Thesis

Progressive myoclonus ataxia – Expanding the phenotype of MT-ATP6-associated disease

A retrospective study

submitted by

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Graz, 21. April 2026 Johanna Caroline Mayrhofer-Grüenbühl m.p.

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Zusammenfassung

Einleitung

Hereditäre Myoklonus-Ataxie-Syndrome (MAS) sind eine genetisch heterogene Gruppe von Erkrankungen mit einem breiten Spektrum klinischer Merkmale (1, 2). Eine seltene mitochondriale Mutation im MT-ATP6-Gen, die m.9176T>C-Variante, wurde mit diesen Erkrankungen in Verbindung gebracht und geht mit sehr variablen klinischen Erscheinungsformen einher (1). Die Abgrenzung einer durch MT-ATP6-Mutationen verursachten progressiven Myoklonus-Ataxie (PMA) von anderen hereditären Ataxien bleibt nach wie vor herausfordernd. In dieser Studie beschreiben wir die klinischen Merkmale einer Familie mit PMA und der m.9176T>C-Variante der MT-ATP6 Mutation und ergänzen dies durch eine systematische Literaturrecherche aller bislang veröffentlichten Fälle dieser Mutation.

Methoden

Die Studie kombiniert eine retrospektive klinische Fallanalyse mit einer systematischen Literaturrecherche. Für ersteres wurden die elektronischen Patientenakten der Bewegungsstörungsambulanz der Abteilung für Neurologie der Medizinischen Universität Graz von Januar 2012 bis September 2022 auf Fälle mit progressiver Myoklonus-Ataxie und der MT-ATP6 Mutation durchsucht. Drei betroffene weibliche Mitglieder einer Familie mit der m.9176T>C-Variante wurden identifiziert und in die Analyse einbezogen, wobei klinische, radiologische und therapiebezogene Daten aus pseudonymisierten Akten extrahiert wurden. Parallel dazu erfolgte eine systematische PubMed-Suche nach allen veröffentlichten Fällen der m.9176T>C-Variante. Dabei wurden insgesamt 25 Publikationen mit 48 Fällen identifiziert. Die klinischen Merkmale unserer drei Patientinnen wurden anschließend mittels deskriptiver Statistik mit den in der Literatur berichteten Phänotypen verglichen.

Ergebnisse

Das Alter beim Symptombeginn beeinflusste die klinische Ausprägung in den aus der Literaturrecherche erhobenen Daten deutlich. Früh einsetzende Fälle (<2 Jahre) waren hauptsächlich mit dem Leigh-Syndrom (LS), Entwicklungsverzögerungen, erhöhtem Lactat und schneller Progression assoziiert, während später einsetzende Fälle (>12 Jahre) mildere, langsam progrediente Bewegungsstörungen wie die hereditäre spastische Paraplegie (HSP) oder Charcot-Marie-Tooth-Krankheit (CMT) zeigten.

Unsere Familie präsentierte einen bislang unbeschriebenen und ungewöhnlich milden Phänotyp mit progressiver Myoklonus-Ataxie. Klinische Charakteristika waren Myoklonus, Ataxie und milde Epilepsie mit minimaler kognitiver und systemischer Beteiligung. MRT und Laktat waren bei der Indexpatientin unauffällig und die Schwere der Erkrankung variierte innerhalb der Familie, was die ausgeprägte intrafamiliäre Variabilität verdeutlicht.

Diskussion

Wir beschreiben einen bislang unberichteten PMA-ähnlichen Phänotyp, der mit homoplasmischer m.9176T>C MT-ATP6-Mutation assoziiert ist und sich vom klassischen früh einsetzenden Leigh-Syndrom (LS) unterscheidet. Die systematische Literaturrecherche bestätigte, dass früher Beginn mit schwereren Phänotypen verbunden ist, während später Beginn meist mildere, langsam progrediente Verläufe zeigt. Trotz Homoplasmie war der Krankheitsverlauf bei unseren Patientinnen mild, was zeigt, dass die Mutationslast allein den Phänotyp nicht vorhersagt. Diese Ergebnisse erweitern das klinische Spektrum der MT-ATP6-assoziierten Erkrankungen und unterstreichen, dass MT-ATP6-Mutationen auch bei PMA-ähnlichen Präsentationen mit vermuteter maternaler Vererbung differentialdiagnostisch berücksichtigt werden sollten.

Abstract

Introduction

Hereditary myoclonus-ataxia syndromes (MAS) are a genetically heterogenous group of disorders with a wide spectrum of clinical features (1, 2). A rare mitochondrial mutation in the MT-ATP6 gene, the m.9176T>C variant, has been linked to these conditions, which show highly variable symptoms (1). Clinically distinguishing progressive myoclonus-ataxia caused by MT-ATP6 mutations from other hereditary ataxias remains challenging. Within this study, we present the clinical characteristics of progressive myoclonus-ataxia (PMA) in a family carrying the m.9176T>C variant of the MT-ATP6 mutation and perform a systematic literature review of all reported cases of this mutation.

Methods

This study combined a retrospective clinical case analysis and a systematic literature review. For the former, electronic patient records from the Movement Disorders Clinic at the Department of Neurology, Medical University of Graz, between January 2012 and September 2022 were searched to identify patients with progressive myoclonus ataxia (PMA) associated with the MT-ATP6 mutation. Three affected female members of a family with the m.9176T>C variant were identified and included in the analysis, and clinical, radiological, and therapy-related data were extracted from pseudonymized records. In parallel, a systematic PubMed search was conducted for all published cases of the m.9176T>C variant. In total, 25 publications comprising 48 cases were identified. The clinical features of our three patients were compared with reported phenotypes using descriptive statistical analysis.

Results

Age at symptom onset had a significant impact on clinical severity in the data collected from the literature review. Early-onset cases (<2 years) were mainly associated with Leigh syndrome (LS), developmental delay, elevated lactate, and rapid progression, whereas later-onset cases (>12 years) showed milder, slowly progressive movement disorders, including hereditary spastic paraplegia (HSP) or Charcot-Marie-Tooth disease (CMT).

Our family presented a novel and unusually mild phenotype of progressive myoclonus-ataxia. Clinical features included myoclonus, ataxia, and mild seizures with minimal cognitive and systemic involvement. MRI and lactate were normal in the index patient, and disease severity varied within the family, demonstrating marked intrafamilial variability.

Discussion

We describe a previously unreported PMA-like phenotype associated with homoplasmic m.9176T>C MT-ATP6 mutation, distinct from classical early-onset LS. The systematic literature review confirmed that earlier onset is linked to more severe phenotypes, while later onset tends to result in milder, slowly progressive courses. Despite homoplasmy, disease severity in our patients was mild, indicating that mutation load alone does not predict phenotype. These findings broaden the clinical spectrum of MT-ATP6–related disorders and emphasize the importance of considering MT-ATP6 mutations in the differential diagnosis of PMA-like presentations with suspected maternal inheritance.

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Abbreviations

ANS	ataxia neuropathy spectrum
ATP	Adenosine triphosphate
CLN2	Ceroid lipofuscinosis, neuronal, type 2
CLN4	Ceroid lipofuscinosis, neuronal, type 4
CMT	Charcot-Marie-Tooth
CSF	Cerebrospinal fluid
CSTB	Cystatin B
CT	Computer tomography
CV	Complex V
DNA	Deoxyribonucleic acid
EEG	Electroencephalography
EMG	Electromyography
EPM1	Progressive myoclonic epilepsy type 1
EPM2A	Epilepsy, Progressive Myoclonus Type 2A-gene
EPM2B	Epilepsy, Progressive Myoclonus Type 2B-gene
G1	Group 1
G2	Group 2
G3	Group 3
HSP	Hereditary spastic paraplegia
IMM	Inner mitochondrial membrane
IVIG	Intravenous immunoglobulin
IQR	Interquartile range
KCNC1	Potassium voltage-gated channel subfamily C member 1
KSS	Kearns-Sayre syndrome
LS	Leigh syndrome
LLS	Leigh-like syndrome
MAS	Myoclonus ataxia syndrome
MEAK	Myoclonic epilepsy and ataxia due to potassium channel mutation
MELAS	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

MEMSA	myoclonic epilepsy, myopathic sensory ataxia
MERRF	Myoclonic red fiber epilepsy
MILS	Maternally inherited leigh syndrome
MRI	Magnetic Resonance Imaging
MT-ATP6	Mitochondrial ATP synthase 6
MTTF	mitochondrially encoded tRNA-Phe (UUU/C)
MTTS1	Mitochondrially Encoded tRNA-Ser (UCN) 1
MTTS2	mitochondrially encoded tRNA-Ser (AGU/C) 2
mtDNA	mitochondrial deoxyribonucleic acid
MTTH	Mitochondrially Encoded TRNA-His (CAU/C)
MT-TK	mitochondrially encoded tRNA-Lys (AAA/G)
MT-TL1	mitochondrially encoded tRNA-Leu (UUA/G) 1
NARP	Neuropathy, ataxia, and retinitis pigmentosa
NEU1	Neuraminidase 1 (gene)
NHLRC1	NHL Repeat Containing E3 Ubiquitin Protein Ligase 1
NCL	Neuronal ceroid lipofuscinosis
NGS	Next generation sequencing
North Sea PME	North Sea Progressive Myoclonus Epilepsy
P1	Patient 1
P2	Patient 2
P3	Patient 3
PMA	Progressive Myoclonus Ataxia
POLG	Polymerase gamma (gene)
PME	Progressive Myoclonus Epilepsy
RCSV	Reversible vasoconstriction syndrome
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SCA1/2/3/6/7	Spinocerebellar ataxia type 1/2/3/6/7
SCA17	Spinocerebellar ataxia type 17
ULD	Unverricht-Lundborg disease
UMN	Upper motor neuron

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1 Introduction

1.1 Movement disorders

Movement disorders may be divided into those characterized by an excess of movement (hyperkinesia) and those characterized by a lack of movement (hypokinesia) (3).
The first may be referred to as hyperkinesias, dyskinesias (abnormal movements) or abnormal involuntary movements. The latter may be called hypokinesias (lack of movement), bradykinesias (slowness of movement) or akinesias (loss of movement) and may be associated with rigidity (so-called akinetic-rigid syndromes) (3, 4).
Furthermore, a subdivision into primary and secondary movement disorders can be made. In primary movement disorders, the cause of the condition is unknown. Secondary movement disorders on the other hand, are the result of another neurological disease (3).

1.1.1 Classification of Hyperkinetic movement disorders

According to C. Marsden, the majority of hyperkinetic movement disorders can be grouped into one of 5 categories: Tremor, Myoclonus, Dystonia, Chorea, Tics (3).
However, in a broader sense, it also includes conditions such as ataxia, hemifacial spasm, restless legs or paroxysmal dyskinesias (4).

1.1.1.1 Tremor

The Consensus statement on the Classification of Tremors 2018 describes Tremor as an involuntary, rhythmic, oscillatory movement of a body part (5).
Tremor can affect one or more parts of the body and has a variety of causes (6). Most commonly, Tremor occurs in the upper limbs, but can also affect the legs, head, jaw, or face (7). Tremors can be categorized into two types: rest tremor and

action tremor (5). During a rest tremor, the patient does not consciously activate the body part, whereas during an action tremor, the patient voluntarily moves against gravity or maintains a position (5).

1.1.1.2 Myoclonus

The hyperkinetic movement disorder myoclonus can be defined as sudden, short, shock-like, involuntary movement. The movement is caused by either muscle contraction (positive myoclonus) or muscle inhibition (negative myoclonus or asterixis) (8).

Classification

Myoclonus can be classified according to body distribution, association with activity and triggering factors (mode of presentation), neurophysiology, and etiology (9, 10). According to its etiology, the classification scheme of Marsden-Hallett-Fahn differentiates between four types of myoclonus: physiological, essential, epileptic, and symptomatic myoclonus (3).

Physiological myoclonus can occur in normal people, is benign, and resolves eventually. Common examples are twitching when falling asleep or hiccups (11).

In the case where myoclonus is the only neurological impairment, it is referred to as *essential myoclonus* (3). This form of myoclonus may be idiopathic, sporadic, or hereditary (8).

Epileptic myoclonus occurs in the context of epilepsy and can be the only manifestation of the seizure, may be only one component of the seizure, or may occur along with other seizure types (8).

What is known as *symptomatic* (secondary) *myoclonus* occurs in the presence of an already existing disorder that may be neurological or non-neurological in origin (12). It is the most common form of myoclonus (12).

Depending on its distribution across the body, myoclonus can be classified as focal, multifocal, segmental, or generalized (9).

As per its mode of presentation, myoclonus can be divided into resting myoclonus, action myoclonus and stimulus-induced myoclonus (10).

Classification by neurophysiology distinguishes cortical, cortical-subcortical, subcortical, segmental, peripheral, and functional myoclonus (8).

1.1.1.3 Dystonia

Dystonia can be characterized by persistent or repeating episodes of muscle contractions that result in abnormal movements or postures (13). This movement disorder is typically triggered by voluntary actions, and movements may be patterned, tortuous, or shaky (13).

1.1.1.4 Chorea

The term "chorea" comes from the Greek word "choreia", which means "dance" (14). This hyperkinetic movement disorder can be characterized by sudden, aimless and non-stereotypical movements that switch between different parts of the body (15).

1.1.1.5 Tics

Tics can manifest themselves in repetitive movements or phonic utterances. Patients often try to suppress the unpleasant urge to express the tic. The urge is relieved for a time by tic production. One of the best known and most important chronic tic disorders is Tourette’s syndrome (15).

1.1.1.6 Ataxia

We can see the lack of coordination as a synonym for ataxia. It may have its origin in congenital cerebellar defects or neurological diseases, such as multiple sclerosis or stroke.
However, abnormal sensory input can also lead to ataxia, which means that not all patients with ataxia may show abnormalities in the cerebellum (16).

The causes of the dysfunction may be located in the cerebellum, its afferent and efferent pathways, or in the spinal cord (11).

The course of ataxia can be divided into acute, subacute, episodic, or chronic and the origin can be genetic or acquired (17). There may also be a classification of ataxias into primary and secondary (18).

The causes of acquired ataxias can be immune-mediated, degenerative, deficit, toxic, or infectious. Hereditary ataxias can occur in an autosomal dominant or recessive, X-linked, or mitochondrial manner (17).

Typical symptoms of ataxia include gait problems, difficulty running or walking on high heels, slurred speech, frequent falls, clumsiness, unsteadiness as well as poor handwriting (16, 17).

Hereditary ataxias must be taken into consideration when the disease shows an inheritance pattern across generations within a family. This concerns in particular the autosomal-dominantly inherited ataxias (19).

At the present time, more than 40 autosomal dominant ataxias are known (17). They can be divided into progressive spinocerebellar ataxias and episodic ataxias, which differ in their disease course (20).

Among spinocerebellar ataxias, those caused by CAG repeat expansions are the most common, such as SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 (16).

So far, 8 different forms of episodic ataxia are known, of which types 1 and 2 are the most frequent (16, 18).

Autosomal recessive ataxias comprise a heterogenous group of disorders, including Friedreich's ataxia, Ataxia Telangiectasia, Ataxia with Oculomotor Apraxia Type 1 and Type, Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay, Abetalipoproteinemia and Cayman Ataxia (19). These conditions usually present in childhood or early adulthood but can also occur later in life course (20).

X-linked ataxias are the result of X-linked recessive mutations (18). Fragile X-tremor ataxia syndrome is currently the most prevalent form of X-linked ataxia (16).

Abnormalities in mitochondrial DNA lead to mitochondrial ataxias. This form usually combines cerebellar and sensory ataxias (20).

Mitochondrial ataxias include maternally inherited ataxias due to point mutations in genes that encode RNAs and subunits of the respiratory chain, as well as deletions/duplications of mitochondrial DNA (18). Examples of this type of ataxia include myoclonic red fiber epilepsy (MERRF), neuropathy, ataxia, and retinitis

pigmentosa (NARP), progressive external ophthalmoplegia, Kearns-Sayre syndrome, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (20).

One of the mitochondrial DNA genes that may be affected is MT-ATP6 (mitochondrial ATP synthase 6), which encodes subunit-α of the F1F0ATP synthase complex. This protein is an essential component of the complex and is responsible for mitochondrial energy production (1).

1.2 Myoclonus ataxia syndromes (MAS)

Among myoclonic syndromes, the most frequent additional movement disorder is ataxia (21).

Myoclonus and ataxia are combined in several disorders. Most MAS have a genetic background. Most of the time, MAS presents as progressive myoclonus epilepsy (PME; see chapter 1.2.2) or progressive myoclonus ataxia (PMA; see chapter 1.2.1) (22).

Cortical myoclonus can be considered the most frequent form of myoclonus in myoclonus ataxia syndromes. Cortical myoclonus in MAS often manifests as action-induced and stimulus-sensitive myoclonus and is especially common in the distal limbs and face (12).

Disorders that belong to the myoclonus ataxia syndromes and in which cortical myoclonus can be observed are Unverricht-Lundborg disease, myoclonic Lafora epilepsy, or, for example, North Sea progressive myoclonus epilepsy.

Myoclonus in MAS may also present as subcortical myoclonus. This is seen in conditions such as ataxia-telangiectasia, spinocerebellar ataxia types 2 and 14, and primary coenzyme Q10 deficiency. In prion disease and opsoclonus-myoclonus-ataxia syndrome, subcortical myoclonus may originate in the brainstem (22).

Most diseases that fall within the spectrum of MAS have abnormal post-translational modification of proteins. Relative to others, specific neuronal groups may show a higher degree of vulnerability to this disorder (21, 22).

The frequent combination of myoclonus and ataxia in movement disorders suggests that pathophysiological mechanisms, such as disruption of the

cerebellothalamicocortical pathway or loss of Purkinje cells, may contribute to the development of myoclonus (22).

1.2.1 Progressive myoclonus ataxia

Disorders that are now grouped under the term progressive myoclonus ataxia (PMA) were formerly known as Ramsay Hunt Syndrome (22).

The disease is named after Sir James Ramsay Hunt, who in 1921 was the first to describe the following symptoms: progressive ataxia and myoclonus, without severe impairment of cognitive functions and sometimes associated with occasional epileptic seizures (23).

Hunt described six patients under the name "Dyssingeria cerebellaris myoclonica - primary atrophy of the dentate system." He believed that the symptoms of the disease were due to degeneration of the dentate system, since autopsy of one of the patients he had described revealed degeneration of the spinocerebellar tracts and posterior columns, along with atrophy of the dentate nuclei and superior cerebellar peduncles (24).

Although PMA can be acquired, in most cases it has a genetic cause (23). Unfortunately, although next generation sequencing (NGS) is frequently used, the exact cause of PMA remains unclear in many cases (22).

Since the term ‘Ramsay Hunt syndrome’ caused confusion because there was no uniform definition, and the term ‘progressive myoclonus epilepsy’ did not cover cases in which patients did not have tonic-clonic seizures or prominent signs of dementia, the term "progressive myoclonus ataxia" was born (24).

The term ‘progressive myoclonus ataxia’ was introduced by the Marseille Consensus Group in 1990 (24). PMA has similarities to PME, which makes the distinction between these two disorders not always easy (22). Compared to PME, epilepsy is minor or absent in PMA. Furthermore, cognitive impairments are minor or absent (24).

However, the demarcation problems between PMA and PME remain. Among other things, there is disagreement about whether at least mild cognitive impairment should be included among the criteria for PMA at all. Similarly, there is disagreement about the assignment to PMA or PME for some disorders. For example, North Sea PME is described in the literature as both PME and PMA (23).

1.2.2 Progressive myoclonus epilepsy

Among the cases of secondary generalized epilepsies, which are characterized by generalized epilepsies in the context of static or progressive encephalopathy, progressive myoclonus epilepsies form a small subgroup. PME, just like PMA, can be seen as a set of symptoms rather than a disease in its own right (24).

Symptoms typically appear between childhood and adolescence, but may also present in adulthood (25). The majority of PMEs with identified molecular causes are passed on in an autosomal recessive manner, while autosomal dominant or mitochondrial inheritance patterns are observed only infrequently (26). PMEs are associated with various diseases, including Lafora body disease and Unverricht-Lundborg disease (27). The clinical outcome of PMEs is dependent on the particular disease (27).

PME and PMA share two common symptoms: spontaneous, action and stimulus-sensitive myoclonus and progressive ataxia. In contrast to PMA, which is characterized by the absence or mild presence of epilepsy and dementia/cognitive decline, PME is characterized by severe epilepsy and progressive dementia/cognitive decline (24, 26).

Myoclonus in patients with PME will typically be action myoclonus, spontaneous myoclonus, or stimulus-sensitive myoclonus. Myoclonic jerks should be distinguished from non-epileptic forms of myoclonus, as well as from movement disorders associated with basal ganglia diseases. Consciousness is typically preserved (24).

Since generalized epileptic myoclonus is more frequent than progressive myoclonic epilepsy (PME), it is important to distinguish between the two. Diagnosing PME can be challenging, especially since the symptoms don’t always appear clearly in the early stages. When more severe seizures and progressive neurological symptoms appear, the diagnosis of progressive myoclonic epilepsy (PME) becomes more likely (24).

1.2.3 Causes of progressive myoclonus ataxia and progressive myoclonus epilepsy

According to C. David Marsden, the following diseases can cause progressive myoclonus ataxia and / or progressive myoclonus epilepsy (24). Forms listed in parentheses indicate the possible clinical presentations: both PMA and PME can occur if both are shown; if one form is in **bold**, it represents the more common presentation.

- *Unverricht-Lundborg disease (**PMA** /PME)*
- *Mitochondrial encephalomyopathy (**PMA**/PME)*
- *Sialidosis (**PMA**/PME)*
- *Lafora body disease (PMA/**PME**)*
- *Neuronal ceroid lipofuscinosis (PMA/**PME**)*
- Spinocerebellar degenerations (PMA/PME)
- Gaucher´s disease (non-infantile neuropathic form) (PMA/PME)
- GM2 gangliosidosis (PMA/PME)
- Biotin-responsive encephalopathy (PMA/PME)
- Neuroaxonal dystrophy (juvenile form) (PMA/PME)
- Pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease) (PMA/PME)
- Atypical inclusion-body disease (PMA,PME)
- Action myoclonus renal failure syndrome (PMA/PME)
- Dentatorubral-pallidoluysian atrophy (PMA/PME)
- Coeliac disease (PMA/PME)
- Whipple´s disease (PMA/PME)
- Progressive myoclonus epilepsy and lipomas (Ekbom´s syndrome) (PME)
- White matter vanishing disease (PMA/PME)
- Histidine abnormalities (PMA/PME

According to Sterre van der Veen, the following diseases can also be causes of PMA: North Sea PME, hypotonia ataxia, delayed development syndrome, nonprogressive congenital cerebellar ataxia (23).

Malco Rossi believes that prion diseases, primary coenzyme Q10 deficiency type 4, autosomal recessive spastic ataxia type 5 and myoclonic epilepsy and ataxia due to potassium channel mutation (a mutation in the KCNC1 gene) also can be causative for PMA (22).

These 5 major causes of PMA are discussed in more detail below: Unverricht-Lundborg disease, Mitochondrial encephalomyopathy, Sialidosis, Lafora body disease, and Neuronal ceroid Lipofuscinosis (24).

1.2.4 Clinical phenotypes of progressive myoclonus ataxia

Van der Veen et al. describe a homogeneous phenotype in which patients with PMA first showed ataxia as a symptom in early childhood around the age of 2. Cortical myoclonus typically appeared around the age of 4, followed by epilepsy, which was relatively rare and manifested with a mean onset age of 9.5 years. The patients' motor symptoms were progressive, and more than half showed mild cognitive deterioration (23).

1.2.4.1 Unverricht-Lundborg disease

Unverricht-Lundborg disease (ULD), which may also be referred to as progressive myoclonic epilepsy type 1 (EPM1), is an autosomal recessive disorder (28). The name of the disease comes from the two first describers, Unverricht and Lundborg. In 1891, Unverricht was the first to describe the disorder based on a few case reports. A few years later, Lundborg included this condition in his classification of myoclonus (24).
While EPM1 is a very rare disease in general, it is regarded as the most frequent form of progressive myoclonus ataxia (24, 29).
According to Sipila et al., Finland is considered the country with the highest prevalence of EPM1, at an incidence rate of 1 in 20.000 live births. The disease is

also more prevalent along the coasts of the Baltic Sea and the Mediterranean Sea. Italy, Tunisia, Morocco and Algeria are also considered endemic areas (30).

The CSTB gene encodes cystatin B, a cysteine protease inhibitor, and is currently the only gene known to be associated with EPM1 (31). The most common mutation is a repeated expansion of a dodecamer sequence, which is located in the promoter region of the CSTB gene (32). In fact, the expansion mutation is responsible for over 90% of genetically tested Unverricht-Lundborg disease cases (24).

CSTB is found in nearly all human tissues. Lack of CSTB is associated with neuronal atrophy in the cerebellum, cortex and hippocampus (29).

Neuronal apoptosis is primarily triggered by the activity of cathepsin, which is physiologically inhibited by CSTB. However, the exact correlation between CSTB deficiency and the symptoms of Unverricht-Lundborg disease remains unclear (29).

Typical symptoms of EPM1 include myoclonus, seizures, ataxia, and cognitive decline (33).

According to Donaldson et al., the first symptoms typically appear between the ages of 6 and 15, often manifesting as stimulus-sensitive myoclonic jerks or tonic-clonic seizures. The myoclonic twitches occur either during movement or as a result of external stimuli (visual, auditory, somatosensory). Other possible symptoms include Disturbances of gait, speech, swallowing or manual dexterity, dystonia, oculomotor apraxia, dysarthria, intention tremor, emotional lability and depression. In the disease course, only mild cognitive impairment typically occurs (24).

Many patients are wheelchair-bound in the late course of the illness (11). Unlike other PMAs, early mortality is uncommon in ULD, and disease severity can range from minimal impairment to severe disability (34).

Atrophy may be seen on cerebral imaging, and spike-wave or polyspike-wave complexes are usually observed electrophysiologically (11).

Valproate is the drug of choice for therapy. Clonazepam, pirazepam, levetiracetam, topiramate, and zonisamide are in use, too. N-acetylcysteine and perampanel have shown success in initial studies (11).

1.2.4.2 Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL, also known as Batten disease) is a heterogeneous group of neurodegenerative diseases belonging to the lysosomal storage disorders (35, 36).

The disease is characterized by intracellular accumulation of the autofluorescent lipopigment ceroid lipofuscin in various cell types, including neurons, macrophages, muscle, and endothelial cells. This leads to progressive neuronal degeneration, resulting in cerebral and cerebellar atrophy, ventricular enlargement, and clinically manifests as epileptic seizures, cognitive and motor decline, and visual impairment (37-40).

Neuronal ceroid lipufuscinosis can be divided into 5 major groups: congenital, infantile, late infantile, juvenile, and adult NCL (39). Mutations in 14 different genes are known to cause neuronal ceroid lipofuscinosis (41). 13 of the gene mutations are inherited autosomal recessively, only one variant (CLN4) is inherited autosomal dominant (36, 39). Most of the affected genes encode lysosomal enzymes or transmembrane proteins of lysosomes (39). Worldwide, there is a wide variation in the incidence of NCL, ranging from 1:12,500 to 1:100,000 (37).

The diagnosis of NCL is made by detecting specific lipopigments in lymphocytes and in biopsies of the skin (11). The gold standard for a definitive diagnosis is confirmation of one of the mutations by genetic testing (39).

Treatment of NCL is primarily symptomatic with antiepileptic drugs (primarily valproate, levetiracetam), muscle relaxants such as baclofen, and botulinum toxin injections. Enzyme replacement therapy has been approved for neuronal ceroid lipofuscinosis type 2 (CLN2) and is currently the only disease-modifying drug on the market (36).

1.2.4.3 Mitochondrial encephalomyopathy

➔ see Chapter 1.3 ‘movement disorders and mitochondrial disease’

1.2.4.4 Sialidosis

Sialidosis (also: mucolipidosis type 1) is a group of diseases with problems of lysosomal storage, inherited in an autosomal recessive manner (11, 42, 43).
They are characterized by N-acetylneuraminidase deficiency, and sometimes a deficiency of beta-galactosidase is also present (24). The incidence of sialidosis is very low at 1: 4,200,000 per live birth (43).
One can divide sialidosis into sialidosis type 1 and type 2, the former also being called "cherry red myoclonus syndrome". Both types are caused by mutations in the neuraminidase gene (NEU1, 6p21), of which more than 40 have been identified so far (24, 43).
Sialidosis type 1 occurs between the ages of 8-30 years and is the milder of the two forms. Typical symptoms include myoclonia, epileptic seizures, ganglionic storage phenomena with cherry red spots on the retina, and progressive visual disturbances; dysarthria, ataxias, and hyperreflexia may also occur (11).
Type 2 sialidosis is more rapidly progressive and usually occurs earlier. Already in the first months of life, this illness can manifest with hepatosplenomegaly, ascites, edema, and proteinuria. The disease is associated with a poor prognosis and patients often die early (11) .
Sialidosis 2 can be divided into three types: congenital or hydropic, infantile, and juvenile sialidosis. The former begins prenatally, infantile sialidosis occurs within the first year of life, and juvenile sialidosis has an onset from about 2 years of age (44).
Most patients with sialidosis type 2 have beta-galactosidase deficiency in addition to alpha-n-acetylneuraminidase deficiency (24).
Determination of alpha-n-acetylneuraminidase activity in lymphocytes or fibroblasts and detection of sialyloligosaccharides in urine are used for diagnosis . Atrophy of the cerebral hemispheres, corpus callosum, cerebellum, and pons may be seen on MRI, and polyspike-wave discharges are evident on EEG (11, 24).
Despite some already promising studies with enzyme replacement therapies and treatment with viral vectors, sialidosis is still treated purely symptomatically (11, 44).

1.2.4.5 Lafora disease

Lafora disease is a severe autosomal recessive inherited disease and belongs to the glycogen storage disorders. More than 90% of diseases are caused by mutations in either the gene encoding the glycol phosphatase laforin (EPM2A) or the gene encoding the E3 ubiquitin ligase malin (EPM2B, also known as NHLRC1) (45, 46).

With a prevalence of 4 patients per 1,000,000 people, Lafora disease is a very rare condition (47). In patients with Lafora disease, cytoplasmic glycol inclusions can be detected in almost all tissues of the body (45). These accumulated polyglucosans are termed Lafora bodies (48). They accumulate in all brain regions and in the cell bodies and dendrites of neurons (48, 49). The involvement of the malin-laforin complex in regulating glycol structure is not yet fully understood (46).

The disease is particularly common in Mediterranean countries, North Africa, the Middle East, and countries with high consanguinity, such as some areas in southern India (48).

Lafora disease typically begins in adolescence with symptoms such as myoclonus, visual and convulsive seizures. Symptoms progress rapidly, and additional abnormalities such as ataxia, neuropsychiatric symptoms, behavioral disturbances and cognitive decline occur. After 10 years of illness, most patients have reached a vegetative stage or have died (46, 50).

The diagnosis of Lafora disease is made based on clinic, EEG changes despite an unremarkable MRI of the brain, and positive skin findings (indicating the presence of Lafora bodies), with molecular genetic analysis being the gold standard for diagnostic confirmation (51).

Treatment to date has been purely symptomatic with antiepileptic drugs to achieve a reduction in myoclonus and seizures. In many cases, though, drug resistance occurs after the patient has passed through the initial stage (50).

1.3 Movement disorders in mitochondrial disease

To date, no consistent association has been demonstrated between the biochemical defects and the clinical phenotype of mitochondrial diseases (24).

Defects in nuclear DNA or mitochondrial DNA encoding mitochondrial subunit proteins lead to defects in mitochondrial electron transport chain complexes. Except for red blood cells, mitochondria are present in all our cells, however in varying numbers. It is mainly in cells of high-energy demand organs, such as the heart, brain, and muscle tissue, that defects lead to serious difficulties (52).

Ghaoui et al. note that mitochondrial diseases present with clinical features such as ptosis, external ophthalmoplegia, proximal myopathy, and cardiomyopathy, but also show a wide range of neurological manifestations. These include seizures, encephalopathy, stroke-like episodes, migraines, dementia, spasticity, and peripheral neuropathy. In addition, movement disorders are frequently observed, with myoclonus and ataxia being the most common presentations. Other movement abnormalities, such as parkinsonism, dystonia, chorea, spasticity, and tics, may also occur (53).

Ataxia in mitochondrial disorders can arise from different genetic causes, including point mutations or large-scale deletions in mitochondrial DNA (mtDNA), as well as defects in nuclear genes responsible for maintaining mtDNA. It represents a prominent clinical feature in several mitochondrial syndromes, including conditions linked to mutations in the POLG gene (53, 54). These include myoclonic epilepsy, myopathic sensory ataxia (MEMSA), and ataxia neuropathy spectrum disorders (ANS). Similarly, ataxia is a typical manifestation of NARP syndrome, which is caused by mutations in ATP6 (53).

Unlike classical Mendelian inheritance, mitochondrial genetics involves maternal inheritance, heteroplasmy, and mitotic segregation. (52). The risk of transmission of maternal mitochondrial DNA defects depends on the number of mutated mitochondrial DNA in the mother. Within a family, the expression of the disease varies depending on the extent to which it was inherited by the respective family member (24).

Heteroplasmy describes the persistence of both mutant mtDNA and wild-type mtDNA when mutations occur. Mitotic division of heteroplasmic cells can result in a shift of daughter cell mtDNA to mutant or wild type. For a pathological phenotype to occur, a certain percentage of mutant mtDNA is required for the metabolism of the cell to be affected. For organs that are particularly metabolically active, such as the brain or skeletal muscle, this threshold is especially low (52).

Donaldson et al. suggest evaluating any patient with PMA in which the cause is unknown for the presence of mitochondrial disease. Elevated lactate levels in serum and cerebrospinal fluid (CSF) are indicative. Signs of myopathy on EMG and spike or spike-wave complexes on EEG are also indicative. MRI or CT scans of the brain may show atrophy, white matter changes, and calcifications in the basal ganglia, brainstem, cerebellum, and white matter. Electron microscopy may show abnormal muscle mitochondria. However, blood tests may be negative despite the presence of mutant mitochondrial DNA due to heteroplasmy, so other tissues must be examined (24).

1.3.1 Mitochondrial encephalomyopathy

According to Marsden, the three major syndromes that combine myoclonic syndromes and defects in mitochondria, and which can be subsumed under the term mitochondrial encephalomyopathy, include Kearns-Sayre syndrome (KSS), red fiber myoclonus epilepsy (MERRF), and mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes (MELAS) (24).

1.3.1.1 Kearns-Sayre syndrome

Kearns-Sayre syndrome (KSS) belongs to the group of mitochondrial encephalomyopathies and is a very rare disorder, occurring in roughly 1 per 100,000 live births (55).

This disease is characterized by external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction abnormalities. Other important indications for the presence of this syndrome are a CSF protein level greater than 1 g/L or cerebellar ataxia. The first symptoms of KSS are usually evident before the age of 20 (56).

The therapy of KSS is purely symptom-oriented and supportive, depending on the particular phenotypic constellation (57).

1.3.1.2 Red fiber myoclonus epilepsy (MERRF)

MERRF can be caused, for example, by mutations in MTTK, MTTL 1, MTTH, MTTS1, MTTS2, MTTF, and the POLG1 gene. Leigh syndrome (LS) may also result from mutations that typically cause MERRF syndrome, which is why the phenotypes of the two disorders overlap (24).

Mutations in the MTTK gene are the most common, accounting for approximately 80% of cases. These mutations prevent the synthesis of mitochondrial proteins necessary for oxidative phosphorylation. Typical symptoms of the disease are myoclonic seizures, ataxia and mitochondrial myopathy. Furthermore, cerebellar ataxia, sensorineural hearing loss, polyneuropathy, short stature, optic atrophy and cutaneous lipomas may occur. Therapy is symptomatic, although there have been treatment trials with coenzyme 10 and L-carnitine (11).

1.3.1.3 Mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes (MELAS)

The mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes-syndrome (MELAS) is one of the better-known mitochondrial disorders and typically begins in childhood (58).

There are over 30 different genes known to cause MELAS syndrome (59). MTTL1 gene mutations are responsible for the majority of cases of MELAS syndrome (58). The phenotype of patients with MELAS syndrome is extremely heterogeneous. The most characteristic features of this syndrome include stroke-like episodes, encephalopathy, dementia, and possibly seizures at a young age (59).

Although most patients recover very well from these episodes in the short term, over time they lead to progressive dementia. Other clinical features of this disease include motor weakness, visual disturbances, peripheral sensorimotor neuropathy, myopathy, cardiomyopathy, elevated serum plasma lactate levels, and growth disturbances (58). Treatment is symptom-based (59).

1.4 MTATP-6 Mutation

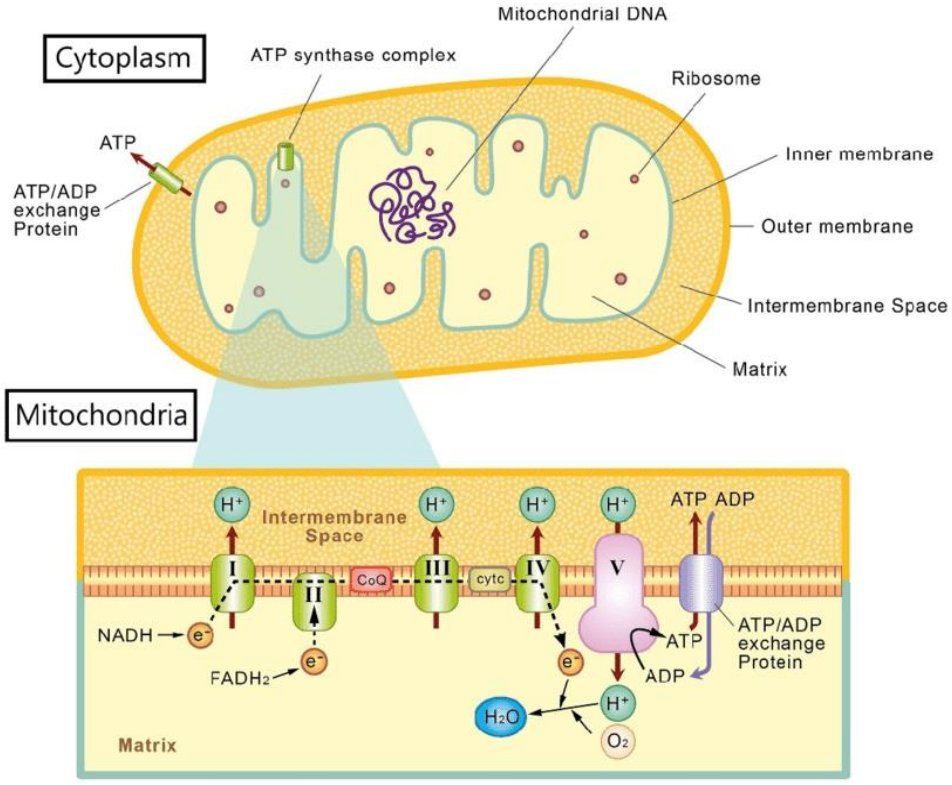
Mitochondria are responsible for cellular energy production through the synthesis of ATP. This process requires the presence of 5 complexes. The electron transport chain consists of complexes I-IV and liberates energy through redox reactions. A potential difference is generated with the assistance of proton pumps and electron transport. Complex V (CV), also known as ATP synthase, releases the potential difference in form of the electrochemical proton gradient along the inner mitochondrial membrane (IMM) and ATP is generated (60-62). Figure 1 shows a simplified illustration of energy production in mitochondria.

CV consists of 15 structural and two assembly-related components. The genetic information required for the assembly of these subunits is distributed between mitochondrial DNA (MT-ATP6 and MT-ATP8) and the nuclear genome (15 subunits). MT-ATP6 is the most common gene causing CV dysfunction. This gene codes for the a-subunit of CV, which provides the proton gradient within the mitochondrial membrane via its protein pump. Heteroplasmy shifts may result in MT-ATP6 mutations appearing homoplastic. The threshold at which heteroplasmic mutations cause a visible clinic is relatively high. On the other hand, individuals without apparent symptoms can have MT-ATP6 heteroplasmy levels similar to those of family members who do show clinical signs. There is generally a higher heteroplasmy load in symptomatic relatives, and the median heteroplasmy burden tends to be higher in patients with an earlier onset. MT-ATP6 disorders with earlier onset have higher mutational heteroplasmy levels than those with later onset. Among the most common chemical abnormalities associated with MT-ATP6 mutations are abnormal mitochondrial membrane potentials, decreased ATP synthesis rates, hydrolysis rates or steady-state levels, and decreased holoenzyme assembly (60, 61).

Stendel et al. studied data from 132 patients with MT-ATP6 mutations and found that the most common mutations were m.8993T>G, m.8993 T>C, m.9176T>C, and m.9185T>C. In this group of 132 patients, the degree of heteroplasmy ranged from 20% to 100%, with an average of 95% (2).

Figure 1

Mitochondrial structure and electron tansport (63)



Phenotypes

The most frequently reported phenotypes linked to MT-ATP6 mutations are LS and the syndrome of neuropathy, ataxia, and retinitis pigmentosa (NARP). LS has a more severe and early onset, while NARP syndrome has a more protracted course and a later onset (2, 60).

In addition to the better-known disorders mentioned above, MT-ATP6 mutations can also cause spinocerebellar ataxia with upper motor neuron signs, axonal Charcot-Marie-Tooth- like peripheral neuropathy, and familial upper motor neuron disease. Less commonly, cardiomyopathies, primary lactic acidosis, methylglutaconic aciduria, and isolated optic neuropathy may occur (60).

A study by Na and Lee describes 13 patients with the m.8993T>G, m.8993T>C, m.9176T>C, or m.9185T>C mutations. The most common initial symptoms were

developmental delay or retardation, gait disturbance, and hypotonia. All patients exhibited multisystem involvement, with consistent impairment of the central nervous system. The muscular system, eyes, and kidneys were commonly affected too. In patients with the m.8993T>G mutation, the disease appeared particularly early, at less than 24 months of age. On MRI examination of the brain, the basal ganglia were affected bilaterally in all patients, and cerebral and cerebellar atrophy as well as involvement of the thalamus were frequently observed. However, patients with m.9176T>C and m.9185t>C did not exhibit brain atrophy, and seizures were not observed. Patients with the m.8993T>G mutation had a relatively more severe course compared with the other 3 mutations (62).

Symptoms most frequently reported by Stendel et al. in a very large cohort of 132 patients were ataxia (81%), cognitive dysfunction (49%), neuropathy (48%), seizures (37%), and retinopathy (14%). LS was the most common phenotype, with nearly half of the patients carrying the m.8993T>G variant. Patients with LS most often carried this variant and also showed a higher incidence of seizures. MRI data were provided for 85 patients in this cohort; 65% had lesions in the basal ganglia and 32% in the brainstem (2).

Within this study, one case in particular illustrates that the phenotype can vary greatly even with the same genotype. Two identical twin sisters with the homoplasmic variant m.8993T>C showed very different phenotypes. While one sister developed severe gait ataxia around 2 years of age, the other sister had only mild gait ataxia beginning at the age of 7 years and could still walk unaided at the age of 16 years, in contrast to her more severely affected sister (2).

The most common clinical symptoms associated with the four most frequent MT-ATP6 mutations are shown in Table 1.

1.4.1 m.8993T>G

According to Finsterer, who described a 4-year-old boy with maternally inherited Leigh syndrome (MILS) caused by the m.8993T>G mutation, this variant is associated with earlier-onset MILS and more rapid clinical course compared to the three other most common MT-ATP6 variants. This variant can manifest as LS, NARP, stroke or cardiomyopathy (60, 64). Moreover, the M.8993T>G variant is

associated with a higher incidence of seizures than other MT-ATP6 variants (65). The m.8993T>G variant was among the first mtDNA mutations to be reported and was discovered over thirty years ago. This variant leads to an increased mitochondrial membrane potential. Consequently, the proton pore cannot discharge the proton gradient. As a result, the ATP synthesis does not work properly (60).
Mutant loads of more than 90% are usually associated with more severe LS, whereas mutant loads of around 60-70% are linked to the milder NARP phenotype (60, 64, 66).
Claeys et al. presented an unusual case of a patient with the m.8993T>G variant. Despite heteroplasmy levels exceeding 90%—indicating an almost homoplasmic mutation load—the 30-year-old patient displayed a NARP phenotype rather than the expected LS phenotype (67). Furthermore, Mancuso et al. reviewed the clinical data of 1200 patients with a particular focus on peripheral polyneuropathy and found that in 33.3% of cases involving the m.8993T>G or m.8993T>C mutation, patients exhibited peripheral, mainly sensorial neuropathy (68).

1.4.2 m.8993T>C

It is believed that typically a higher mutant load is needed for the T>C mutation (80-90%) to develop NARP syndrome in patients with one of the m.8993 mutations than for the T>G mutation (60-70%). Furthermore, this mutation usually exhibits milder clinical manifestations than the m.8993T>G mutation (69, 70) .
This is supported by Craig et al., who described a three-generation family in which the most prominent phenotype was adult-onset ataxia, associated with this mutation (71). Gelfand et al. reported a family in which a mother and her four daughters were identified as carriers of the m.8993T>C mutation. The mother and three of the daughters suffered from NARP-syndrome with mutation loads between 87-99%, whereas one daughter, with a mutation load of 54%, showed no signs of neurological disease and had a normal phenotype (69).
In addition, Martikainen et al. reported the case of severe, late-onset myoclonus ataxia related to this mutation in a 74-year-old patient, demonstrating broad phenotypic variability (72).

1.4.3 m.9185T>C

The 9185T>C variant leads to a reduced mitochondrial membrane potential in affected individuals. As a result, protons are released irregularly through the proton pore, which compromises ATP synthesis (60).
Piekutowska-Abramczuk et al. reviewed the data of 81 patients from 16 families with this variant and found that most individuals showed first symptoms with mild severity at childhood (73).
Pitceathly et al. reported on a total of 270 Charcot-Marie-Tooth (CMT) type 2 patients, the most frequent inherited neuromuscular disorder, who were screened for MT-ATP6/8 mutations. Within this study, four unrelated families harboring this mutation were identified. Family members of patients with the m.9185T>C mutation were examined further, and affected individuals could be classified into four clinical groups according to mutant load:
Group 1: unaffected individuals (<64% mutant load)
Group 2: asymptomatic carriers with isolated upper motor neuron (UMN) signs on examination (64%-79% mutant load)
Group 3: clinically affected patients with signs of UMN but no neuropathy (80%-91% mutant load)
Group 4: motor-predominant CMT2 phenotype (92%-100% mutant load) (74)

Auré et al. noted that m.9185T>C mutations can lead to episodic limb paralysis and progressive motor neuropathy. Furthermore, pyramidal syndrome, proprioceptive ataxia and episodic diplopia were observed. None of the 13 individuals screened for this mutation in this study expressed Leigh syndrome. This observation cannot be attributed solely to differences in the mutation load (75).

1.4.4 m.9176T>C

The m.9176T>C – variant was the third most common variant (23%) reported in a study by Stendel et al. (2). To date, only one patient with this mutation presenting with myoclonus has been described in the literature (76). This individual, together

with his brother, was also part of the first reported case of the m.9176T>C mutation, as described by Thygarajan et al. (76).

Na and Lee selected 13 patients with genetically verified MT-ATP6-related LS with three of these patients harboring the m.9176T>C mutation. Patients with this variant showed a milder clinical course in comparison to the m.8993 mutations (62).

Moreover, Stendel et al. described the case of a patient with the m.9176T>C mutation who atypically showed chronic progressive external ophthalmoplegia as the first symptom of the disease. Patients with the m.9176T>C variant had less frequent cognitive dysfunction than patients with any of the other mutations in the group studied by Stendel et al. (2).

Table 1

Most common clinical symptoms of the mutations m.8993T>G, m.8993T>C, m.9176T>C, m.9185T>C

feature	m.8993T>G	m.8993T>C	m.9176T>C	m.9185T>C
Age of onset	Infancy/early childhood (62, 66, 77),	Childhood/adulthood; high variability (2, 60, 72)	Infancy/early childhood; occasionally later (62, 78, 79)	Childhood/adulthood; often adolescence (73, 80, 81)
Progression	Typically rapid, severe (2, 66, 82, 83), (83)	Typically later onset, more slowly progressive; faster decline only in rare high-mutation-load cases (2, 70, 72)	Highly variable; patients may show early-childhood progressive LS or later-onset, more slowly progressive disease (84-86)	Typically mild progression; more severe when homoplasmic (86, 87)

feature	m.8993T>G	m.8993T>C	m.9176T>C	m.9185T>C
Main clinical phenotype	LS; severe NARP when lower heteroplasmy levels (2, 82, 88)	Typically NARP; LS only at very high mutant load (2, 70, 72, 89)	LS (84, 86, 90)	LS/Leigh-like-Syndrome with slow progression (73, 87)
LS	Very common, typically severe (2, 64, 82)	Rare (only at very high heteroplasmy) (52, 69, 91)	Common, spectrum varies (2, 84, 90)	Common, often with partially recovery (73, 80)
Ataxia	Frequent, severe (2, 88)	Frequent (2, 60, 71, 72, 89)	Frequent (1, 62, 90, 92)	Frequent; mild/moderate (80, 81)
Cognitive Dysfunction	Frequent (2, 82, 93)	Frequent, typically mild/moderate (cognitive dysfunction reported in NARP/LS patients but variant-specific neuropsychological data very limited) (2, 94)	Frequent (79, 84, 95)	Frequent, typically Mild/moderate (variant-specific neuropsychiological data very limited) (73, 96)

feature	m.8993T>G	m.8993T>C	m.9176T>C	m.9185T>C
Neuropathy	Frequent (2, 88, 97)	Frequent (→NARP) (2, 60, 89)	Frequent (98, 99)	Frequent; typically prominent axonal sensomotoric neuropathy (74, 86, 100)
Seizures	Common in severe LS (2, 65)	Occasional (especially at higher heteroplasmy rates) (2, 101)	Common in LS (84, 98)	Occasional, usually mild (81, 96)
Retinitis pigmentosa	Very common (66, 88, 94)	Common (→NARP) (2, 94)	Rare; Less frequent reported than 8993 variants (86, 102)	Sporadic reports of a NARP-phenotype in connection with this mutation (73, 81)
Cardiac symptoms	Rare; cardiomyopathy reported in a few LS cases (82, 103, 104)	Rare; WPW reported (2)	Rare (limited data) (86, 105)	Rare; WPW and hypertrophic cardiomyopathy reported (2, 81)

feature	m.8993T>G	m.8993T>C	m.9176T>C	m.9185T>C
Myoclonus	Very rare; Licchetta et al. reported about 4 cases (65)	Occasional (limited data available) (72)	only one reported case to date (76)	No specific case reports identified
Heteroplasmy	>70-85% → severe, childhood-onset LS 60-70% → adult-onset NARP <60% → mild, subclinical (2, 69, 70, 106)	>80-90% → risk for LS/NARP (T>C requires higher heteroplasmy than T>G to cause severe NARP/Leigh) (69, 107-109); homoplasmic asymptomatic carriers reported (77)	Very high phenotypic threshold level (>90%) required for LS, but no clear phenotypic threshold defined; asymptomatic carriers with very high levels reported (79, 86, 90); homoplasmic asymptomatic	Uncertain, variable penetrance; typically very high phenotypic threshold level (86); Cases with homoplasmic mutations and mild to asymptomatic course reported (73, 77, 81, 96)

feature	m.8993T>G	m.8993T>C	m.9176T>C	m.9185T>C
			carriers reported (77)	
Distinctive Characteristics	Most pathogenic in comparison to the other 3 mutations; most predictable genotype-phenotype correlation; strongly associated to infantile-onset MILS (2, 60)	Milder than T>G; very high heteroplasmy threshold required for clinical manifestation (69)	Intermediate severity (less severe than m.8993T>G), broad spectrum; high phenotype-variability (76, 84, 110)	Mildest variant; symptoms only with high heteroplasmy levels (86)

Note. WPW = Wolff-Parkinson-White syndrome; NARP = syndrome of neuropathy, ataxia, and retinitis pigmentosa; LS = Leigh syndrome.

1.4.5 Leigh syndrome

Of all inherited mitochondrial disorders, Leigh syndrome (LS; synonym: subacute necrotizing encephalomyelopathy) is the most common pediatric manifestation. Over 80 genes are known to cause this neurodegenerative disease, most of which code for proteins in mitochondria (111).

Leigh syndrome is caused by mutations that impair the electron transport chain. Complex V, belongs to this chain and consists of 19 subunits, with 2 encoded by mtDNA (mitochondrial DNA) and 17 by nDNA (nuclear DNA). Mutations in any of the 19 genes can lead to dysfunction of the complex. Mutations in the MT-ATP6 gene represent the most frequent cause of LS associated with complex V deficiency. MT-ATP6 is one of the two mtDNA genes that contribute to the Fo domain of complex V (52).

In 1951, Denis Leigh first described this disease. He documented the case of a 5-month-old boy whom he examined postmortem after his death at 7 months of age. Characteristic were the focal, bilaterally symmetrical subacute neurotic lesions in the thalamus, brainstem and spinal cord (111, 112).

To date, there are no precise criteria for the diagnosis of LS. The diagnosis is made based on the clinic, family history, imaging, muscle biopsies, and detection of specific mutations in mitochondrial or nuclear DNA (112).

According to Lake et al, the diagnosis of LS requires the following: a characteristic clinic with psychomotor retardation and/or regression with progressive neurological deterioration, radiological findings of basal ganglia or brainstem lesions that show hyperintensity on T2-weighted MRI, laboratory findings of impaired energy metabolism, and the presence of a mutation in a distinctive gene (113).

Clinically, LS is manifested by motor dyskinesia, akinesia, ataxia, dystonia, mental retardation, hypotonia, and brainstem symptoms such as dysphagia or respiratory symptoms. Symptoms often start in infancy, gradually worsen, and end with early death. However, there are also cases in which the disease begins later and, with appropriate treatment, a number of years of life can be gained (112).

The disease is rare and has an estimated probability of 1 in 5,000 to 1 in 10,000 per live birth. Unfortunately, Leigh syndrome can currently only be treated symptomatically (52).

1.4.6 Atypical Leigh syndrome

Since Leigh syndrome can have an impact of every level of the neuraxis, it presents with a wide clinical spectrum, including numerous atypical presentations (114).
In 1996, Rahman et al. investigated 67 cases of LS and found that 32 of these cases were to be classified as atypical LS or Leigh-like syndrome: these cases did not meet the criteria for inclusion in the strictly defined group of LS cases due to atypical neuropathological findings, including variations in lesion distribution or morphology, extensive cortical destruction, normal or atypical CT findings, and typical neuroradiology despite normal lactate levels (115).
Additionally, non-neurological symptoms, including renal failure, cardiomyopathy, and diabetes as well as gastrointestinal dysfunction, may be present in atypical cases of LS. Uittenbogaard et al. described a case study of a 6-year-old male subject with probable atypical Leigh syndrome. The patient exhibited typical symptoms as well as atypical features such as dysmorphism (bilateral ptosis, pendulous lips, small chin, and myopathic facial appearance) and radiological findings of absent thalamic massa intermedia, residual cavum septum pellucidum/vergae, and hypoplasia of the anterior commissure, optic pathway, and olfactory system (116).
Huntsman et al. reported on five patients with atypical clinical symptoms of Leigh syndrome. These symptoms included progressive flaccid paralysis, encephalopathy, respiratory failure, progressive diplegia, bronchiolitis, apnea, tonic seizures, and developmental delay (114).
Two further cases of atypical Leigh syndrome are described by Thomé et al. The first case is a patient with an atypical late presentation at the age of 10 years. The patient's predominant symptom was dystonia and the evolution of neurological symptoms was slow. The second case was also a late onset with the first symptoms following a respiratory infection at the age of 6. This patient had encephalopathy and ophthalmoplegia with periods of exacerbation and remission (117).

1.4.7 NARP syndrome

Neuropathy, ataxia and retinitis pigmentosa define this syndrome, which typically presents in late childhood or adulthood. Other common clinical manifestations

include learning difficulties, seizures, developmental delay, other ocular manifestations such as nystagmus, ophthalmoplegia, night blindness and proximal neurogenic muscle weakness. The main genetic cause of NARP is heteroplasmic point mutations affecting MT-ATP6 (118).

The m.8993T>G variant in the MT-ATP6 gene represents the mutation most commonly linked to NARP (94, 119).

Besides the m.8993T>G variant, other known mutations known to cause the syndrome are: m.8839G>C, m.8989G>C, m.8618insT, p.Thr33Hisfs*32, 9185T >C, m.8993T>C, m.5789T>C tRNA cysteine, 8729G>A, m.9032T>C (p.Leu169Pro) and m.9127-9128delAT (120-122).

Furthermore, there are a few cases of NARP patients associated with pathogenic variants in MT-ND6 and MT-TV, which encode a complex I subunit and tRNAVal, respectively. The latter is a transfer RNA molecule that carries L-valine during protein synthesis (118).

Patients carrying the m.8993T>C variant usually require higher heteroplasmy levels to exhibit the NARP phenotype than those with the m.8993T>G variant. Patients with levels above 90% typically present with LS (2, 69, 122). The occurrence of both NARP syndrome and Leigh syndrome within the same family can be explained by the fact that affected individuals have different mutation loads (123).

2 Material and Methods

2.1 Study design

This study consisted of two complementary methodological components:

1. a systematic review of the literature on the MT-ATP6 mutation m.9176T>C, and
2. a retrospective analysis of clinical patient data from our movement disorders clinic.

The aim was to compare the phenotypic characteristics observed in our patients with those reported in the literature.

2.2 Retrospective case analysis

Within the retrospective analysis, we report on a family with progressive myoclonus ataxia syndrome comprising three affected members carrying the MT-ATP6 mutation m.9176T>C treated at our movement disorders clinic.

Electronic patient records were reviewed using the MEDOCS hospital information system. Data from outpatient and inpatient visits at the Department of Neurology, Medical University of Graz, between January 2012 and September 2022 were analyzed. Patients were identified via a keyword search in MEDOCS using the following German terms: “Progressive Myoklonus-Ataxie”, “Myoklonus-Ataxie Syndrom”, “Ramsay-Hunt Syndrom”, “MT-ATP6”, “Progressive Ataxie”, “Myoklonus-Epilepsie”, “Leigh-Syndrom”, “Leigh-Like Syndrom”, “multisystemische Ataxie”

Inclusion Criteria

Patients were included if they met the following criteria:

- Presentation as an inpatient or outpatient at the Movement Disorders Outpatient Clinic of the Department of Neurology between January 2012 and September 2022
- Diagnosis of progressive myoclonus ataxia associated with an MT-ATP6 mutation

Outcome Measures

- Primary outcome measure: frequency of different clinical features in patients with progressive myoclonus ataxia due to MT-ATP6 mutation
- Secondary outcome measures: age, sex, mode of disease onset, disease duration, age at last follow up, clinical manifestations, phenotypic expression, associated symptoms, comorbidities, radiological findings, laboratory findings, mutation loads, therapeutic interventions (response and tolerability), and clinical outcome

Data were extracted from medical records, outpatient reports, and physicians' letters. All patient data were pseudonymized prior to analysis.

2.3 Literature search and study collection

A systematic literature search was performed in PubMed to identify all reported cases of patients with the MT-ATP6 mutation m.9176T>C**.**

To gain a comprehensive overview of the literature on myoclonus-ataxia syndromes associated with MT-ATP6 mutations, a structured search was performed using the following terms:

"progressive myoclonus ataxia", "myoclonus ataxia syndrome", "MT-ATP6-associated disease", "progressive ataxia", "myoclonus epilepsy", "Leigh syndrome", "Leigh-like syndrome", "NARP", "syndrome of neuropathy, ataxia, and retinitis pigmentosa", "nonsyndromic sensorimotor neuropathy", "NARP syndrome", "multisystemic ataxia", "myoclonic disorders", "MT-ATP6 variants", "MT-ATP6 mutations"

These search terms were used to identify relevant publications reporting clinical cases, phenotypes, and disease manifestations related to MT-ATP6 mutations, providing a foundation for summarizing the phenotypic spectrum and variability of myoclonus-ataxia syndromes in affected patients.

Furthermore, a systematic PubMed search was conducted to identify all reported phenotypes of the m.9176T>C variant and their frequency. The search using the term "m.9176T>C" initially yielded 17 results. (reference date: 23 December 2025)**.** After screening titles and abstracts, 6 publications were excluded due to lack of

relevant case reports. Screening the references of the remaining articles identified 14 additional relevant publications.

In total, 25 publications describing 48 patients were included. The study selection process is presented in the PRISMA flowchart (Figure 2).

2.4 Study aims

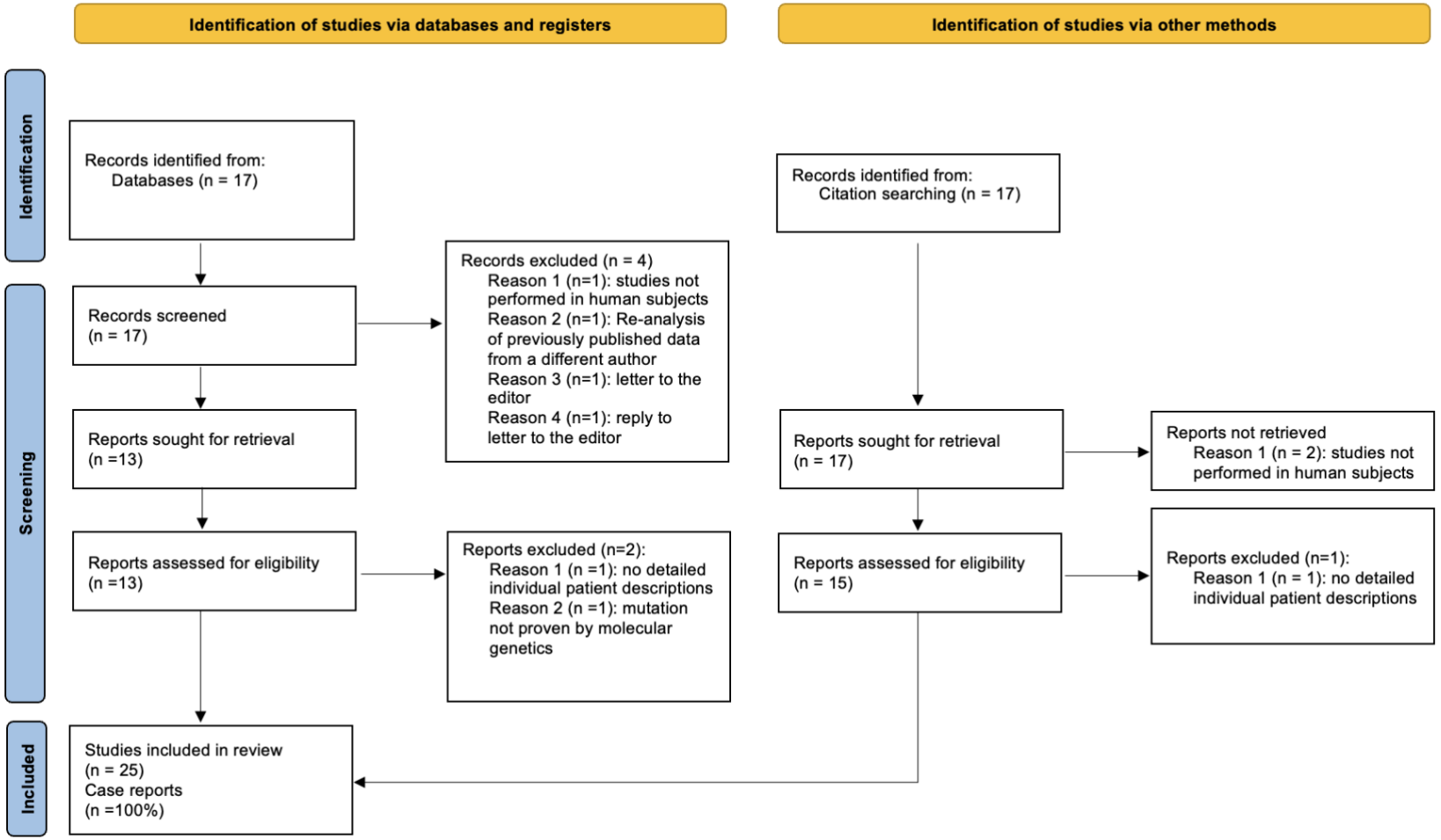
The aim of this study was to investigate the clinical characteristics of progressive myoclonic ataxia associated with the m.9176T>C variant of the MT-ATP6 gene in patients from a neurological clinic, including their respective frequencies, and to compare them with previously reported features in the literature in order to facilitate more precise diagnosis in the future.
The study was approved by the Ethics Committee (vote number 35-128 ex 22/23). All patient-related data were pseudonymized for the purposes of the study.

2.5 Statistical Analysis

The clinical data of the affected family members were compared with phenotypic characteristics reported in the literature. For the SPSS analysis, a table was created including the relevant phenotypic variables extracted from the literature case reports. Given the small sample size of the retrospective analysis (n = 3), only descriptive statistics were applied and results are presented as absolute numbers and percentages. Statistical analyses of the phenotypic variables extracted from the literature were performed using IBM SPSS Statistics (version 30). Graphical representations were created using Microsoft Excel (version 16.106.3) based on data exported from IBM SPSS Statistics. In addition to descriptive statistics, the frequencies of clinical characteristics in the three own patients were compared with cases from the literature. Means and standard deviations were calculated for normally distributed metric data and medians and quartiles for non-normally distributed data. Categorical data were presented as absolute and relative frequencies.

Figure 2

Search strategy of literature review for the m.1976T>C mutation based on the PRISMA 2020 flow diagram for systematic reviews (124)



3 Results

3.1 m.9176T>C – Variant – Systematic Literature Review

3.1.1 Demographics

Of the 48 patients, 26 were male and 22 were female (see Figure 3).

Based on age at onset, patients were categorized into three groups:

very early onset (< 2 years, hereafter referred to as Group 1 or **G1**)

childhood onset (2 to 12 years, **G2**)

adolescent/adult onset (>12 years, **G3**)

There were 14 patients in the < 2 years age-of-onset group (G1), 15 patients in the 2 to 12 years group (G2), and 14 patients in the > 12 years group (G3).

Age at onset was not reported for 5 patients (10.4%). These cases were excluded from the visual representation in the pie chart (Figure 4).

The median age at onset was 8 years with an interquartile range of 21 years. The youngest patient presented at four months of age, whereas the oldest developed first symptoms at over 62 years, which highlights the presence of outliers and a strongly right-skewed distribution.

Figure 3

Gender distribution of reported patients with m.9176T>C mutation

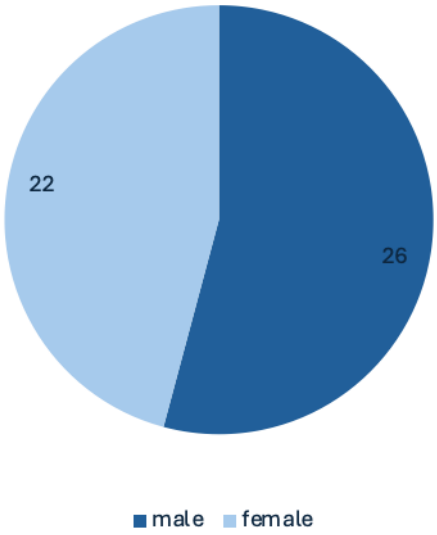
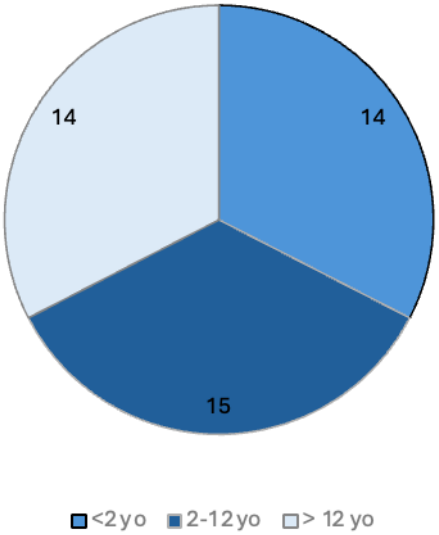


Figure 4

Classification into groups according to age of onset



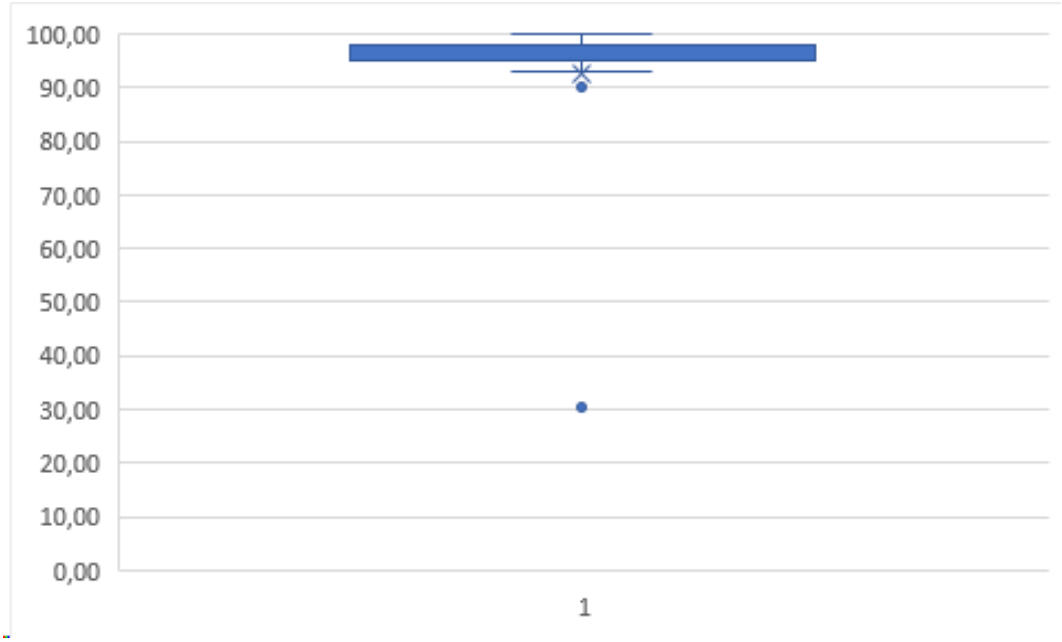
Note. yo = years old; the data shown in the figures represents the absolute frequency.

3.1.2 Mutation load and laboratory findings

When examining the different levels of mutation load, information was available for 39 cases (81.3%), while no data were reported for 9 patients. Among all patients, 37.5% carried a homoplasmic m.1976T>C mutation, and 43.8% had heteroplasmic mutation loads. Notably, several cases exhibited mutation loads that were nearly homoplasmic. When mutation load was measured in multiple tissues, the lowest reported value was used for the analysis. The median mutation load was 99.9 % with an interquartile range (IQR) of 5 %. The lowest reported mutation load was 30.5%, observed in a case reported by Ronchi et al. (84). This value was found in the mother of a 22-year-old daughter diagnosed with Leigh syndrome, who carried an almost homoplasmic m.9176T>C mutation. In the mother, only mild mental retardation was reported. Age of onset of the mother is unknown. Figure 5 presents a box plot of the mutation load distribution, highlighting an outlier at 30.5%.

Figure 5

Distribution of mutation loads among patients with the m.9176T>C variant



Note. The box shows the interquartile range (IQR, 25th–75th percentile), the line inside the box indicates the median, and whiskers extend to the minimum and maximum values within 1.5 × IQR. Outliers are plotted as individual points.

Regarding laboratory findings, special attention was given to the presence of lactate increase in CSF or serum, since an increase in lactate is an important factor for the diagnosis of LS. Lactate increase was reported in almost half of the cases (47,9%). The number of available cases (n) and corresponding percentage are presented in Table 2.

Table 2

Frequency of lactate elevation in investigated patients with the m.9176T>C mutation

Variable	Available n/N (%)	Present n/n (%)	Proportion of total group (n/N) (%)
Lactate increase	30/48 (62.5)	23/30 (76.7)	23/48 (47.9)

3.1.3 Clinical phenotypes

A summary of the characteristics of all 48 patients can be found at the end of Chapter 3.1 in Table 14.

Information on the occurrence of developmental delay was available for 25 of the 48 patients (52%). Of these, 14 patients (56%) had developmental delay, whereas 11 patients (44%) showed no signs of developmental delay. Information on cognitive dysfunction was available for 16 of the 48 patients. Of these, 11 (69%) had cognitive dysfunction and 5 (31%) did not. Frequencies are presented in Table 3.

Table 3

Frequency of developmental delay or cognitive dysfunction among patients with the m.9176T>C variant

Variable	Available n/N (%)	Present n/n (%)	Proportion of total group (n/N) (%)
Developmental delay	25/48 (52.1)	14/25 (56.0)	14/48 (29.2)
Cognitive dysfunction	16/48 (33.3)	11/16 (68.7)	11/48 (22.9)

Information regarding the presence of LS/LLS was available for approximately 85.4% (n = 41) of patients. Of these patients, 75.6% had LS or LLS, while 24.4% exhibited no symptoms suggestive of LS or LLS.

Out of the whole group (n=48), seizures were reported in 5 patients (10,4%), ataxia was reported in 16 patients (33,3%), dystonia was reported in 9 patients (18,8%) and chorea was present in 4 patients (8,3%).

Myoclonus was reported in only 1 patient (2.1%). The patient was a 16-month-old boy presenting with impaired fine and gross motor coordination. He had developmental delay, and at 8 years of age his condition worsened following a viral illness, with a decline in cognitive function. He then presented with dystonia and choreiform movements. No other movement abnormalities were noted. At the age of 11 years old, the patient had poor motor coordination and motor tics. His younger brother did not show myoclonus, but he had sustained ankle clonus, dystonic tongue movements, and cerebellar ataxia. These two siblings were the first reported cases with the m.9176T>C mutation. In 1995, Thyagarajan et al. described the cases. Both were diagnosed with Leigh-like syndrome (LLS), and MRI findings were consistent with familial bilateral striatal necrosis. Since that report, myoclonus has not been described in other patients carrying the m.9176T>C mutation (76).

A hereditary spastic paraplegia (HSP)-like phenotype was reported in 5 (10.4%) patients. Verny et al. reported on these patients, who were five siblings with an unusual late onset of the disease between ages 30 and 50. While the mutation load of all the siblings was homoplasmic, each sibling experienced a different course of the disease. Some experienced severe progression and became wheelchair-bound, while others experienced a very mild course with reduced vibration sense, spasticity in the lower limbs, and painful legs (125).

A Charcot-Marie-Tooth(CMT)-like phenotype was reported in 5 patients (10.4%). Bardakjan et al. reported on one of those patients, a 22-year-old woman, and her mother, who both harbored the m.9176T>C mutation. Only the daughter was diagnosed with CMT. She experienced progressive lower extremity weakness and stiffness and had difficulty walking, having fallen several times. Her mother had a very mild case with mild weakness and moderate denervation in her distal leg muscles (99). The second report of CMT in patients with the m.9176T>C mutation was by Synofzik et al., who studied a four-generation family. The index patient and her daughter both harbored the homoplasmic mutation and had a mild course. The

mother and grandmother of the index patient also had an unusually mild course (126).

Other movement disorders or motor disorders were reported in 5 patients. These were ankle clonus, pyramidal syndrome, extrapyramidal features, Parkinson's disease and an undiagnosed gait disorder. The frequencies of the clinical characteristics mentioned above are summarized in Table 4.

Table 4

Frequencies of LS, seizures and movement/motor disorders among investigated patients with the m.9176T>C variant

Variable	Available n/N (%)	Present n/n (%)	Proportion of total group (n/N) (%)
LS	41/48 (85.4)	31/41 (75.6)	31/48 (64.6)
Seizures	6/48 (12.5)	5/6 (83.3)	5/48 (10.4)
Myoclonus	1/48 (2.1)	1/1 (100)	1/48 (2.1)
Ataxia	21/48 (43.8)	16/21 (76.2)	16/48 (33.3)
Dystonia	9/48 (18.8)	9/9 (100)	9/48 (18.8)
Chorea	4/48 (8.3)	4/4 (100)	4/48 (8.3)
HSP	5/48 (10.4)	5/5 (100)	5/48 (10.4)
CMT	5/48 (10.4)	5/5 (100)	5/48 (10.4)
Other	5/48 (10.4)	5/5 (100)	5/48 (10.4)

Note. LS = Leigh syndrome; HSP = (Hereditary spastic paraplegia)-like phenotype ; CMT = (Charcot-Marie-Tooth disease)-like phenotype.

Furthermore, the frequencies of the following symptoms were examined: ocular manifestations, neuropathy, hypotonia, headache, hearing loss, and cardiomyopathy. Of these clinical manifestations, ocular manifestations were the most common, occurring in 43.8% of cases. Ocular manifestations included: blepharoptosis, diplopia, inferior oblique muscle palsy, strabismus, right eye exotropia, bilateral impairment of vertical gaze, nystagmus, myasthenia oculi, external ophthalmoparesis, oculomotor dyspraxia, bulbar palsy, limited eye ocular motility, retinitis pigmentosa, ocular motor palsy, bilateral cataract, blurry vision, bilateral optic atrophy, upward gaze paresis, internal ophthalmoplegia. Hearing loss and cardiomyopathy were only documented in two cases each. See Table 5 for the exact distributions.

Table 5

Frequencies of different symptoms in investigated patients with m.9176T>C variant

Variable	Available n/N (%)	Present n/n (%)	Proportion of total group (n/N) (%)
Cardiomyopathy	2/48 (4.2)	2/2 (100)	2/48 (4.2)
Neuropathy	11/48 (22.9)	11/11 (100)	11/48 (22.9)
Ocular manifestation	26/48 (54.2)	21/26 (80.8)	21/48 (43.8)
Hearing loss	2/48 (4.2)	2/2 (100)	2/48 (4.2)
Hypotonia	9/48 (18.8)	9/9 (100)	9/48 (18.8)
Headache	6/48 (12.5)	6/6 (100)	6/48 (12.5)

3.1.4 MRI abnormalities

Imaging abnormalities were detected in 38 of all cases (79.2%). Magnetic resonance imaging (MRI) was performed in 36 cases, while computed tomography (CT) was done in only two cases. The most frequently reported abnormalities were located in the basal ganglia (35.4%) and the brainstem (33.3%). The exact frequency distributions can be viewed in the Table 6.

Table 6

Frequencies of different CT/MRI abnormalities

Variable	Available n/N (%)	Present n/n (%)	Proportion of total group (n/N) (%)
CT/MRI abnormality	38/48 (79.2)	28/38 (73.7)	28/48 (58.3)
Brainstem	28/48 (58.3)	16/28 (57.1)	16/48 (33.3)
Basal ganglia	31/48 (64.6)	17/31 (54.8)	17/48 (35.4)
Diencephalon	16/48 (33.3)	6/16 (37.5)	6/48 (12.5)
Cerebellum	18/48 (37.5)	8/18 (44.4)	8/48 (16.7)
White matter lesions	14/48 (29.2)	4/14 (28.6)	4/48 (8.3)
Leukodystrophy	12/48 (25.0)	2/12 (16.7)	2/48 (4.2)

Note. CT = Computertomography; MRI = Magnetic resonance imaging.

3.1.5 Therapy and Medication in Documented Cases

The medication administered to patients was documented in ten of all cases. All of these patients had been diagnosed with LS.

Ohyama-Tamagake et al. described a 26-year-old female patient harboring a homoplasmic m.9176T>C mutation. In addition to LS, the patient was diagnosed with reversible vasoconstriction syndrome (RCSV), which was successfully treated with calcium channel blockers (85).

Chen et al. presented a case of a 13-month-old boy with an almost homoplasmic mutation (99.97%). When his condition worsened following an infectious disease, he received anti-infective medication. As the treating physicians suspected possible neuromyelitis optica spectrum disorder (NMOSD), immunoglobulin and glucocorticoid therapy were initiated. For the treatment of LS, the patient was given a long-term “cocktail therapy” (127).

Ichikawa et al. reported on a 10-year-old boy with an almost homoplasmic mutation (99.8%) who was treated with vitamins, as well as biotin, levocarnitine and coenzyme Q. Following therapy, serum lactate levels decreased and the patient showed almost no progression of symptoms (128).

Liang et al. described a 12-year-old boy with a homoplasmic mutation. The patient had an infectious disease with fever lasting two months and was treated with antiviral medication and measures to reduce intracranial pressure. He also received medication for LS but died two months later (129).

The report by Chuquillin et al. concerned a 20-year-old female patient with a homoplasmic mutation, whose symptoms worsened subacutely after a motor vehicle accident. Following plasmapheresis treatment, her symptoms improved. When infusions were delayed, the symptoms worsened. The patient began receiving intravenous immunoglobulin (IVIG) infusions every 4 weeks and was also given supplements. (95).

Jacobs et al. described three siblings affected by LS. No treatment was reported for one of the siblings, who died at the age of four. The other two siblings received treatment with vitamins and carnitine. The boy experienced a more severe disease course than his sister, with symptoms including ataxia, dystonic movements and severe intellectual disability (79).

Oh et al. reported on a 21-year-old female patient whose MRI lesions decreased mildly and whose symptoms improved after a two-week treatment with thiamine, suspected to be Wernicke's encephalopathy. She got diagnosed with LS, and it was unclear whether this was accompanied by Wernicke's encephalopathy, meaning that the symptoms improved, or if the symptoms of LS decreased due to the thiamine treatment (130).

In a report by Chourasia et al., a 15-month-old boy with hypotonia and motor delay was described. When a regressive episode occurred at 5 years of age, the patient received methylprednisolone due to possible cerebellitis. He then recovered with mild residual dysarthria and ataxia. One year later, during a viral illness, the symptoms progressively worsened (92).

Ronchi et al. described the case of a 22-year-old female. The patient experienced generalized seizures and was treated with benzodiazepine and anticonvulsant therapy, as well as beta-blockers and calcium antagonists to treat tachycardia (84).

A summary of the patients who received medication and their outcomes is presented in Table 7.

Table 7

Therapy and Medication in Reported Cases

Case Nr.	Paper	Sex	Onset	Diagnoses	Symptoms/Course	Treatment/Medications	Outcome
1	(85)	f	26 yo	LS, RCSV	Cardiomyopathy, headache; OC	Multivitamin supplementation; 5-aminolevulinic acid hydrochloride; calcium channel blockers	Neurological symptoms resolved
2	(127)	m	13 mo	LS; NMOSD suspected	Rapidly progressive; respiratory failure; DD	Immunoglobulin and glucocorticoid therapy; coenzyme Q10; L-carnitine; multiple vitamins	Symptoms improved, but significant DD and feeding via gastric tube
9	(128)	m	10 yo	LS	OC; nausea; dyspnea	Vit B1, B2, C and E; biotin; levocarnitine; coenzyme Q	Decrease in lactate levels; almost no progression for 2 years

Case Nr.	Paper	Sex	Onset	Diagnoses	Symptoms/Course	Treatment/Medications	Outcome
12	(129)	m	12 yo	LS	Rapidly progressive; infection with fever for 2 m	Vit B complex; vit C, E; coenzyme Q10; carnitine; adenosintriphosphat	Died 2 months later
13	(95)	f	20 yo	LS	OC; CD; frequent falls	Plasmapheresis; IVIG infusions every 4 weeks; carnitine; coenzyme Q10; vit B50 complex; lipoic acid; vit E, C; selenium	Symptoms improved; patient could walk again
15	(79)	m	4 yo	LS	Severe course; ataxia; dystonia; headache; DD; CD	Vit B complex; vit E; carnitine	Progressive course; can only speak a few words at 8 yo
16	(79)	f	2 yo	LS	Ataxia; dystonia; DD; CD	Vitamin B complex; vitamin E; carnitine	Delayed language development at 6 yo
20	(130)	f	21 yo	LS; WE suspected	OC; CD	Two-week treatment with thiamine	Symptoms improved; 1 y later

Case Nr.	Paper	Sex	Onset	Diagnoses	Symptoms/Course	Treatment/Medications	Outcome
							Regressive episode with diplopia and headache
30	(92)	m	15 mo	LS	Ataxia; OC, motor delay; hypotonia; regressive episodes	Methylprednisolone	Recovered with mild dysarthria and ataxia; symptoms worsened 1y later
41	(84)	f	22 yo	LS	Generalized seizures; ataxia; tachycardia	Benzodiazepine; anticonvulsant therapy; beta blockers and calcium antagonists (for tachycardia)	Rapidly progressive course

Note. m = male; f = female; y = year; yo = years old; m =months old; LS = Leigh syndrome; RCSV = reversible vasoconstriction syndrome; NMOSD = neuromyelitis optica spectrum disorder; IVIG = intravenous immunoglobulin; DD = developmental delay; CD = cognitive dysfunction; OC = ocular manifestation; vit = vitamine; WE = Wernicke´s encephalopathy.

3.1.6 Follow-up and clinical course

Information on age at last follow-up was available for 28 of the 48 patients. The median age at last follow-up was 15.5 years, with an interquartile range of 37 years, reflecting a highly heterogeneous age distribution among patients. In total, 8 patients (16.7 %) were reported deceased. The median time from disease onset to death was 2 months, with an IQR of 12 months. The shortest and longest durations were 3 weeks and 36 months, respectively, highlighting the presence of outliers and a highly skewed distribution. Reported causes of death were cardiac arrest (n = 1), recurrent apnea/respiratory arrest (n = 3), and progressive brainstem dysfunction (n = 2).

Among the deceased patients, 7 of 8 had a rapidly progressive disease course. The only patient with a slowly chronic course was an 82-year-old woman. The onset of her disease was unknown, she had not been diagnosed with LS or LLS, and her disease course was very mild (126).

For the remaining deceased patients, disease onset occurred either before 2 years of age (n = 5) or between 2 and 12 years (n = 2).

Six of the 8 deceased patients were male, and 7 had a diagnosis of LS or LLS. Seizures and ataxia were each observed in 2 cases. Dystonia occurred in 1 patient, while chorea, myoclonus and HSP were not reported in any of the 8 patients. CMT was present in only 1 case, and developmental delay was reported in 5 patients. Other reported features included neuropathy (n = 1), ocular manifestations (n = 3), hearing loss (n = 2), and hypotonia (n = 4). CT or MRI abnormalities were found in 6 of the deceased patients, most commonly affecting the brainstem (n = 4) and basal ganglia (n = 4). Elevated lactate levels were observed in 6 of the 8 deceased patients. The main characteristics of those patients are summarized in Table 8.

Table 8

Main characteristics of the deceased patients

Patient ID	Sex	AO	AD	Major clinical symptoms	Cause of death	Disease duration
#6	m	9 m	9 m	LS, seizures, DD, hypotonia, coma	NA	Few hours
#7	m	9 m	9 m	LS, seizures, DD, coma	Cardiac arrest	3 weeks
#10	m	3 yo	4 yo	LS, ataxia, hypotonia	Recurrent apnea	1 y
#12	m	12 yo	12 yo	LS, fever, inability to walk, respiratory and circulatory failure, myasthenia oculi, ptosis	Progressive brainstem dysfunction	2 m
#14	f	1 yo	4 yo	LS, ataxia, DD, fever, dystonia, stomachache, dyspnea	Progressive brainstem dysfunction	3 y
#29	f	NA	82 yo	CMT, N, bilateral cataract	NA	NA
#39	m	5 m	7 m	LS, DD, hearing loss, hypotonia, no visual contact, swallowing difficulties	Respiratory arrest	2 m
#40	m	5 m	10 m	LS, DD, bilateral optic atrophy, nystagmus, hearing loss, hypotonia	Respiratory arrest	5 m

Note. AO = age at onset; Age at death; y = years; m = months; yo = years old; NA = not available; LS = Leigh syndrome; DD = developmental delay; N = neuropathy.

3.1.7 Clinical Characteristics According to Age at Onset

3.1.7.1 Demographics, Laboratory Findings, and Mutation Load

When analyzing sex distribution across the three age-at-onset groups, a clear predominance of male patients was observed in the <2 years group (G1), with 12 of 14 patients being male (80%). In G2, 9 patients (60%) were male and 6 (40%) female. In contrast, G3 showed a female predominance, with 10 of 14 patients (71.4%) being female.

The median mutation load was high and relatively similar across all groups. In G1, the median was 96.4% (minimum 90%), in G2 97.3% (minimum 92%), and in G3 99.6% (minimum 96%). The highest median mutation load was thus observed in the group with the latest age at onset.

Regarding laboratory findings, elevated lactate levels were documented in 9 of 14 patients in G1 (64.3%), while data were unavailable for the remaining 5 patients. In G2, lactate was elevated in 10 of 15 patients (66.7%), normal in 1 patient, and not reported in 4 cases. In G3, elevated lactate was less frequent, occurring in 4 of 14 patients (28.6%), whereas 6 patients (42.9%) had normal levels and data were missing for 4 (28.6%). Overall, elevated lactate was more common in the earlier-onset groups. The values mentioned above are summarized in Table 9.

Table 9

Demographic and biochemical characteristics of Groups G1 - G3

Group	n/N (%)	Sex		Lactate increase n/n (%)	Mutant load (mean)
		male n/n (%)	female n/n (%)		
G1	14/48 (32.6)	12/14 (85.7)	2/14 (14.3)	9/14 (64.3)	96.5%
G2	15 /48 (34.9)	9/15 (60.0)	6/15 (40.0)	10/15 (66.7)	97.6%
G3	14/48 (32.6)	4/14 (28.6)	10/14 (71.4)	4/14 (28.6)	99.6%

Note. NA = not available; m = male; f = female.

3.1.7.2 Clinical phenotypes

All 14 patients (100%) in G1 were diagnosed with LS or LLS. In G2, 12 patients (80%) had LS/LLS, while 1 patient did not and information was missing for 2 cases. In G3, LS/LLS was present in 5 of 14 patients (35.7%) and absent in 8 (57.1%), suggesting a decreasing frequency with increasing age at onset.

Developmental delay was reported in 10 patients in G1 (71.4%), whereas data were unavailable for the remaining 4 patients. In G2, developmental delay was present in 4 patients (26.7%), absent in 6 (40.0%), and not reported in 5 (33.3%). In G3, developmental delay was not observed in 3 patients (21.4%); for the remaining 11 patients (78.6%), no information was available.

Cognitive dysfunction was documented in 2 of 14 patients in G1 (14.3%). In G2, it was present in 6 patients (40%) and absent in 4 (26.7%), with missing data in 5 (33.3%). In G3, cognitive dysfunction was reported in 2 patients (14.3%), while information was lacking for the rest of the patients in this group.

Seizures were reported in 3 patients in G1 (21.4%), 1 patient in G2 (9.1%), and 1 patient in G3 (5.6%). Myoclonus was observed in only 1 patient overall, belonging to G1.

Ataxia was reported in 3 patients in G1 (21.4%). In contrast, it was more common in G2, affecting 11 patients (73.3%), while only 2 patients in G3 (14.3%) were reported to have ataxia.

Dystonia was observed in 7 patients in G1 (50%) and in 2 patients in G2 (13.3%). No data on dystonia were available for G3.

Chorea was reported in 3 patients in G1 (21.4%) and in 1 patient in G2 (6.7%), but not in G3. HSP was not documented in G1 or G2, whereas it was present in 5 patients in G3 (35.7%). Similarly, CMT was absent in G1, occurred in 1 patient in G2 (6.7%), and in 3 patients in G3 (21.4%).

Cardiomyopathy was reported exclusively in G3, affecting 2 patients (14.3%). Neuropathy was not observed in G1, but was reported in 3 patients in G2 (20%) and 6 patients in G3 (42.9%).

Ocular involvement was documented in 4 patients in G1 (28.6%), 9 in G2 (60%), and 7 in G3 (50%). Five patients in G2 (35.7%) had no ocular manifestations; data were unavailable for the remaining cases across all groups.

Hearing loss was reported only in G1 (2 patients, 14.3%). Hypotonia was observed in 7 patients in G1 (50%) and in 2 patients in G2, but not in G3. Headache was reported sporadically across all groups (1 patient each in G1 and G2, and 4 patients in G3).

CT/MRI abnormalities were frequent in G1 (10 patients, 71%) and G2 (13 patients, 86%), but less common in G3 (5 patients, 35.7%). A summary of the frequencies of the different clinical features is presented in Tables 10-13.

Table 10

Frequencies of LS, Seizures, Ataxia, Myoclonus, Dystonia and Chorea

Group	LS/LLS n/n (%)	Seizures n/n (%)	Ataxia n/n (%)	Myoclonus n/n (%)	Dystonia n/n (%)	Chorea n/n (%)
G1	14/14 (100)	3/14 (21.4)	3/14 (21.4)	1/14 (7.1)	7/14 (50.0)	3/14 (21.4)
G2	12/15 (80.0)	1/15 (6.7)	11/15 (73.3)	NA	2/15 (13.3)	1/15 (6.7)
G3	5/14 (35.7)	1/14 (7.1)	2/14 (14.3)	NA	NA	NA

Note. LS = Leigh syndrome, LLS = Leigh-like syndrome; NA = not available.

Table 11

Frequencies of HSP, CMT, Developmental Delay and Cognitive Dysfunction

Group	HSP n/n (%)	CMT n/n (%)	Developmental delay n/n (%)	Cognitive dysfunction n/n (%)
G1	NA	NA	10/14 (71.4)	2/14 (14.3)
G2	NA	1/15 (6.7)	6/15 (40.0)	6/15 (40.0)
G3	5/14 (35.7)	3/14 (21.4)	3/14 (21.4)	2/14 (14.3)

Note. HSP = Hereditary spastic paraplegia; CMT = Charcot-Marie-Tooth; NA = not available.

Table 12

Frequencies of Organ Manifestations and Different Symptoms in Group G1 - G3

Group	CM n/n (%)	NP n/n (%)	OC n/n (%)	Hearing loss n/n (%)	Headache n/n (%)	Hypotonia n/n (%)
G1	NA	NA	4/14 (28.5)	2/14 (14.3)	1/14 (7.1)	7/14 (50)
G2	NA	3/15 (20.0)	9/15 (60.0)	NA	1/15 (6.7)	2/15 (13.3)
G3	2/14 (14.3)	6/14 (42.9)	7/14 (50.0)	NA	4/14 (28.8)	NA

Note. CM = cardiomyopathy, NP = neuropathy, OC = ocular manifestation; NA = not available.

Table 13

Frequencies of different CT/MRI abnormalities in Group G1 - G3

Group	CT/MRI abnormality n/n (%)	BS n/n (%)	BG n/n (%)	D n/n (%)	C n/n (%)	WM n/n (%)	LD n/n (%)
G1	10/14 (71.4)	5/14 (35.7)	7/14 (50.0)	1/14 (7.1)	4/14 (28.6)	2/14 (14.3)	2/14 (14.3)
G2	13/15 (86.7)	6/15 (40.0)	7/15 (46.7)	3/15 (20.0)	4/15 (26.7)	2/15 (13.3)	NA
G3	5/14 (35.7)	5/14 (35.7)	3/14 (21.4)	2/14 (14.3)	NA	NA	NA

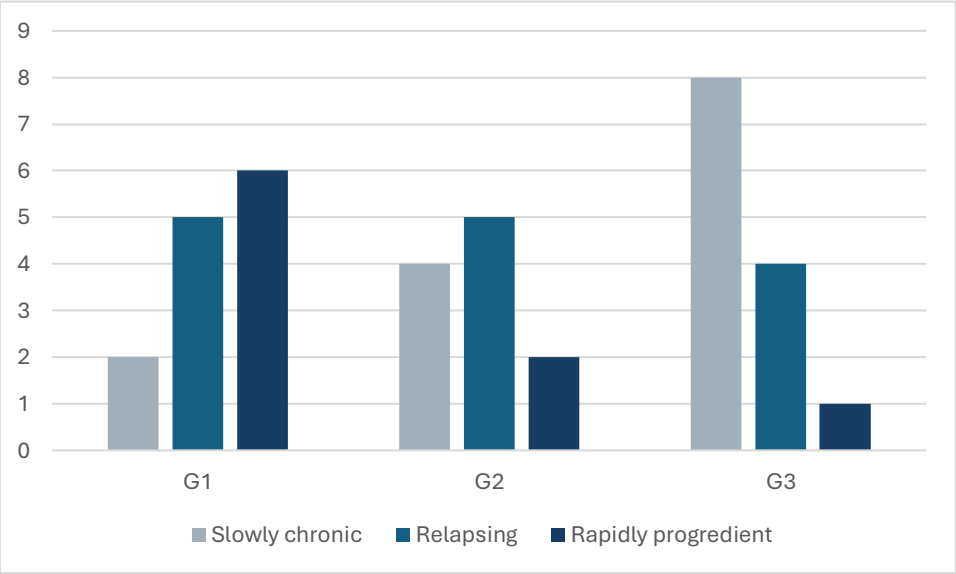
Note. BS = brainstem; BG = basal ganglia; D = Diencephalon; C = Cerebellum, WM = white matter; LD = Leukodystrophy; NA = not available.

3.1.7.3 Course and Survival

In G1, most patients showed a rapidly progressive course (42.9%), while 35.7% had a relapsing course and 14.3% a slowly progressive chronic course.
In G2, the most common pattern was a relapsing course (33.3%), followed by a slowly progressive chronic course (26.7%) and a rapidly progressive course (13.3%).
In G3, most patients had a slowly progressive chronic course (57.1%), whereas 28.6% had a relapsing course and only 1 patient (7.1%) showed a rapidly progressive course. Overall, earlier onset was associated with a more aggressive disease course, while later onset tended to follow a more chronic course.
Five deaths occurred in G1 and 2 in G2, whereas no deaths were reported in G3. Frequencies of the different disease courses and of deceased patients are presented in Figure 6.

Figure 6

Frequencies of Disease Courses in Group G1-3



Note. Values on the Y-axis are shown in absolute numbers.

Table 14

Summary of Clinical Characteristics of Patients 1–48

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(85**)**	1	f	26 yo	+	NA	NA	+	+	Cardiomyopathy; headache, OC; RCSV	Neurological symptoms resolved after therapy
(127)	2	m	13 mo	+	NA	NA	+	+	Dystonia; H; DD; CD; respiratory failure	Condition improved; but significant retardation; feeding through gastric tube
(72)	3	f	1 yo	+	NA	NA	NA	NA	Dystonia; chorea	Stepwise progression
(72)	4	m	1 yo	+	NA	NA	NA	NA	dystonia	stepwise progression

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(72)	5	m	1 yo	+	NA	NA	+	+	Dystonia; chorea	Acute onset, stepwise progression
(110)	6	m	9 mo	+	+	NA	NA	NA	Headache; H; DD	Died at 9m
(110)	7	m	9 mo	+	+	NA	+	+	DD	Died at 9m
(131)	8	m	20 yo	+	NA	NA	+	+	OC	NA
(128)	9	m	10 yo	+	NA	NA	+	+	OC; nausea; dyspnea	Only mild progression after 2 years
(90)	10	m	3 yo	+	NA	+	+	+	Headache; H	died at 4yo
(90)	11	f	childhood	NA	NA	+	NA	+	OC; DD; CD	Ataxia, nystagmus, mental retardation at 22yo

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(129)	12	m	12 yo	+	NA	NA	+	+	OC; infectious disease	Died at 2m
(95)	13	f	20 yo	+	NA	NA	+	+	OC; CD	Symptoms improved after monthly IVIG
(79)	14	f	21 mo	+	NA	+	+	+	Dystonia; bladder incontinence; DD	Died at 4yo
(79)	15	m	2 yo	+	NA	+	+	+	Dystonia; headache; DD; CD	Pyramidal syndrome and mental retardation at 8yo
(79)	16	f	2 yo	+	NA	+	+	+	Dystonia; DD; CD	Delayed language development at 6yo

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(76)	17	m	4 mo	+	NA	+	+	+	Dystonia; headache; OC; H; DD	Neurological condition static; needs to hold onto furniture at 6yo
(76)	18	m	< 16 mo	+	NA	NA	NA	+	Myoclonus; dystonia; chorea; DD; CD	Learning disability; motor tics; poor balance and coordination at 11yo
(132)	19	m	27 yo	+	-	+	NA	+	OC; CD	NA
(130)	20	f	21yo	+	NA	NA	NA	+	OC; CD	Improvement after thiamine-treatment; 1y later diplopia and headache

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(99)	21	m	22 yo	-	NA	NA	NA	-	CMT; N	Minimally worsened deficits at 52yo
(99)	22	f	NA	NA	NA	NA	NA	NA	N	Mild course
(133)	23	m	6 mo	+	+	NA	+	+	OC; H; DD	Bedridden at 10yo
(133)	24	f	8 yo	+	NA	+	+	+	Chorea; OC; N; CD	Slowly progressive
(133)	25	m	3 yo	+	NA	+	+	+	OC; CD	Slowly progressive
(126)	26	f	10 yo	+	NA	-	-	+	CMT; N	Still fully ambulant without ataxia at 49yo
(126)	27	f	14 yo	+	NA	-	NA	NA	CMT; N	Very mild course

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(126)	28	f	> 62 yo	+	NA	-	NA	NA	CMT; OC; N	Very mild course
(126)	29	f	NA	+	NA	-	NA	NA	CMT; headache; OC; N	Very mild course; died at 82yo
(92)	30	m	15 mo	+	NA	+	+	+	OC; N; H; DD	Regressive episodes at 5 and 6yo
(134)	31	f	3 yo	+	NA	+	+	+	HSP; OC	No more episodes up to 8yo
(134)	32	f	29 yo	NA	NA	+	-	-	HSP; OC	Asymptomatic at follow-up after 9m
(134)	33	m	5 yo	+	+	+	+	+	HSP; H	Good recovery; residual coordination and lethargy

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
										problems, absences at 10yo
(125)	34	m	30 yo	-	NA	NA	-	-	HSP; N	Moderate course
(125)	35	m	48 yo	-	NA	NA	-	-	HSP; N cardiomyopathy	Wheelchair-bound; severe progression
(125)	36	f	50 yo	-	NA	NA	-	-	N	Mild course
(125)	37	f	38 yo	-	NA	NA	-	-		Very mild course
(125)	38	f	30 yo	-	NA	NA	-	-		Pyramidal syndrome, gait impairment
(78)	39	m	5 mo	+	NA	NA	+	+	Hearing loss; H; DD	Died at 7m
(78)	40	m	5 mo	+	NA	NA	+	+	Hearing loss;	Died at 10m

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
									OC; H; DD	
(84)	41	f	22 yo	+	+	+	+	+	OC	Rapidly progressive course
(84)	42	f	NA	NA	NA	NA	NA	-	CD	NA
(135)	43	m	12 yo	+	NA	+	NA	-	OC	Ataxia as predominant feature
(135)	44	f	NA	NA	NA	NA	NA	NA		Parkinson disease
(75)	45	m	NA	NA	NA	-	NA	NA		Lower limb weakness
(136)	46	m	1 yo	+	NA	NA	NA	-		NA
(136)	47	f	12 yo	NA	NA	NA	NA	NA		Neuropathic and myopathic damage

Paper	Case Nr.	Sex	Onset	LS/ LLS	Seizures	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
(137)	48	m	2yo	+	NA	+	+	+	OC; N; DD	NARP

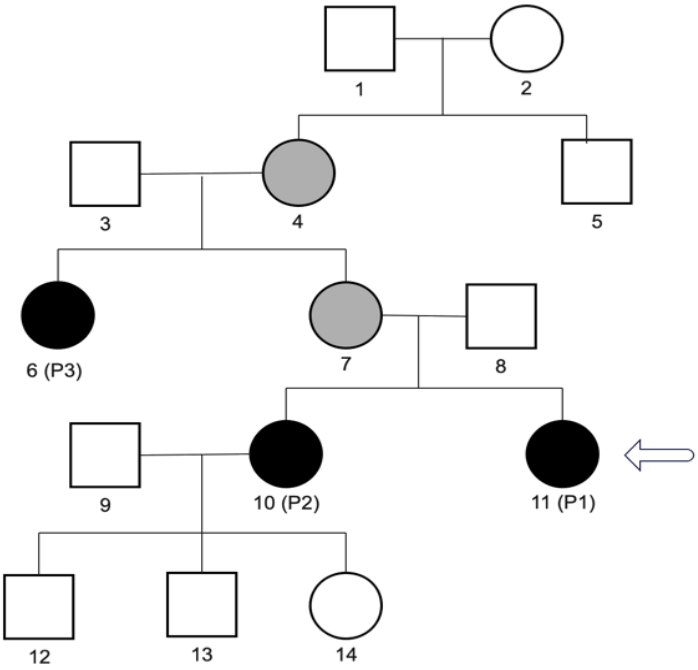
Note: y = years; yo = years old; mo = months; m = male; f = female; OC = ocular manifestation; IVIG = intravenous immunoglobulin; RCSV = Reversible cerebral vasoconstriction syndrome; N = neuropathy; H = hypotonus; CMT = Charcot-Marie-Tooth; HSP = Hereditary spastic paraplegia; DD = developmental delay; CD = cognitive dysfunction; + = present; - = not present; NA = not available.

3.2 Patient case report

The following report describes three family members with the m.9176T>C variant. Their relationships are illustrated in the family tree below (Figure 7).

Figure 7

The Pedigree of the Reported Family with m.9176T>C Mutation



Note. Circles indicate female relatives and squares indicate male relatives. Filled black symbols indicate patients with a molecular genetically confirmed mutation, whereas grey symbols indicate a high probability of a mutation. The mother of P1 (7) and the grandmother of P1 (4) have phenotypes similar to P1, but molecular genetic testing has never been performed.

3.2.1 Patient 1 (P1)

In patient 1, PCR amplification and sequencing of the specific regions of the MT-ATP6 gene revealed the variant m.9176T>C being homoplasmic.

Patient 1 (P1) first presented to the University Clinic for Pediatrics and Adolescent Medicine in Graz in 2009 at the age of 13. At that time, she complained about shaking of both arms and difficulties with writing and other fine motor tasks. In stressful situations, these symptoms intensified and sometimes a glove-like, livid discoloration was observed on the hands. She further noticed mild unsteadiness when going downstairs, however she was still able to participate in all sports activities at school.

The pediatricians observed a generalized hyperkinetic movement disorder, which was back then labeled as “tremor”, as well as problems in fine motor skills. The tremor started about an hour after getting up. At this time, walking and running were still possible without problems. 8 months after the initial presentation, now at the age of 14, the tremor had deteriorated, and an intention tremor and ataxia of the trunk were mentioned for the first time in the medical notes. Tendon reflexes of upper and lower extremities were increased. Sensory perception was decreased, especially in the legs.

Cardiac examination revealed discrete flow acceleration in the left pulmonary artery; the remaining findings were unremarkable. The MR of the brain and an EEG were also reported as normal.

Six months later, a further worsening of the “tremor” was noted, as well as increased sweating. The patient also reported subjectively perceived twitching. A first therapy attempt was made with propranolol to reduce the tremor.

At the age of 16, the tremor continued to deteriorate, and she complained about frequent headaches. Nocturnal seizures also occurred for the first time at this age. EEG findings showed evidence of a left parietal focus and regional signs of increased cerebral excitability. Continuous anticonvulsant therapy with oxcarbazepine was initiated.

At the age of 16, the patient suffered a generalized seizure for the first time, resulting in diazepam being prescribed as an on-demand medication in case of a seizure.

Due to disturbances in sensory perception, medication was switched from oxcarbamazepine to topiramate.
At age 17, trunk ataxia and head intention tremor continued to increase. At this time, a straight gait was difficult. Also, a voice tremor was noted. By now, the patient had experienced three falls and complained about subjective weakness of the legs. The patient was switched from diazepam to lorazepam as on demand medication in case of seizures.

In 2014 at age 19, the patient first presented to the outpatient movement disorders clinic at the Department of Neurology of the Medical University in Graz. Falls without loss of consciousness occurred 1-2 times per week. The hyperkinesia that had previously been regarded as tremor were now categorized as myoclonus and propranolol was stopped. Intermittent discrete facial myoclonus and stimulus-sensitive action myoclonus of upper limbs, lower limbs, and the trunk were observed. There was mild dystonic posturing of the hands. Mild spasticity was noticed in the lower limbs, tendon reflexes were increased, and Babinski sign was negative. Gait was mildly unsteady due to action myoclonus in the legs.
For treatment of myoclonus she received levetiracetam, topiramate was continued as antiepileptic drug.
At that time an EEG and MRI of the brain were repeated and were reported as normal. A neuropsychological assessment indicated mild depression and very mild to mild impairment of memory and attention/ concentration.
As myoclonus was not improved, she was switched to valproate, which led to marked deterioration of the generalized myoclonus. She was not able to leave the bed or hold subjects due to the twitching. Symptoms improved after withdrawal of valproate. Levetiracetam was increased up to 3000 mg/day. However, no major improvement was noticed. She further complained about a chronic daily headache.
At 19 years of age, pulmonological findings show mild hyperinflation of the lungs with minimal restriction of vital capacity, which could be explained by the underlying disease. In addition, there was mild sensorineural hearing loss on the right side. An add-on therapy with clonazepam was initiated, which led to mild improvement of the myoclonus. Due to the depressive mood, a therapy attempt with venlafaxine was made. In addition, baclofen was prescribed for the spasticity in the thighs but was

discontinued because of the associated gait deterioration. Pregabalin was prescribed for the treatment of panic attacks.

At age 21, there was intermittent dystonic posturing of the left upper extremity with elbow flexion, pronation of the forearm, and wrist flexion with radial duction. One year later she also had dystonic posturing of the left foot and the right hand. At age 22, she suffered from increased spasticity and myoclonus, especially in the legs. In addition, there was pain in the lumbar spine. Transthoracic echocardiography showed mild tricuspid regurgitation. A muscle biopsy was performed for the first time and histopathologic findings showed pathologic arrangement of mitochondria and presumed lipid deposition. However, no red fibers were detected.

Genetic testing revealed a homoplasmic mutation in the MT-ATP6 gene with the variant m.9176T>C. A lumbar puncture revealed no abnormalities of the cerebrospinal fluid. Ophthalmologic examination was normal.

At the age of 26, the pain increased, also in the plantar regions of the feet and upper arms. At age 27 she had a severe depressive episode and drank alcohol on a regular basis after problems with her partner.

At the age of 28, the patient still presented with moderate generalized stimulus-sensitive and action-induced myoclonus, slightly increased muscle tone in the neck, mild spasticity in the upper limbs and moderate spasticity in the lower limbs. She could get up from the chair with slight insecurities - but unaided at the first attempt. On walking she was mildly unsteady due to myoclonus but walked without aid with a broad-based gait. There was no evidence of cardiomyopathy in the context of the mitochrondiopathy on echocardiography, laboratory chemistry, or ECG. The 3-day Holter ECG showed no arrhythmias requiring treatment. At this time, she received the following medication: Levetiracetam 2500mg/day, clonazepam 1mg/day, duloxetine 30 mg/day, tizanidine 6 mg/day and pregabalin 140 mg/day.

Over the following months, the patient experienced an increasing number of difficulties when walking, such as dragging her legs, feeling weak and falling. This happened especially when performing activities involving the upper extremities simultaneously. Due to daily episodes of tachycardia and exercise-induced dyspnea, a possible cardiomyopathy was ruled out again by the cardiology department. From a cardiological point of view, there was no indication for therapy due to arrhythmias that did not require treatment and a very low resting heart rate.

At the age of 29, the patient experienced a worsening of the leg pain. A neurological examination revealed an increase in generalized stimulus-sensitive and action-induced myoclonus. There had been no epileptic seizures in the previous months. Due to an increase in sweating and worsening of the pain, treatment with 10 mg/day of amitriptyline was started but was discontinued a few months later due to side effects. Duloxetine was also discontinued due to side effects, after which milnacipran was started and the daily dose of pregabalin was increased to 300 mg due to generalized anxiety. Milnacipran was discontinued after one year due to side effects, which resulted in an exacerbation of the anxious state. Tianeptine was started instead. The medication she received at this time was: Levetiracetam 2500 mg/day, clonazepam 3 mg/day, tizanidine 6 mg/day, pregabalin 350 mg/day, tianeptine 37.5mg/day.

At the age of 30, the pain in both lower extremities and myoclonus worsened. An MRI at this time showed disc protrusions in the lumbal regions with narrowing of the neuroforamina. Due to depressive symptoms and chronical pain, tianeptine was stopped and treatment with venlafaxine was started. Due to worsening myoclonus and increased sweating, the pregabalin dosage was reduced to 300 mg/day due to possible causative side effects. The medication at this point consisted of: Levetiracetam 2500 mg/day, clonazepam 3 mg/day, tizanidine 6 mg/day, pregabalin 300 mg/day, venlafaxine 37.5 mg/day. Thanks to good tolerability and improvement in pain and psychiatric symptoms, the dose of venlafaxine was increased to 75 mg/day.

Shortly after there was a significant worsening of action-induced myoclonus, resulting in significant impairment of the upper extremity and increased gait instability. There was also worsening of the tremor in the hands. Levetiracetam was increased to 2750 mg/day. Due to the worsening of the myoclonus, the venlafaxine dosage was reduced again after 4 months to 37.5 mg daily, which improved the condition. The dosage of levetiracetam was decreased again after a few months to 2500mg/day since the previous increase did not lead to any improvement of the myoclonus.

The patient was eventually admitted to the hospital and received pain medication due to an acute exacerbation of the chronic lumboischialgia especially on the right side related to multisegmental degenerative spinal changes with numbness in the right leg. She currently takes the following medication: tizanidine 8 mg/day,

pregabalin 350 mg/day, clonazepam 3 mg/day, levetiracetam 2500 mg/day, venlafaxine 37.5 mg/day.

3.2.1.1 Family history

Affected family members who had a neurological examination with genetic testing:

3.2.1.1.1 Patient 2 (P2)

Patient 2, the sister of P1, first presented at the neurological clinic of Graz in 2005 at the age of 21 while pregnant with her second child. She reported falling to the floor since the age of 9, which increased in frequency since the age of 15, occurring once to four times a month. Additionally, she experienced uncertainty when walking and weakness. At the age of 14, she had her first seizure with loss of consciousness and generalized convulsions. Subsequently, she had episodes every two months, usually at night, lasting three to five minutes, with tongue and cheek biting.

The falls occurred while walking and were accompanied by leg shaking and subsequent leg slackening. After two minutes, she was able to get up and continue walking. These incidents typically occurred after longer periods of rest. During the visit, hand tremors were occasionally present. Short myoclonic movements of the trunk were noticed when standing up, as well as a discrete 'intention tremor' on the left and a broad-based gait.

At the age of 26, when P2 visited in 2010, she reported problems with frequent urination and difficulty controlling urination. Additionally, convergence weakness of the eyes was noted. During the motor skills test, the patient exhibited clear myoclonus in her upper extremities during both touch and passive movement. Additionally, she displayed ataxia in her hands. Myoclonus was particularly noticeable during intentional movements, at rest, and while maintaining posture. The patient experienced difficulty initiating walking and her gait was broad-based with short steps. At the time of evaluation, P2 was started on valproic acid for her myoclonus and tizanidine for her muscle spasms.

In 2015, at the age of 30, the patient presented to the outpatient clinic for movement disorders for the first time. At that time, she experienced nocturnal seizures approximately once per year. Her symptoms worsened rapidly between the ages of 16 and 18, followed by an improvement between 18 and 19 years of age. A further deterioration was reported at the end of each pregnancy. During her third pregnancy at the age of 23, she experienced seizures approximately every two weeks. Thereafter, her symptoms improved, and her condition has since remained stable.
At the age of 30, she began experiencing falls once a day, which were sometimes triggered by touch or when someone addressed her. She was treated with oxcarbazepine 600 mg/day and propranolol 120 mg/day, which, according to the patient, had no effect on her condition. During the neurological examination, intermittent spontaneous myoclonus was observed in the upper extremities, more frequently on the left than on the right, along with stimulus-sensitive myoclonus upon touch and in response to acoustic stimuli. The patient also exhibited spasticity in both upper and lower extremities, requiring assistance when attempting to stand up due to myoclonus in the lower extremities. Additionally, the patient's gait was spastic and unstable, with myoclonus observed during walking, but no ataxia was present.

During the 2015 visit, it was decided to discontinue the use of propranolol due to its lack of effectiveness. Levetiracetam 500 mg was added to the medication regimen while oxcarbazepine was maintained.
The genetic testing conducted in 2015 identified a homoplasmic mutation in the MT-ATP6 gene with the variant m.9176T>C.

3.2.1.1.2 Patient 3 (P3)

Further human genetic testing was performed on the maternal aunt (P3) of P1 and P2, which again revealed a homoplastic mutation in the gene MT-ATP6, also with the variant m.9176T>C. During the time of the genetic testing, P3 required assistance to walk and used a wheelchair due to her atactic gait disturbance. Additionally, she experienced epileptic seizures and myoclonias. P3 declined additional medical evaluations and treatment.
The clinical features of the three family members are summarized in Table 15.

Table 15

Summary of the Clinical Characteristics of the 3 Patients of our Patient Case Report

Patient	Sex	Onset	LS/LLS	Seizures	Myoclonus	Ataxia	Lactate increase	CT/MRI abnormality	Other	Course
P1	f	13	-	+	+	+	-	-	Tremor; dystonia; headache very mild CD; mild hearing loss	Slowly chronic; gait instability
P2	f	9	-	+	+	+	NA	-	Tremor; dystonia; very mild CD; convergence weakness of the eyes; urinary incontinence	Slowly chronic; gait instability
P3	f	NA	-	+	+	+	NA	NA	Very mild CD	Slowly chronic; wheelchair dependence

Note: f = female; CD = cognitive dysfunction; NA = not available; '+' indicates the presence of the clinical manifestation, while a '-' indicates its absence.

4 Discussion

4.1 Classification of the Newly Described Phenotype

In this study, we report a phenotype of the m.9176T>C mutation which has never been described in literature so far. We describe the phenotype of progressive myoclonus ataxia with homoplasmic mutation and slowly progressive disease course, distinct from the classical LS/LLS phenotype of early-onset patients. All three patients from our movement disorders clinic exhibited myoclonus, ataxia, mild seizures and only minimal cognitive impairment and minimal systemic involvement. None of our patients had developmental delay and all three showed a slowly progressive course, which we classify as mild compared to the other variants described in literature.

4.2 Impact of Age at Symptom Onset

Regarding the age of onset, our study showed that the age at which symptoms begin influences the phenotypical expression. Our family suits the type of later onset and milder clinical course. Nonetheless, the progressive myoclonus ataxia phenotype our family showed represents its own subgroup within the later onset groups.
Regarding our systemic literature review, in our youngest age of onset group, there was a clear predominance of male patients. In contrast, our oldest onset group G3 showed a female predominance. The presence of elevated lactate levels was more common in the two earlier onset groups G1 and G2, which matches with the higher frequency of Leigh syndrome diagnoses in the earlier onset groups. LS was diagnosed in all of the patients of the earliest onset group and in most of the patients of the G2 group, whereas only 35.7 % of the patients of the latest onset group were diagnosed with this disease. Developmental delay was most frequently observed in the earliest onset group G1 with a frequency of 71.4%. Seizures were most prevalent in group G1, whereas ataxia was more frequently observed in group G2. HSP and CMT-like phenotypes were reported most frequently in the latest onset group, indicating a shift toward peripheral phenotypes in the later-onset group.

Neuropathy was only reported in the two later onset groups (20% in G2 and 42.9% in G3), suggesting increasing peripheral involvement with later onset. Hypotonia was only observed in the earlier onset groups with the majority of it observed in the earliest onset group. CT/MRI abnormalities were also more frequent in G1 (71%) and G2 (86%), while it was less common in the latest onset group.

Regarding different disease courses, G1 was the group in which most of the rapidly progressive courses were observed, while relapsing courses and slowly chronic courses were common in the G2 group and in the latest onset group, a slowly chronic disease course was the most common type. Furthermore, deaths were only observed in the two earlier onset groups G1 and G2. These findings suggest that earlier disease onset is linked to a more severe clinical course.

4.3 Correlation Between Mutation Load and Phenotype

In the past, among the most common MT-ATP6 mutations, high mutation loads and homoplasmy have been linked to more severe phenotypes, such as Leigh syndrome or early death (76, 90, 110). In our affected family, however, the disease course was relatively mild, with a slowly progressive PMA-like phenotype, normal brain imaging, and normal serum lactate in our index patient (P1). Furthermore, rare cases of asymptomatic homoplasmic carriers of the m.9176T>C mutation have been described in the literature (2). These observations underscore that mutation load alone does not reliably predict the phenotype for the m.9176T>C variant, suggesting that additional factors contribute to the high variability observed.

Experimental data support the role of such modifying factors. D'Aurelio et al. studied cybrids from five patients harboring different MT-ATP6 mutations and demonstrated that the mtDNA background can significantly influence both biochemical abnormalities and clinical outcomes in patients with NARP or MILS (138). However, the limited number of patients makes it difficult to identify the determinants of phenotypic variability. Autoimmune processes triggered by mitochondrial dysfunction have been proposed as one possible factor, which may explain reports of clinical improvement after immunotherapy (95, 127).

Other potential influences have also been discussed. Mutation loads can differ between tissues in the same patient, which may partly explain the variability in clinical presentations (137). Yet high mutation loads have also been observed in

tissues that are less clinically affected, indicating that tissue-specific mutation load alone cannot fully explain phenotypic variability. Differences in mtDNA haplotypes may also play a role, though patients from different ethnic backgrounds carrying the m.9176T>C mutation can show similar phenotypes (84). For example, haplogroup J appears to have a protective effect in certain mitochondrial disorders (139). The phenotype may also be affected by additional modifying factors within the mtDNA sequence.

Environmental and metabolic factors may contribute as well. In our systematic review, twelve cases reported symptom worsening in association with viral infections or fever, highlighting the potential impact of metabolic stress. One case described a female patient whose symptoms worsened following a motor vehicle accident, suggesting that physical and possibly psychological stressors may also affect disease course (95). Environmental factors like smoking, and possibly alcohol, have been shown to modify penetrance in other mtDNA-related disorders like Leber hereditary optic neuropathy, suggesting a similar role in MT-ATP6–related disease (140). Oxidative stress may also contribute, as Verny et al. reported reduced activity of aconitase, a ROS-sensitive enzyme, in the most severely affected patients (125). Mechanistically, the m.9176T>C variant impairs ATP synthase assembly and stability, leading to reduced ATP synthesis and consequent energy deficits in tissues with high metabolic demand such as neurons and muscles, which may explain the associated neurological and muscular manifestations (141). Furthermore, age-related differences in heteroplasmy could theoretically influence the phenotype; however, studies on m.8993T variants with long-term follow-up have shown no relevant changes in mutation load, suggesting that this effect is likely limited (142).

In our three patients, all carrying the homoplasmic m.9176T>C mutation, there was notable intrafamilial variability in disease severity, ranging from mild gait disturbances to wheelchair dependence. While mutation load remains an important determinant of disease severity, it is clearly insufficient to explain the observed variability. Multiple genetic, environmental, and possibly immune-mediated factors likely interact to shape the clinical phenotype. Further research is required to clarify these influences and improve the predictability of outcomes in patients with MT-ATP6 mutations.

4.4 Implications for Diagnosis and Classification

PMA should be considered in the differential diagnosis of patients presenting with myoclonus and ataxia, mild epilepsy, minimal or no cognitive impairment, and normal CT or MRI findings. Importantly, MT-ATP6 mutations, including the m.9176T>C variant, should also be considered in families with maternally inherited MAS or PMA-phenotypes and only mild systemic involvement, rather than being limited to patients with the classical Leigh syndrome or NARP phenotype.

Van der Veen et al. defined PMA as a clinical syndrome marked by progressive myoclonus and ataxia which may be associated with mild cognitive deficits and infrequent, treatment-responsive epileptic seizures. In their cohort, the disease typically began with ataxia at a young age (median onset around 2 years), followed by the development of myoclonus, most commonly cortical myoclonus, at a median age of approximately 4 years. Seizures were less frequent and usually occurred later in the course of the disease, with a median onset at 9.3 years (23, 143).

When comparing our family to this definition of PMA, the clinical presentation largely fits within the described spectrum, as myoclonus and ataxia are present, epileptic seizures are infrequent, mild, and responsive to treatment, and cognitive impairment is only very mild. However, the first symptoms in our index patient appeared at the age of 13 years, which is considerably later than the typical age of onset reported for PMA. Moreover, the disease course in our three patients is clearly milder than the typical course described for this condition, with slower progression and less functional impairment. Overall, our family deviates from the typical PMA cases as described by van der Veen et al. The unusual late onset of symptoms at 13 years, combined with the mild progression, suggests that the clinical course is significantly less severe than in the classical presentation. In this context, the disease in our patients can be considered a mild or attenuated form of PMA, likely influenced by the underlying m.9176T>C mutation. This highlights that PMA associated with mitochondrial mutations may present as a broader clinical spectrum than previously recognized, extending beyond the early-onset, more severe phenotype.

In the context of genetic counselling, MT-ATP6 mutations should be considered in patients showing symptoms resembling PMA, particularly when there is a maternal pattern of inheritance. At the same time, counselling regarding prognosis should

consider the high inter- and intrafamilial variability that can be observed in the clinical expression of these mutations. Deterministic assumptions, such as the generalization that homoplasmy inevitably leads to a severe disease course, should therefore be avoided. Instead, the broad phenotypic spectrum associated with MT-ATP6 mutations should be carefully considered when counseling affected families regarding prognosis and disease expectations.

4.5 Therapeutic Approaches and Disease Management

The therapeutic approaches reported in the literature remain highly heterogeneous and mostly symptom-directed, reflecting the absence of established disease-modifying treatments for MT-ATP6–related disorders. In many cases, patients received so-called mitochondrial “cocktail therapies”, typically consisting of combinations of vitamins, coenzyme Q10, and L-carnitine. While some reports described stabilization of symptoms or biochemical improvement, such as reduced lactate levels, the clinical benefit remains difficult to interpret due to the limited evidence and the absence of controlled studies.

In several cases, clinical improvement occurred after treatment targeting additional or suspected comorbid conditions. Immunomodulatory therapies such as plasmapheresis, intravenous immunoglobulins, or corticosteroids were administered when autoimmune or inflammatory processes were suspected, with partial clinical improvement reported in some patients (92, 95, 127). Similar observations have been reported in other mitochondrial disorders, and such findings have supported the hypothesis that mitochondrial dysfunction may influence immune pathways and, in some patients, trigger secondary immune-mediated mechanisms (144). However, the current evidence is limited to individual case reports, and it remains unclear whether the observed improvements reflect a direct therapeutic effect on the mitochondrial disease itself or rather the treatment of overlapping inflammatory conditions. Consequently, the potential role of immunotherapy in MT-ATP6–related disorders remains uncertain and requires further investigation.

Symptomatic treatments, including anticonvulsants or calcium channel blockers, were also used to manage specific clinical manifestations. It should be noted, however, that valproic acid is generally contraindicated in patients with

mitochondrial disease. In our index patient, neurological symptoms worsened markedly after initiation of valproate therapy, which raised the suspicion of an underlying mitochondrial disorder. Valproic acid has been reported to induce mitochondrial toxicity and may lead to hepatic dysfunction and secondary carnitine deficiency (145). In addition, it can impair mitochondrial function by reducing oxygen consumption and ATP production. It also inhibits oxidative phosphorylation, affecting respiratory chain complexes I and IV (146-148). These mechanisms may exacerbate neurological symptoms in patients with mitochondrial disorders and highlight the relevance of considering mitochondrial disease in patients presenting with atypical forms of epilepsy.

Overall, the available reports emphasize the mostly symptom-directed nature of current therapeutic strategies and underline the need for further research into targeted treatments for mitochondrial diseases associated with MT-ATP6 mutations.

4.6 Strengths of the Study

This study has several strengths. By combining a detailed literature review with our own case series, we were able to assemble a relatively large cohort for this rare MT-ATP6 mutation, allowing for a more comprehensive understanding of the clinical spectrum. The systematic comparison of clinical features across age-of-onset groups provides insights into how the phenotype may vary depending on when symptoms first appear, highlighting patterns that might not be apparent from individual case reports. In addition, detailed intra- and interfamilial comparisons within our own case series allowed us to observe phenotypic variability within and between affected family members. Finally, the inclusion of therapeutic interventions and clinical outcomes, although only based on individual cases, adds practical value for diagnostic considerations and genetic counselling, providing guidance on when testing for MT-ATP6 mutations may be necessary and what clinicians might expect regarding disease course and variability.

4.7 Study Limitations

This study also has several limitations. First, its retrospective design and reliance on published literature introduce potential bias, particularly as more severe or atypical cases are more likely to be reported. Second, our own case series includes a small number of patients, which limits the generalizability of observations and makes reliable statistical analysis more challenging. Third, neuropsychological and longitudinal data were limited both for cases reported in the literature and for our two additional patients (P2 and P3), restricting insights into cognitive function and disease progression over time. Fourth, clinical assessment can be challenging due to the recurring confusion between tremor and myoclonus. Tremor is a rhythmic, oscillatory movement, whereas myoclonus consists of sudden, brief, shock-like jerks, although myoclonic jerks can occasionally appear rhythmic and mimic tremor (3, 6, 12, 149). Such misclassification may lead to inaccuracies in reported phenotypes, potentially affecting comparisons across patients and literature cases.

4.8 Conclusion

In summary, our study identifies a previously unreported, mild PMA-like phenotype associated with the m.9176T>C variant of the MT-ATP6 mutation, defined by late onset, slowly progressive myoclonus and ataxia, mild seizures, and minimal cognitive or systemic involvement. The timing of symptom onset appears to strongly influence the clinical presentation, and mutation load alone does not predict severity. These findings expand the known clinical spectrum of MT-ATP6–related disease, underscore the need to consider this mutation in atypical PMA presentations, and highlight the importance of individualized prognosis and genetic counseling.

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During the preparation of this manuscript, the author used DeepL (https://www.deepl.com/) to translate individual words or phrases and ChatGPT 4.0 for linguistic revision. The author has reviewed and edited the output and takes full responsibility for the content of this publication.