipids and glucosylceramide in macrophages, delay in red blood cells clearance, increased levels of inflammatory cytokines, elevated levels of chitotriosidase, impaired chemotaxis, reduced production of intracellular ROS. Decreased neural TFEB levels, defective bone matrix protein and mineral deposition, defective Ca^{2+}-dependent exocytosis and homeostasis. Astrocyte reactivity. mTOR hyperactivity	[104, 177-197]
10.3.5.	Krabbe disease	245200	**GALC** c.461 C>A/c.1244 G>A	Not performed	Not performed	[198]
10.3.6.	Metachromatic leukodystrophy	250100	**ARSA** c.465+ 1G>A/ c.1223_1231del9; c.465+ 1G>A; P426L; c.459+ 1G>A/ c.1049 A>G c.1178 C>G	Neural progenitor cels, β3-Tubulin^{+} neurons, astrocytes, oligodendrocytes	Sulfatide accumulation, expansion of the endolysosome system, intracellular ROS production, oligodendroglial loss, disorganized neuronal network	[199-202]

10.3.7.	Fabry disease	301500	**GLA** c.485 G>A; c.658 C>T; G485A; C658T; IVS4+919 G>A; c.708 G>C W287S	Cardiomyoctes, vascular endothelial-like cells	Accumulation of globotriaosylceramide, cellular hypertrophy, up-regulation of IL-18, increased ROS production, decreased energy metabolism, arachidonate 12/15-lipoxygenase upregulation. Altered cardiomyocyte electrophysiology and calcium handling. Dysfunctional angiogenesis. Autophagic flux impairment	[203-214]
10.3.8.	Niemann-Pick disease type A or B	257200	**SMPD1** L302P; P330fs p.L43-A44delLA	Neural progenitor cells	Enlarged multilamellar lysosomes, sphingomyelin accumulation	[215-217]
10.3.9.	Niemann-Pick disease type C1	257220	**NPC1** c.1628 delC /E612D; I1061T/P237S; I1061T; 1920 delG/1009 G>A; 1920 delG; c.1180 T>C V1023fs/pG992R	Neural progenitor cells, β3-Tubulin^{+} neurons, hepatocytes, astrocytes	Lysosomal cholesterol accumulation, enlarged lysosomes, impaired cholesterol trafficking to ER, block in autophagic flux, abnormal VEGF levels and sphingolipid metabolism, increased gene expression of genes involved in neural calcium signaling, disruption of genes involved in neural WNT signaling, glycosphingolipid GM2 accumulation in neurons, increased number of reactive astrocytes, increased activation of the necroptotic pathway	[218-231]
10.3.10.	Niemann-Pick disease type C2	607625	**NPC2** c.58 G>T/c.140 G>T	Neurons and Glia cells	Cholesterol and sphingolipids accumulation.	[232, 233]

10.4. Ceroid lipfuscinoses, neuronal (CLN)						
10.4.1.	CLN1, Santavuori-Haltia disease	256730	**PPT1** Y247H/M1I	Neural progenitor cells	Enlarged lysosomes, accumulation of lipids	[234]
10.4.2.	CLN2, Jansky-Bielschowsky disease	204500	**TPP1** R127X/R208X; R127Q/IVS5-1 G>C	Neural progenitor cells	Enlarged lysosomes, accumulation of lipids, accumulation of subunit C of mitocondrial ATP synthase	[234, 235]
10.4.3.	CLN3, Batten Spielmeyer-Vogt disease	204200	**CLN3** 1.02-kb del Ex 7-8; c.1056+3 A>C/ c.1247 A>G; 1.02-kb del/ L101del3CTC	Neural progenitor cells, β3-Tubulin^{+} neurons, retinal cells, brain microvascular endothelial cells	Cytoplasmic vacuolations, accumulation of subunit C of mitocondrial ATP synthase, bigger autophagic vacuoles, reduced multivesicular bodies, defect in late-stage autophagosome maturation, abnormal calcium handling. Mitochondrial dysfunction, impaired barrier function	[235-238]
10.4.4.	CLN5 Finnish variant	256731	**CLN5** c.1175_1176delAT (Y392X)	Neural progenitors cells	Enlarged lysosomes, endoplasmic reticulum, accumulation of subunit C of the mitochondrial ATP synthase, disturbed sphingolipid transport	[239]
10.5. Lysosomal export disorders						
10.5.1.	Cystinosis	219800	**CTNS** 57kb del/L158P	Kidney organoids	Elevated cystine levels, defective autophagy, increased apoptosis	[240]

10.6. Other lysosomal disorders

10.6.1.	Wolman/cholesterol ester storage disease	278000	**LIPA** c.594dupT(A199Cfs*13)/ c.796 G>T(p.G266X)	Neural progenitor cells, hepatocyte-like organoids	Accumulation of neutral lipids, increased lysosomal content. Steatosis after oleic acid exposure, increased the fibrosis P3NP biomarker, increased stiffness and ROS production	[241, 242]
10.6.2.	Pompe disease, GSD type II	232300	**GAA** del ex18/del ex18; c.1935 C>A; c.1935 C>A/c.2040 +1 G>T; p.D645E/c.1935 C>A; del Ex18/del525T; c.1062 C>G; p.Y354X/c.1935 C>A; IVS1-13 T>G/ del Ex18; 1441delT/2237 G>A; c.796 C>T/c.1316 T>A; IVS1-13 T>G/ del525T; IVS1-13 T>G/ c.923 A>T c.2560C > T (p.R854X); c.1822C>T, p.R608X; c.2662G>T, p.E888X	Cardiomyocytes, skeletal muscle cells, neural progenitors cells, neurons, hepatocytes	Increased lysosomal glycogen accumulation, mitochondrial dysfunction, multiple ultrastructure aberrances, large glycogen-containing vacuoles, glycan processing abnormality, increased oxidative stress, suppressed mTORC1 activation	[36-51]
10.6.3.	Danon disease	300257	**LAMP2** c.129–130 insAT; IVS-1 c.64+1 G>A; c.183_184insA; c.520 C>T; IVS6+1_4delGTGA c.467 T>G; c.247 C>T	Cardiomyocytes, $Map2^{+}$ neurons	Defect in autophagic flux, cellular hypertrophy, abnormal calcium handling, excessive mitochondrial oxidative stress, accumulation of $LC3^{+}$ autophagosomes, oxidative stress-induced apoptosis, impaired autophagy of depolarized mitochondria, mitochondrial dysfunction, defect in autophagosome-lysosome fusion	[243-250]

10.6.4. Hermansky-Pudlak Syndrome	203300	**HPS1** c.1472_1487dup16 **AP3B1** R509X/E659X	Melanocytes, alveolar type 2 cells	Reduced melanosomes and pigmentation, altered distribution, enlargement, and impaired secretion of lamellar bodies in alveolar cells	[251-254]
11. Peroxisomal disorders					
11.1. Disorders of peroxisome biogenesis					
11.1.1. Zellweger spectrum disorder	214100	**PEX1** I700fs/G973fs; G843D **PEX10** L113fs; L297P **PEX12** S320F **PEX26** R98W	Neural progenitor cells, Tuj1^{+} neurons, oligodendrocyte precursor cells, hepatocytes	Poorly branched oligodendrocytes, reduced sVLCFA and phosphatidylethanolamine plasmalogen levels in iPSC, peroxisome assembly defect	[255]
11.2. Disorders of peroxisomal alpha-, beta and omega-oxidation					
11.2.1. X-linked adrenoleukodystrophy	300100	**ABCD1** c. 253_254insC; c.1847 C>T (A616V); c.1534 G>A; c.1968_1970delCAT; c.1661 G>A; c.1240-1253del6ins; c.2013insA	Oligodendrocytes, neurons, astrocytes, brain microvascular endothelial cells	Abnormal VLCFA accumulation, increased *ELOVL1* expression and proinflammatory cytokines, *CH25H* overexpression, 25-hydroxycholesterol (25-HC)-dependent NLRP3 inflammasome activation, defective barrier function	[256-264]

11.3. Other peroxisomal disorders					
11.3.1. Primary hyperoxaluria type I	259900	**AGXT** I244T p.G170R/R122X	Not performed	AGT protein aggregation	[29-32]
12. Disorders of neurotransmitter metabolism					
12.1. Disorders in the metabolism of biogenic amines					
12.1.1. Tyrosine hydroxylase deficiency	191290	**TH** R129*/R231P	Not performed	Not performed	[265]
12.1.2. Aromatic L-amino acid decarboxylase (AADC) deficiency	608643	**DDC** c.1039C>G, p.R347G c.19C>T, p.Aeg7*/c.229G>C, p.C100S	Dopaminergic neurons	Dysregulated dopamine metabolism, alterations in synaptic maturation and neuronal electrical properties	[266]
13. Disorders in the metabolism of vitamins and (non-protein) cofactors					
13.1. Disorders of cobalamin absorption, transport and metabolism					
13.1.1. Defect in adenosylcobalamin synthesis-cbl B	251110	**MMAB** I96T/S174Cfs*23	Not performed	Not performed	[267]
13.2. Disorders of pterin metabolism					
13.2.1. Guanosine 5 triphosphate cyclohydrolase I deficiency	233910	**GCH1** L79_S80del	Not performed	Not performed	[268]
13.2.2. 6-Pyruvoyl-tetrahydropterin synthase deficiency	261640	**PTS** c.243 G>A /c.259 C>T	Dopaminergic neurons	Reduction in BH4 amount, TH protein level and extracellular dopamine	[269]
13.2.3. Quinoid dihydropteridine reductase deficiency	261630	**QDPR** c.52 G>T/c.176 C>A	Dopaminergic neurons	Reduced TH protein and extracellular dopamine level, increase of dihydrobiopterin	[269]

13.3. Other disorders of vitamins and cofactors					
13.3.1. Pantothenate kinases deficiency	234200	**PANK2** Y190X; F419fsX472; R481Lfs/G521R; IVS4-1 G>T/M437T; R278L/L564P; c.1259delG	Glutamatergic neurons, cortical neurons	Defects in membrane excitability, premature death, increased ROS production, increased mitochondrial membrane potential. Altered iron content and mitochondrial aggregates, altered calcium homeostasis	[270-272]
14. Disorders in the metabolism of trace elements and metals					
14.1. Disorder of copper metabolism					
14.1.1. Menkes syndrome	309400	**ATP7A** c4005 + 5G>A; c121-930_2626/488del M1311V	Neural progenitor cells, mesenchymal stem cells, osteoblast, motor neurons	Aberrant switch of E-cadherin to N-cadherin, impaired neural rosette formation, impaired osteogenesis. Protein deslocalization in motor neurons, copper accumulation, decreased dendritic complexity and survival.	[273-275]
14.1.2. Wilson disease	277900	**ATP7B** R778L; H1069Q/E1064A; M769V; P992L; c.180-181del	Hepatocytes, neural progenitor cell, osteoblasts	Abnormal cytoplasmic localization of mutated ATP7B, copper-export defect. Lower osteogenic activity	[276-288]
14.2. Disorder of zinc metabolism					
14.2.1. Acrodermatitis enteropathica	201100	**ZIP4** 192+19 G>A/P200L	Enterocytes	Impaired zinc uptake	[289]
14.3. Disorder of magnesium metabolism					
14.3.1. Hypomagnesaemia type 5, renal with ocular involvement	248190	**CLDN19** G20D	Retinal progenitor cells	Altered retinal neurogenesis and maturation in culture	[290]
14.3.2. Gitelman syndrome	263800	**SLC12A3** c.46-47del/c.2963 T>C	Not performed	Not performed	[291]

15. Disorders and variants in the metabolism of xenobiotics

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