**Additional files:**

Additional table 1:

|  |  |
| --- | --- |
| IEM0007 | Phosphoribosylpyrophosphate synthetaseÂ superactivity |
| IEM0016 | Xanthine oxidase deficiency |
| IEM0017 | Hypoxanthine guanine phosphoribosyltransferase deficiency |
| IEM0018 | Adenine phosphoribosyltransferase deficiency |
| IEM0068 | Cystinuria type A |
| IEM0069 | Cystinuria type B |
| IEM0070 | Lysinuric protein intolerance |
| IEM0126 | Methylmalonyl-CoA epimerase deficiency / |
| IEM0127 | Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency |
| IEM0128 | Acyl-CoAÂ synthetase family member 3 deficiency |
| IEM0218 | Methylmalonic aciduria, cblA type |
| IEM0219 | Methylmalonic aciduria, cblB type |
| IEM0269 | Vitamin D 24-hydroxylase deficiency |
| IEM0278 | Molybdenum cofactor sulfurase deficiency |
| IEM0370 | Glucose-6-phosphatase deficiency |
| IEM0387 | Lactate dehydrogenase A deficiency |
| IEM0410 | S-adenosylmethionine carrier deficiency |
| IEM0503 | Mitochondrial RNA import protein deficiency |
| IEM0504 | Ribonuclease P 5' tRNA processing enzyme deficiency |
| IEM0505 | Ribonuclease Z 3' tRNA processing enzyme deficiency |
| IEM0508 | Mitochondrial methionyl-tRNA formyltransferase deficiency |
| IEM0509 | tRNA 5-taurinomethyluridine modifier deficiency |
| IEM0510 | tRNA 5-carboxymethylaminomethyl transferase deficiency |
| IEM0513 | tRNA methyltransferase 5 deficiency |
| IEM0516 | Mitochondrial ribosomal large subunit 3 deficiency |
| IEM0517 | Mitochondrial ribosomal large subunit 44 deficiency |
| IEM0519 | Mitochondrial ribosomal small subunit 16 deficiency |
| IEM0520 | Mitochondrial ribosomal small subunit 22 deficiency |
| IEM0521 | Mitochondrial ribosomal small subunit 34 deficiency |
| IEM0524 | RMND1 deficiency |
| IEM0525 | Mitochondrial elongation factor G1 deficiency |
| IEM0527 | Mitochondrial elongation factor Ts deficiency |
| IEM0528 | Mitochondrial elongation factor Tu deficiency |
| IEM0529 | C12orf65 release factor deficiency |
| IEM0552 | Mitochondrial alanyl-tRNA synthetase deficiency |
| IEM0554 | Mitochondrial asparaginyl-tRNA synthetase deficiency |
| IEM0556 | Mitochondrial cysteinyl-tRNA synthetase deficiency |
| IEM0557 | Mitochondrial glutamyl-tRNA synthetase deficiency |
| IEM0562 | Mitochondrial phenylalanyl-tRNA synthetase deficiency |
| IEM0565 | Mitochondrial valyl-tRNA synthetase deficiency |
| IEM0593 | Mitochondrial intermediate peptidase deficiency |
| IEM0609 | Sideroflexin 4 deficiency |
| IEM0610 | AIFM1 deficiency |
| IEM0613 | C1q binding protein deficiency |
| IEM0734 | Lecithin cholesterol acyltransferase deficiency |
| IEM0844 | α-Galactosidase A deficiency |
| IEM0873 | Cystinosin deficiency |
| IEM0903 | Alanine-glyoxylate aminotransferase deficiency |
| IEM0905 | Glyoxylate reductase/hydroxypyruvate reductase deficiency |
| IEM0906 | 4-hydroxy-2-oxoglutarate aldolase 1 deficiency |

Additional table 2:

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **Sub-Group** | **Disease** | **Count** |
| Disorders of Nitrogen-Containing Compounds | Disorders of purine metabolism | Hypoxanthine guanine phosphoribosyltransferase deficiency | **2** |
| Disorders of creatine metabolism | Creatine transporter deficiency | **2** |
| Disorders of choline metabolism | Flavin monooxygenase 3 deficiency | **1** |
| Disorders of ammonia detoxification | N-acetylglutamate synthase deficiency | **1** |
| Carbamoylphosphate synthetase I deficiency | **3** |
| Ornithine transcarbamylase deficiency | **43** |
| Argininosuccinate synthetase deficiency | **14** |
| Argininosuccinate lyase deficiency | **9** |
| Mitochondrial ornithine transporter deficiency | **4** |
| Carbonic anhydrase VA deficiency | **1** |
| Disorders of amino acid transport | Cystinuria type A | **4** |
| Cystinuria type B | **1** |
| Lysinuric protein intolerance | **2** |
| Aminoacylase deficiencies | Aspartoacylase deficiency | **1** |
| Aminoacylase 1 deficiency | **1** |
| Disorders of monoamine metabolism | Tyrosine hydroxylase deficiency | **1** |
| Aromatic L-amino acid decarboxylase deficiency | **1** |
| Disorders of phenylalanine and tetrahydrobiopterin metabolism | Phenylalanine hydroxylase deficiency | **169** |
| Autosomal recessive GTP cyclohydrolase 1 deficiency | **1** |
| Autosomal dominant GTP cyclohydrolase 1 deficiency | **1** |
| 6-pyruvoyl-tetrahydropterin synthase deficiency | **4** |
| Dihydropteridine reductase deficiency | **1** |
| Disorders of tyrosine metabolism | Homogentisic acid oxidase deficiency | **2** |
| Fumarylacetoacetase deficiency | **15** |
| Disorders of sulfur amino acid and sulfide metabolism | Methionine adenosyltransferase I/III deficiency | **1** |
| S-adenosylhomocysteine hydrolase deficiency | **2** |
|  Adenosine kinase deficiency | **1** |
| Cystathionine β-synthase deficiency | **34** |
| Cystathionine γ-lyase deficiency | **2** |
| Mitochondrial sulfur dioxygenase deficiency | **2** |
| Disorders of branched-chain amino acid metabolism | Branched-chain ketoacid dehydrogenase E1α deficiency | **13** |
| Branched-chain ketoacid dehydrogenase E1β deficiency | **9** |
| Dihydrolipoyl transacylase deficiency | **1** |
| Branched-chain ketoacid dehydrogenase kinase deficiency | **1** |
| Isovaleryl-CoA dehydrogenase deficiency | **8** |
| 2-Methylbutyryl-CoA dehydrogenase deficiency | **2** |
| 3-Methylcrotonyl-CoA carboxylase 1 deficiency | **1** |
| 3-Methylcrotonyl-CoA carboxylase 2 deficiency | **1** |
| 3-methylglutaconyl-CoA hydratase deficiency | **1** |
| Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency | **2** |
| HSD10 disease | **1** |
| 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency | **3** |
| Propionic acidemia due to propionyl-CoA carboxylase α subunit deficiency | **8** |
| Propionic acidemia due to propionyl-CoA carboxylase β subunit deficiency | **6** |
| Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency | **10** |
| Disorders of lysine metabolism | α-aminoadipic semialdehyde dehydrogenase deficiency | **3** |
| Glutaryl-CoA dehydrogenase deficiency | **18** |
| Disorders of glutamate metabolism | Glutamate dehydrogenase superactivity | **5** |
| Ionotropic glutamate receptor NMDA type subunit 2A dysregulation | **1** |
| Ionotropic glutamate receptor NMDA type subunit 2B dysregulation | **4** |
| Disorders of glycine metabolism | Glycine encephalopathy due to glycine decarboxylase deficiency | **1** |
| Glycine encephalopathy due to aminomethyltransferase deficiency | **1** |
| Disorders of Vitamins, Cofactors and Minerals | Disorders of cobalamin metabolism | Hereditary intrinsic factor deficiency | **1** |
| Transcobalamin receptor deficiency | **1** |
| Methylmalonic aciduria and homocystinuria, cblJ type | **1** |
| Methylmalonic aciduria and homocystinuria, cblC type | **36** |
| cblD disease | **1** |
| Methionine synthase reductase deficiency | **1** |
| Methionine synthase deficiency | **5** |
| Methylmalonic aciduria, cblA type | **2** |
| Methylmalonic aciduria, cblB type | **3** |
| Methylmalonic aciduria and homocystinuria, cblX type | **1** |
| Disorders of folate metabolism | 5,10-methylenetetrahydrofolate reductase deficiency | **4** |
| Disorders of biotin metabolism | Biotinidase deficiency | **22** |
| Holocarboxylase synthetase deficiency | **3** |
| Disorders of thiamine metabolism | Mitochondrial thiamine pyrophosphate transporter deficiency | **1** |
| Disorders of riboflavin metabolism | Riboflavin transporter 3 deficiency | **1** |
| Electron transfer flavoprotein α subunit deficiency | **2** |
| Electron transfer flavoprotein dehydrogenase deficiency | **3** |
| Disorders of pyridoxine metabolism | Tissue-nonspecific alkaline phosphatase deficiency | **2** |
| Disorders of molybdenum metabolism | Cyclic pyranopterin monophosphate synthase deficiency | **1** |
| Disorders of Carbohydrates | Disorders of carbohydrate transport and absorption | Blood-brain barrier glucose transporter 1 deficiency | **6** |
| Congenital sucrase-isomaltase deficiency | **1** |
| Disorders of galactose metabolism | Galactose-1-phosphate uridylyltransferase deficiency | **33** |
| Galactokinase deficiency  | **2** |
| Disorders of fructose metabolism | Aldolase B deficiency | **5** |
| Disorders of the pentose phosphate pathway and polyol metabolism | Glucose-6-phosphate dehydrogenase deficiency | **2** |
| Disorders of insulin secretion and signaling | ATP-sensitive potassium channel regulatory subunit deficiency | **2** |
| Uncoupling protein 2 deficiency | **1** |
| Glycogen storage diseases | Hepatic glycogen synthase deficiency | **3** |
| Glucose-6-phosphate transporter deficiency | **7** |
| α-glucosidase deficiency | **22** |
| Glycogen debranching enzyme deficiency | **12** |
| Glycogen branching enzyme deficiency | **1** |
| Hepatic phosphorylase kinase α2 subunit deficiency | **23** |
| Phosphorylase kinase β subunit deficiency | **2** |
| Disorders of gluconeogenesis | Glucose-6-phosphatase deficiency | **18** |
| Fructose-1,6-bisphosphatase deficiency | **3** |
| Pyruvate carboxylase deficiency | **1** |
| Disorders of glycolysis | Glucokinase superactivity | **1** |
| Muscle phosphofructokinase deficiency | **1** |
| Mitochondrial Disorders of Energy Metabolism | Disorders of pyruvate metabolism | Pyruvate dehydrogenase E1-α deficiency | **3** |
| Disorders of metabolite repair | L-2-hydroxyglutarate dehydrogenase deficiency | **1** |
| Disorders of mitochondrial carriers | Cytosolic glycerol-3-phosphate dehydrogenase deficiency | **3** |
| Disorders of complex I subunits | NADH dehydrogenase flavoprotein 1 deficiency | **1** |
| NADH dehydrogenase iron-sulfur protein 8 deficiency | **1** |
| NADH dehydrogenase iron-sulfur protein 4 deficiency | **1** |
| NADH dehydrogenase core subunit 1 deficiency | **3** |
| NADH dehydrogenase core subunit 4 deficiency | **4** |
| NADH dehydrogenase core subunit 5 deficiency | **4** |
| Disorders of complex I assembly | NADH dehydrogenase α subcomplex assembly factor 6 deficiency | **1** |
| Disorders of complex II subunits | Succinate dehydrogenase subunit A deficiency | **2** |
| Disorders of complex III assembly | LYRM7 deficiency | **1** |
| Disorders of complex IV assembly and ancillary proteins | SURF1 deficiency | **1** |
| APOPT1 deficiency | **1** |
| Disorders of complex V subunits | Mitochondrial ATP synthase F0 subunit 6 deficiency | **2** |
| Disorders of complex V assembly | Transmembrane protein 70 deficiency | **1** |
| Disorders of mitochondrial DNA depletion, multiple deletion, or intergenomic communication | Mitochondrial deoxyguanosine kinase deficiency | **1** |
| Disorders of mitochondrial tRNA | Mitochondrial tRNA(Leu) 1 deficiency | **19** |
| Mitochondrial tRNA(Lys) deficiency | **3** |
| Disorders of mitochondrial tRNA incorporation and recycling | Mitochondrial aspartyl-tRNA synthetase deficiency | **1** |
| Mitochondrial glutamyl-tRNA synthetase deficiency | **1** |
| Mitochondrial phenylalanyl-tRNA synthetase deficiency | **1** |
| Mitochondrial tryptophanyl-tRNA synthetase deficiency | **1** |
| Disorders of mitochondrial fusion | OPA1 deficiency | **5** |
| Disorders of mitochondrial phospholipid metabolism | Tafazin deficiency | **3** |
| Primary CoQ10 deficiencies | COQ4 deficiency | **1** |
| Disorders of Lipids | Disorders of carnitine metabolism | Primary carnitine deficiency | **3** |
| Carnitine palmitoyltransferase 1A deficiency | **1** |
| Carnitine palmitoyltransferase 2 deficiency | **2** |
| Carnitine-acylcarnitine translocase deficiency | **2** |
| Disorders of fatty acid oxidation and transport | Short-chain acyl-CoA dehydrogenase deficiency | **2** |
| Medium-chain acyl-CoA dehydrogenase deficiency | **48** |
| Very long-chain acyl-CoA dehydrogenase deficiency | **15** |
| Trifunctional protein α subunit deficiency | **34** |
| Trifunctional protein β subunit deficiency | **4** |
| TANGO2 deficiency | **3** |
| Disorders of ketone body metabolism | Mitochondrial acetoacetyl-CoA thiolase deficiency | **4** |
| Disorder of fatty aldehyde metabolism | Fatty aldehyde dehydrogenase deficiency | **1** |
| Disorders of cytoplasmic triglyceride metabolism | Lysophosphatidic acid acyltransferase deficiency | **1** |
| CGI-58 deficiency | **1** |
| Disorders of phosphoinositide metabolism | Phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase deficiency | **1** |
| Disorders of lipoprotein metabolism | Hypercholesterolemia due to ligand-defective apo B | **1** |
| Apolipoprotein B deficiency | **1** |
| Sitosterolemia due to ABCG5 deficiency | **1** |
| Lipoprotein lipase deficiency | **2** |
| Disorders of cholesterol biosynthesis | Mevalonate kinase deficiency | **12** |
| 24-dehydrocholesterol reductase deficiency | **1** |
| 7-dehydrocholesterol reductase deficiency | **28** |
| Disorders of bile acid synthesis | Sterol 27-hydroxylase deficiency | **2** |
| Disorders of Tetrapyroles | Disorders of heme metabolism | Ferrochelatase deficiency | **1** |
| Disorders of bilirubin metabolism and biliary transport | UDP-glucuronosyltransferase A1 deficiency | **1** |
| Storage Disorders | Disorders of autophagy | EPG5 deficiency | **1** |
| Neuronal ceroid lipofuscinosis | Tripeptidyl-peptidase 1 deficiency | **2** |
| Sphingolipidoses | Glucocerebrosidase deficiency | **34** |
| β-galactosidase deficiency, GM1 gangliosidosis phenotype | **4** |
| β-hexosaminidase α-subunit deficiency | **2** |
| β-hexosaminidase β-subunit deficiency | **1** |
| β-galactosylceramidase deficiency | **1** |
| Arylsulfatase A deficiency | **2** |
| α-Galactosidase A deficiency | **6** |
| Mucolipidoses | UDP-N-acetylglucosamine-1-phosphotransferase γ subunit deficiency | **1** |
| Mucopolysaccharidoses | α-iduronidase deficiency | **11** |
| Iduronate sulfatase deficiency | **4** |
| Heparan N-sulfatase deficiency | **4** |
| N-acetylglucosaminidase deficiency | **2** |
| N-acetylgalactosamine 6-sulfatase deficiency | **5** |
| N-acetylgalactosamine 4-sulfatase deficiency | **2** |
| Disorders of lysosomal cholesterol metabolism | Niemann-Pick disease type C1 | **14** |
| Lysosomal acid lipase deficiency | **8** |
| Disorders of lysosomal transport or sorting | Cystinosin deficiency | **2** |
| Disorders of Peroxisomes and Oxalate | Disorders of plasmalogen synthesis | Glycerone 3-phosphate acyltransferase deficiency | **1** |
| Disorders of peroxisomal ß-oxidation | X-linked adrenoleukodystrophy | **18** |
| Disorder of peroxisomal ß-oxidation | Phytanoyl-CoA hydroxylase deficiency | **1** |
| Disorders of peroxisomal biogenesis | Peroxin 14 deficiency | **1** |
| Congenital Disorders of Glycosylation | Disorders of N-linked glycosylation | Phosphomannomutase 2 deficiency | **14** |
| X-linked recessive UDP-N-acetylglucosamine transferase catalytic subunit deficiency | **1** |
| Lipid-linked oligosaccharide flippase deficiency | **1** |
| ALG3 α-1,3-mannosyltransferase deficiency | **1** |
| ALG6 α-1,3-glucosyltransferase deficiency | **1** |
| Disorders of monosaccharide synthesis and interconversion | Phosphoglucomutase 1 deficiency | **1** |
| **Total** | **1047** |