**Table e-1:** Reported *MT-TG* variants and associated clinical phenotypes referenced against mt-tRNA pathogenicity scoring system criteria1

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mutation** | **Age / clinical phenotype** | **More than one independent report (score)** | **Evolutionary conservation (Fig. e-1) (score)** | **Variant heteroplasmy (score)** | **Segregation with disease**  **(score)** | **Histochemical evidence (score)** | **Biochemical defect in CI, II or IV (score)** | **Segregation with biochemical defect on single-fibre analysis (score)** | **Positive *trans*mitochondrial cybrid studies (score)** | **Total score** | **Pathogenicity** |
| **m.9997T>C** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1 | 8mo, HCM, SUD. FH of HCM +/- chronic bowel immotility and renal disease2, 3 | No (0) | No (0) | 92% muscle  40% urine  15% blood  Yes (2) | Yes (2) | ND (0) | Yes (2) | ND (0) | Yes (5) | 11 | Definite |
| **m.10006A>G** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1 | CIPO. Carrier of 12308A>G and 12246C>A4 | Yes (2) | No (0) | Unknown | ND (0) | Yes, weak (1) | No (0) | Negative (0) | ND (0) | 3 | Neutral polymorphism (not pathogenic in isolation) |
| Case 2 | Detected in EOM of aged deceased at PM with other mtDNA variants5 | Unknown |
| Case 3 | 2yrs, encephalopathy, myopathy, CPEO, neuropathy, deafness, bowel symptoms. Carrier of 12246C>A6 | Homoplasmic No (0) |
| **m.10010T>C** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1 | 20yrs, f, short stature, low IQ, seizures, ataxia, dystonia, tetraparesis, optic atrophy, SNHL, glucose intolerance7 | Yes (2) | Yes (2) | Yes (2) | Yes (2) | Yes, strong (2) | Yes (2) | Yes (3) | ND (0) | 15 | Definitely pathogenic |
| Case 2 | 28yrs, f, myalgia, EI, fatigue, hyperCKaemia, septal MI aged 388 |
| Case 3 | 22yrs, m, myalgia, EI, axonal motor neuropathy, hyperCKaemia, GTCS, encephalopathy9 |
| Case 4 | 1yr, m, dystonia, psychomotor retardation, LD and cerebellar atrophy on MRI. Also carrier of MT-ND3 m.10191T>C (confirmed cause of LD)10 |
| **m.10014A>G** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1 | 9yrs, m, Myopathy with EI. Carrier of 1664G>A6 | No (0) | No (0) | No (0) | ND (0) | Yes, strong (2) | ND (0) | ND (0) | ND (0) | 2 | Neutral polymorphism (insufficient data) |
| **m.10038G>A** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1  (Present study) | Adolescence, f, Short stature, secondary amenorrhoea, SNHL, cataracts, retinal dystrophy, hypothyroidism | No (0) | Yes (2) | Yes (2) | Yes (2) | Yes, strong (2) | Yes (2) | Yes (3) | ND (0) | 13 | Definitely pathogenic |
| **m.10044A>G** |  |  |  |  |  |  |  |  |  |  |  |
| Case 1 | 8mo, died from encephalopathy; sibling SUD, 6 sibs with multisystem disease apparent life threatening events (cyanosis +/- bradycardia +/- limpness), GORD, asthma, sinusitis, learning disability, ADHD11 | Yes (2) | No (0) | Yes (2) | Yes (2) | No (0) | Yes (2) | ND (0) | ND (0) | 8 | Possibly pathogenic (but present in healthy controls) |
| Cases 2-6 | 2 cases with SNHL, 1 with DM and 2 healthy controls12 |
| Case 7 | 3mo, healthy control13 |

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; CI, complex I; CII, complex II; CIV, complex IV; CIPO, chronic intestinal pseudo-obstruction; CPEO, chronic progressive external ophthalmoplegia; DM, diabetes mellitus; EI, exercise intolerance; EOM, extraocular muscles; f, female; FH, family history; GORD, gastro-oesphageal reflux disease; GTCS, generalised tonic-clonic seizure; HCM, hypertrophic cardiomyopathy; hyperCKaemia, raised blood creatine kinase; LD, learning difficulties; m, male; MI, myocardial infarction; mo, months; ND, not done; PM, post mortem; SNHL, sensorineural hearing loss; SUD, sudden unexplained death; yr(s), year(s).

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