**Supplementary Table 1. Overview of disease genes associated with dystonia and optic atrophy which are of interest in the differential diagnosis of NDUFA12-associated mitochondrial disease**

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| **Gene** | **MOI** | **Dystonia** | **Movement disorder** | **Pyramidal signs** | **Ataxia** | **Muscle/ nerve involvement** | **Seizures** | **Cognitive impairment/delay** | **Type of ocular involvement** | **Magnetic Resonance Imaging** | **Hearing loss** | **Other findings** |
| ***NDUFA12***  | AR | Focal or generalized dystonia. | In some cases, extrapyramidal syndrome  | Spasticity | No  | Muscle atrophy, uncommon | Rare | Variably present  | Common optic atrophy | Hyperintensities  | No | Scoliosis, facial dysmorphisms |
|  |
| **Disorders in which dystonia and optic atrophy are prominent manifestations** |
| ***C19orf12****1* | AD/AR | Generalized or oromandibular dystonia. | Mild parkinsonism, variable | Spasticity | Variably present  | Distal muscle weakness, motor axonal neuropathy | No | Variably present  | Bilateral optic atrophy | Iron accumulation, cerebellar atrophy | No |   |
| ***MECR2*** | AR | Yes, main phenotype, childhood onset. | Chorea variably present | Spasticity | Yes, variable, dysarthria. | One with neck muscle weakness  | No | Rare | Bilateral optic atrophy | Bilateral hyperintense T2-weighted signal in one or more structures of the basal ganglia |   | Dysphagia |
| ***TIMM8A3*** | XLR | Main phenotype, progressive, adult-onset | Parkinsonism | Spasticity, variably present | Variably present | Variable Peripheral neuropathy | No | Variably present | Either optic atrophy or cortical visual impairment | Symmetrical caudate head atrophy | Yes |   |
| ***NDUFS1****4* | AR | Frequent | Common hyperkinetic movements |   |   | Uncommon | Variably present | Frequent | Frequent optic atrophy | White matter changes, basal ganglia involvement  |   | Feeding difficulties |
| ***SDHA****5* | AR/AD | Frequently associated with biallelic mutations  | Myoclonus | Spasticity | Cerebellar gait ataxia | Muscle weakness, sensory neuropathy  | Yes | Yes | Optic atrophy (both AR and AD) | Cerebellar atrophy, Leigh-like pattern |   | Cardiomyopathy |
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|  |
| **Other disease genes associated with dystonia and/or optic atrophy** |
| ***AUH****6,7* | AR | Variably present | Choreoathetoid movements variably present | Variable (spasticity, quadriplegia) | Yes (gait and dysarthria) | No | Yes (variably present) | Mental retardation | Optic atrophy | Diffuse white matter lesions or basal ganglia involvement |   |   |
| ***TSFM8*** | AR | Dystonic posturing reported | Tremor, hyperkinetic movement disorder | No | Yes  | Axonal sensorimotor neuropathy variably present | Variably present | Global developmental delay | Optic atrophy/ neuropathy | Basal ganglia involvement  |   | Dilated cardiomyopathy |
| ***MT-ND6****9* |  | Alone or in association with pathogenic MT-ND4 point mutation10 | Tremor, myoclonus | No | Variable | Muscle atrophy | Yes | Psychomotor delay | Leber hereditary optic neuropathy | Typical Leigh syndrome pattern |   | No |
| ***AFG3L2****11* | AD/AR | Rare | Myoclonus, parkinsonism in concurrence with SPG7 mutation | Spasticity | Main phenotype | Variably present  | Homozygous mutations linked to intractable seizures. | Homozygous mutations linked to regression of developmental milestones, heterozygous associated with mild ID | Isolated or syndromic | Variable, from cerebellar atrophy to basal ganglia involvement, “eye-of-the tiger” sign.  |   | Uncommon |
| ***DNM1L****12,13* | AD/AR  | In few de novo, dystonia | Myoclonus | Mild spasticity in one case | Yes. de novo | In few de novo, muscle atrophy and sensory neuropathy | De novo, also status epilepticus | Mild to moderate developmental delay | De Novo missense variant isolated optic atrophy | Variable involvement of basal ganglia, thalamus, hippocampus, frontal, and temporal lobe. |   |   |
| ***MFF****14* | AR | Dystonia of the foot | No | Spasticity | No | Muscle weakness | Rare myoclonic seizure | Developmental delay | Temporal disc pallor | Cerebellar atrophy, basal ganglia involvement | Yes |   |
| ***OPA1****15* | AR/AD | In one case cervical dystonia | Syndromic parkinsonism | Spasticity | Yes | Mitochondrial myopathy and peripheral neuropathy | Rare, focal occipital epilepsy  | Developmental delay or dementia | Bilateral optic atrophy, external ophthalmoplegia.  | White matter abnormalities | Deafness |   |
| ***OPA3****15-17* | AR/AD | Variably present | Choreatetosis, extrapyramidal signs, variably present  | Pyramidal sign always present, spasticity | Dysarthria, gait, and limb ataxia. | Variably present, axonal peripheral neuropathy | Uncommon | Not usually impaired, but possible developmental delay or regression | Bilateral optic disc atrophy, nystagmus | Chiasmal thinning and cerebellar atrophy | Yes | Gastrointestinal dysmotility |
| ***SPG7****18* | AR | Rare | Rare | Spasticity, Babinski  | Cerebellar ataxia | Muscle weakness | No | Rare | Rare | Cerebellar atrophy in half cases |   | Bladder and anal sphincter dysfunction  |
| ***ATAD3A****19,20* | AD, AR | Reported  | No | Spastic paraplegia in some cases | Cerebellar ataxia | Muscle wasting in some cases | Uncommon  | Variably present developmental delay, from mild to severe | Congenital cataracts, variable presence of optic atrophy | Pontocerebellar hypoplasia  |   | Hypertrophic cardiomyopathy |
| ***FDXR****21* | AR | Uncommon | Involuntary movements  | Variably present spasticity | Variably present  | Axial weakness, uncommon neuropathy | Uncommon | Common developmental delay/ regression | Optic atrophy, cataracts  | Cerebral atrophy, basal ganglia involvement, delayed myelination  | Acoustic neuropathy | Microcephaly and facial dysmorphisms |
| ***POLG****22* | AR/AD | Rarely | Parkinsonism | Rare | Sensory or cerebellar ataxia, variably present  | Common muscle weakness, peripheral neuropathy, less frequent isolated distal myopathy  | Uncommon in neonatal onset phenotypes, common intractable seizure in childhood onset , RHADS on EEG | Common developmental delay or developmental regression  | Uncommon Cataracts , ophthalmoplegia,  | Stroke-like lesions, less commonly thalamic, basal ganglia and cerebellar involvement  | Yes  | Hepatic impairment with liver failure, renal dysfunction  |
| ***ALG3****23,24* | AR | Variably present | No | Rare | No | Muscular hypotonia  | Common | Frequent developmental delay  | Common, including strabismus and optic atrophy | Cerebral anomalies (dysmorphic hemisphere, dysplasia, atrophy, rarely Dandy Walker)  | Yes | Craniofacial abnormalities, feeding problems , cardiac anomalies. |
| ***DNAJC19****25* | AR | Variably present | Variably present | Variably present | Non progressive cerebellar ataxia  | Variably present muscular atrophy | Rare/ uncommon | Variably present  | Variably present | Bilateral basal ganglia involvement or cerebellar atrophy | Yes | Dilated cardiomyopathy, facial dysmorphisms |
| ***FXN****26* | AR | Rare laringeal dystonia  | No | Extensor plantar responses | Frequent ataxia, dysarthia | Muscle weakness, sensory neuropathy | No | No | Optic tract atrophy | Cerebellar atrophy | Deafness | Foot deformities |
| ***NDUFS3****27* | AR | Axial dystonia in few cases | No | Pyramidalsigns | Yes | Muscle hypotonia | Febrile seizures | Yes | Optic atrophy | High T2 signal intensity in the putamen, the white matter, and the brain stem |   | Dysphagia |
| ***MTPAP****28,29* | AR | Rarely dystonic posturing | No | Spasticity | Spastic ataxia | No | No | Lethal encephalopathy in 3 cases | Optic atrophy | Diffuse T2 white matter hyperintensities  |   |   |
| ***NDUFS2****30* | AR | Rarely dystonic posturing | No | Pyramidal signs | No  | Muscle hypotonia | No | Developmental regression, uncommon | Optic neuropathy common | Leukodystrophy, brain atrophy |   | Cardiomyopathy |
| ***SLC25A462****31-34* | AR | Cervical dystonia reported | Tremor and myoclonus variably present, also associated with Parkinson. | Rare | Gait ataxia | Motor and/or sensory neuropathy | No | Uncommon, associated with Pontocerebellar Hypoplasia type 1 | Bilateral optic atrophy | Cerebellar atrophy and diffuse cerebellar hyperintensities, but in some cases MRI normal |  | Probably associated with Hashimoto’s thyroiditis  |

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