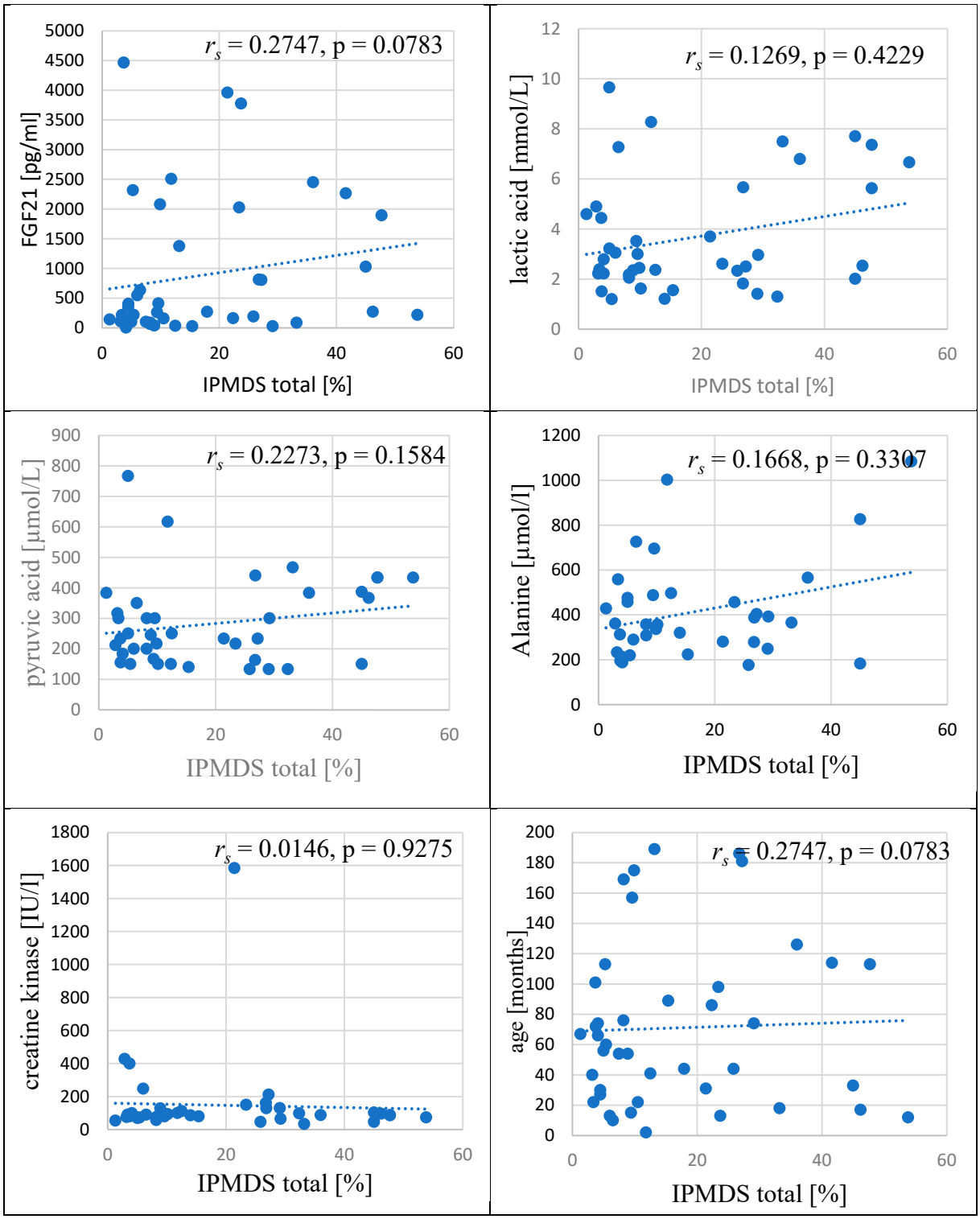


Figure S1. Correlation between individual biomarkers of mitochondrial disease and patients' age and disease severity (IPMDS)

Table S1. Patient data in the study groups

| Group | No | Age at study entry (months) | Gender | Follow-up time (months) | Genetic diagnosis | Predominant clinical symptoms at study entry |
|---|---|---|---|---|---|---|
| Group 1: MD + KD | 1.1 | 113 | M | 13 | *MT-TK* | Myopathy, myoclonus, ataxia, hearing loss, short stature, PEG |
| | 1.2 | 10 | M | 12 | *PDHA1* | Delayed psychomotor development, short stature |
| | 1.3 | 41 | M | 13 | *PDHA1* | Delayed psychomotor development, ataxia, tremor, short stature |
| | 1.4 | 157 | M | 12 | *MTND5* | Intellectual disability (mild), optic nerve atrophy, epilepsy, precocious puberty, hypertrophic cardiomyopathy |
| | 1.5 | 74 | M | 15 | *PDHA1* | Tetraparesis, ataxia, tremor, peripheral neuropathy |
| | 1.6 | 33 | F | 11 | *SLC25A12* | Developmental delay, tetraparesis, hypotonia, epilepsy, dysphagia, PEG |
| | 1.7 | 181 | F | 5 | mtDNA del | Myopathy, ptosis, ataxia, tremor, hearing loss, weight deficiency |
| | 1.8 | 56 | F | 11 | *PDHA1* | Tremor, hypotonia, exercise intolerance, epilepsy, short stature |
| | 1.9 | 12 | M | 5 | *PDHA1* | Developmental delay, tetraparesis, hypotonia, refractory epilepsy, microcephaly, short stature, PEG |
| | 1.10 | 60 | F | 12 | *PDHA1* | Myalgia, exercise intolerance, short stature |
| | 1.11 | 66 | M | 8 | *BCS1L* | Exercise intolerance, muscle weakness, hearing loss, pili torti |
| Group 2: MD without KD | 2.1 | 98 | M | 16 | *MT-TK* | Myopathy, myoclonus, ataxia, hearing loss, short stature |
| | 2.2 | 2 | M | 11 | *FBXL4* | Lack of progress in psychomotor development, increased muscle tone, epilepsy, cardiomyopathy, fed by nasogastric tube |
| | 2.3 | 101 | F | 12 | *MT-TL1* | Myopathy, reduced muscle tone, short stature |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 2.4 | 40 | F | 14 | *PDHA1* | Tremor, ataxia, hypotone, short stature |
| | 2.5 | 15 | M | 12 | *MT-ATP6* | Delayed psychomotor development, hypotonia, cardiomyopathy, weight deficiency |
| | 2.6 | 175 | F | 14 | mtDNA del | Myopathy, intention tremor, ptosis, sensorineural hearing loss, diabetes |
| | 2.7 | 13 | M | 9 | *NUBPL* | Trochlear nerve palsy |
| | 2.8 | 18 | M | 12 | nd | Delayed psychomotor development, reduced muscle tone, epilepsy, microcephaly, short stature |
| | 2.9 | 31 | F | 13 | *COQ8A* | Delayed speech development, developmental regression, ataxia |
| | 2.10 | 76 | M | 10 | *POLG* | Epilepsy, intention tremor, post-acute liver failure |
| Group 3 KD without MDDK bez CM | 3.1 | 79 | M | 13 | *SLC2A1* | Delayed psychomotor development, clumsiness, intention tremor |
| | 3.2 | 55 | F | 12 | *ASLD* | Developmental delay, spastic tetraparesis, epileptic encephalopathy, microcephaly, PEG |
| | 3.3 | 107 | M | 6 | *MOCS1* | Spastic tetraparesis, epileptic encephalopathy |
| | 3.4 | 19 | M | 3 | *GLUL* | Delayed psychomotor development, epileptic encephalopathy |
| | 3.5 | 20 | M | 12 | nd | Delayed psychomotor development, epilepsy, microcephaly, CNS defect, ocular hypoplasia |
| | 3.6 | 202 | M | 13 | *SLC2A1* | Intellectual disability, dystonia |
| | 3.7 | 77 | M | 12 | nd | Delayed psychomotor development, spastic tetraparesis, involuntary movements, epilepsy |
| | 3.8 | 62 | F | 13 | nd | Visual impairment, hearing loss, epilepsy |
| | 3.9 | 18 | F | 3 | nd | Delayed psychomotor development, spastic |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | tetraparesis, epileptic encephalopathy |
| | 3.10 | 162 | M | 12 | nd | Intellectual disability, epilepsy |
| Group 4 without MD and without KD | 4.1 | 39 | F | 13 | *RANSET2* | Spastic tetraparesis, strabismus, leukoencephalopathy |
| | 4.2 | 11 | M | 7 | nd | Delayed psychomotor development |
| | 4.3 | 72 | F | 12 | nd | Healthy, no symptoms |
| | 4.4 | 11 | F | 16 | *ADAR* | Spastic tetraparesis, encephalopathy |
| | 4.5 | 11 | M | 10 | nd | Delayed psychomotor development, epilepsy, microcephaly, CNS defect |
| | 4.6 | 8 | M | 16 | nd | Delayed psychomotor development, West syndrome |
| | 4.7 | 31 | M | 9 | nd | Delayed psychomotor development |
| | 4.8 | 78 | M | 12 | *ABCD1* | Adrenal insufficiency |
| | 4.9 | 72 | M | 15 | *OTC* | Delayed psychomotor development, epilepsy |
| | 4.10 | 46 | F | 8 | nd | Delayed psychomotor development |
| | 4.11 | 31 | F | 15 | nd | Delayed psychomotor development, ataxia |

F – female KD – ketogenic diet, MD - mitochondrial disease, M – male, nd – no date, PEG – percutaneous feeding gastrostomy

Table S2. Biochemical parameters in patients with mitochondrial disease (group 1 + 2) and in patients without disease (group 3 + 4)

| Biochemical parameters (normal range) | Group 1 + 2 Median (range) | Group 3 + 4 Median (range) |
|---|---|---|
| FGF21 [pg/mL] (normal range < 275) | 412.6 (4.1 – 4466.9) | 52.9 (6.1 – 294.4) |
| Lactic acid [mmol/L] (normal range: 0.5 – 2.2) | 3.0 (1.2 – 9.6) | 1.7 (0.9 – 6.0) |
| Pyruvic acid [µmol/L] (normal range: 50 – 200) | 233.4 (133.4 – 766.9) | 166.7 (66.7 – 316.7) |
| Alanine [µmol/L] (normal range: 144 – 418) | 361 (182 – 1084) | 241 (173 – 297) |
| Creatine kinase [IU/l] (normal range: 0 – 154) | 93 (34 – 1584) | 107 (38 – 972) |

Table S3. Biochemical parameters in patients with mitochondrial disease at visit V0 and V12

| Biochemical parameters (normal range) | Group 1 (MD + KD) Median (range) V0 | Group 1 (MD + KD) Median (range)V12 | Group 2 (MD without KD) Median (range)V0 | Group 2 (MD without KD) Median (range)V12 |
|---|---|---|---|---|
| FGF21 [pg/ml] (normal range < 275) | 220.5 (4.1 – 1895.9) | 141.2 (29.2 – 2453.0) | 1288.6 (65.5 – 4466.9) | 381,.3 (102.3 – 3776.0) |
| Lactic acid [mmol/L] (normal range: 0.5 – 2.2) | 2.8 (1.2 – 9.6) | 2.3 (1.5 – 6.8) | 3.3 (2.2 – 8.2) | 3.1 (1.2 – 7.2) |
| Pyruvic acid [µmol/L] (normal range: 50 – 200) | 266.7 (133 – 767) | 250.0 (133 – 383) | 216.7 (164 – 617) | 250.0 (133 – 433) |
| Alanine [µmol/l] (normal range: 144 – 418) | 439 (182 – 1084) | 278 (175 – 565) | 346 (232 – 1002) | 374 (319 – 826) |
| Creatine kinase [IU/l] (normal range: 0 – 154) | 87 (46 – 212) | 85 (46 – 161) | 96 (34 – 1584) | 90 (65 – 428) |