# Malformations of cerebral development and clues from the peripheral nervous system

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*Published in:*
European Journal of Paediatric Neurology

*DOI:*
10.1016/j.ejpn.2021.08.006

*Publication date:*
2022

**Malformations of cerebral development and clues from the peripheral nervous system: a systematic literature review.**

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**ABSTRACT**

Clinical manifestations of malformations of cortical development (MCD) are variable and can range from mild to severe intellectual disability, cerebral palsy and drug-resistant epilepsy. Besides common clinical features, non-specific or more subtle clinical symptoms may be present in association with different types of MCD. Especially in severely affected individuals, subtle but specific underlying clinical symptoms can be overlooked or overshadowed by the global clinical presentation. To facilitate the interpretation of genetic variants detailed clinical information is indispensable. Detailed (neurological) examination can be helpful in assisting with the diagnostic trajectory, both when referring for genetic work-up as well as when interpreting data from molecular genetic testing. This systematic literature review focusses on different clues derived from the neurological examination and potential further work-up triggered by these signs and symptoms in genetically defined MCDs. A concise overview of specific neurological findings and their associations with MCD subtype and genotype are presented, easily applicable in daily clinical practice. The following pathologies will be discussed: neuropathy, myopathy, muscular dystrophies and spastic paraplegia. In the discussion section, tips and pitfalls are illustrated to improve clinical outcome in the future.

**Keywords: MCD, polyneuropathy, myopathy, muscular dystrophy, spastic paraplegia**

**Abbreviations:** HSP – hereditary spastic paraplegia**,** IEM – inborn errors of metabolism, MCD – malformations of cortical development, PNS – peripheral nervous system

**Acknowledgements:** AJ is supported by a Senior Clinical Investigator fellowship from the Research Foundation Flanders (FWO SCI 1805321N). SB is supported by Wetenschappelijk Fonds Willy Gepts. KS, AJ and SB are members of the COST Action CA16188 Neuro-MIG (https://www.cost.eu/actions/CA16118; www.neuro-mig.org)

**Declarations of interest**: none

## 1. INTRODUCTION

Malformations of cortical development (MCD) form a heterogeneous spectrum of brain malformations. MCD are caused by disruption of neuronal proliferation, migration and/or post-migrational organization [1].

Clinical manifestations are variable and can range from mild to severe intellectual disability, cerebral palsy and drug-resistant epilepsy. It is estimated that 40 to 50 % of drug-resistant epilepsies are caused by MCD [2]. Besides common clinical features, non-specific or more subtle clinical symptoms, such as ophthalmologic, cardiac or gastro-intestinal abnormalities may be present in association with different types of MCD. Especially in severely affected individuals, subtle but specific underlying clinical symptoms can be overlooked or overshadowed by the global clinical presentation [3]. Detection of these phenotypic features can aid in the selection of additional non-genetic tests or help delineate a particular syndrome, ultimately pinpointing to a specific genetic diagnosis or be helpful in the interpretation of genetic variants [3]. An important pitfall is the misdiagnosis as, or attribution of the described clinical symptoms to cerebral palsy, a feature that is also commonly present in individuals with MCDs.

On imaging, brain malformations can be focal or diffuse, uni- or bilateral, and associated malformations of, for example, the corpus callosum, basal ganglia, brainstem or cerebellum are variably present [1, 2].

The classification of MCDs is based on characteristic clinical and imaging features [1, 2, 4]. Oegema et al. (2020) have defined ten MCD subtypes which are listed in Box 1.

Causes of MCD are variable and include environmental factors, such as congenital infections, prenatal vascular insults, or genetic causes. MCDs have been linked to a wide range of copy number variants as detected by chromosomal microarray analysis [5–7]. In addition, monogenetic disorders are a common cause of MCD and to date, more than 200 genes have been linked to the occurrence of MCD [8].

Advances in brain imaging techniques and molecular diagnostics have significantly improved our understanding of MCDs in the past years. Despite this progress, about 50% of all individuals with MCD still do not receive a causal diagnosis [9]. The diagnostic yield is variable between different MCD subtypes and reaches up to 75-81% in lissencephaly and cobblestone malformations, while for individuals with polymicrogyria a molecular diagnosis can be established only in 20% [4, 10, 11].

To facilitate the interpretation of genetic variants in rare diseases in general, and in MCD in particular, detailed clinical information is indispensable. Detailed neurological examination can be helpful in assisting with the diagnostic trajectory, both when referring for genetic work-up as well as when interpreting data from molecular genetic testing. Nevertheless, variant interpretation remains challenging due to heterogeneity among individuals with variants in the same gene.

This article focusses on different clues derived from the neurological examination and potential further work-up triggered by these signs and symptoms. In the next paragraphs a concise overview of specific neurological findings and their associations with MCD subtype and genotype are presented. The following pathologies will be discussed: neuropathy, myopathy, muscular dystrophies and spastic paraplegia.

## 2. METHODOLOGY

Preferred reporting items for systematic review (PRISMA) guidelines were followed for this systematic literature review. A review protocol can be found in Appendix A.

A search on PubMed was performed by three reviewers (ER, SB, ACJ) in April and May 2021. Each of the ten currently defined MCDs was combined with each clinical entity ("peripheral nerve", "neuropathy", "myopathy", "muscular dystrophy" and "spastic paraplegia") using both abbreviation and MESH terms [2, 4]. Filtering for "Human" subjects was activated. The title and abstract were screened, and subsequent screening of selected full text articles was used to detect eligible studies. To identify additional studies, the references of included studies were also screened. Figure 1 represents the search strategy used for one example (Fig.1).

Studies were included only if at least one individual was reported with MCD, one of the neurological symptoms described above was present and a molecular diagnosis had been confirmed in a gene linked to the development of MCD. Articles that report individuals with MCD and one of the clinical signs but without a confirmed genetic diagnosis were excluded.

The included studies were searched for information regarding the type of MCD, the clinical features and the molecular data.

## 3. MCD associated with disorders of the peripheral nervous system

We searched the literature to identify reports of different MCD subtypes with an established genetic diagnosis that have been associated with peripheral nervous system involvement. We identified 149 studies corresponding to our inclusion criteria (Supplementary table 1).

In the following paragraphs, the four main categories (polyneuropathy, myopathy, muscular dystrophy and hereditary spastic paraplegia) will be discussed in relation to MCD. Each section provides an overview of the most frequently occurring phenotypic entities. Infrequent or 'occasional' associations are mentioned briefly. A systematic overview is provided in Table 2.

### 3.1 POLYNEUROPATHY

Polyneuropathy is a general term for conditions that impact (peripheral) nerve function in different parts of the body. Neuropathy can affect sensorial fibres (sensory neuropathy) or motor fibres (motor neuropathy). Clinical effects of polyneuropathy can differ widely, depending on the affected nerves. Common features are weakness, numbness, and burning pain [12].

Polyneuropathy co-occurs with microcephaly in a wide range of genetic disorders. Clinical heterogeneity often causes diagnostic challenges but variants in *PTRH2* and *PNKP* are commonly associated with the combination of microcephaly and polyneuropathy.

Bi-allelic pathogenic variants in *PTRH2* are associated with infantile multisystem neurologic-endocrine-pancreatic disease (IMNEPD). Individuals with IMNEPD present with intellectual disability characterized by global developmental delay, postnatal microcephaly, ataxia, sensorineural hearing loss, and exocrine pancreatic insufficiency. More variable manifestations include hypotonia, growth retardation, peripheral demyelinating neuropathy, dysmorphic facial features, and additional endocrine abnormalities. Brain imaging may show progressive cerebellar atrophy in some individuals [13, 14].

Microcephaly with seizures (MCSZ) and Ataxia with oculomotor apraxia type 4 (AOA4) are two entities with overlapping clinical features that are associated with recessive pathogenic variants in *PNKP*. PNKP, or polynucleotide kinase phosphatase, is a DNA-repair factor [15]. MCSZ is characterized by microcephaly associated with seizures, hyperactivity and developmental delay [16]. In AOA4, cerebellar function is disturbed which results in a profound loss of motor control, cerebellar degeneration, oculomotor apraxia (abnormal saccadic eye movement) and often dystonia and peripheral neuropathy [17]. Pathogenic variants in *PNKP* are also associated with and Charcot-Marie-Tooth disease type 2B2 (CMT2B2). In contrast to MCSZ and AOA4, microcephaly is not a clinical feature of CMT2B2. CMT2B2 is a sensorineural axonal peripheral neuropathy manifesting with distal muscle weakness and atrophy and distal sensory impairment. The disorder predominantly affects the

lower limbs, resulting in gait impairment, although upper limb and hand involvement also occurs. The age at onset and severity is variable, but most have onset in the third decade. The disorder is slowly progressive. More variable features may include ataxia, dysarthria, cerebellar atrophy, and eye movement abnormalities [18]. As described above, pathogenic variants in *PNKP* give rise to a wide range of clinical phenotypes. The reason underlying this high degree of phenotypic variability is not well understood, but it is likely there are one or more other genetic or epigenetic modifiers [15].

Pontocerebellar hypoplasia (PCH) is a group of rare heterogeneous conditions characterized by prenatal development of an abnormally small cerebellum and brain stem and progressive microcephaly which is usually associated with profound psychomotor retardation. Although the clinical features vary widely, PCH is usually associated with profound intellectual disability and delayed or absent psychomotor milestones. In PCH type 1 (most severe type) newborns appear floppy and have respiratory insufficiency. At birth, multiple congenital contractures of large joints (arthrogryposis multiplex congenita) may be present. Clinical examination may reveal areflexia and combined motor signs [19–21]. PCH type 1 usually results in death during the first year of life [22]. Bi-allelic variants in *VRK1* are associated with PCH1A. Other complex neuromotor phenotypes associated with *VRK1* include spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) [23]. Recessive variants in *EXOSC3* are associated with PCH1B, resulting in postnatal progressive microcephaly, cerebral and cerebellar atrophy, cerebellar cysts, axonal neuropathy as well as muscle atrophy [19–21].

Cockayne syndrome or progeria-like syndrome is caused by recessive bi-allelic pathogenic variant in *ERCC6* and *ERCC8*. Clinical features are short stature, microcephaly, premature aging (progeria), severe photosensitivity, failure to thrive and moderate to severe intellectual disability. *ERCC8* is predominantly associated with Cockayne syndrome type A, also called “classic” or "moderate" Cockayne syndrome, diagnosed during early childhood. *ERCC6* is predominantly associated with Cockayne syndrome type B, also referred to as the “severe” or "early-onset" type [24]. Besides Cockayne syndrome, variants in *ERCC6* are also associated with Cerebro-oculo-facio-skeletal (COFS) syndrome. COFS syndrome is a degenerative disorder with microcephaly, intellectual disability, severe hypotonia, impaired reflexes, vision impairment, microphthalmia, low-set ears, and micrognathia. Children with COFS syndrome are usually diagnosed at birth [25].

Autosomal recessive variants in *PRUNE1* are responsible for brain malformations including microcephaly, progressive cortical atrophy, cerebellar hypoplasia and delayed myelination. Clinically, affected individuals present with hypotonia (with muscle atrophy), neuropathy or myopathy, associated with global developmental delay and severe intellectual disability [26].

Polyneuropathy has also rarely been reported in several other genes primarily linked to microcephaly (Table 1 and 2).

Another subtype of MCD that is occasionally found in individuals with polyneuropathy is polymicrogyria. Goldberg-Shprintzen Megacolon syndrome (GOSHS) is characterised by microcephaly, polymicrogyria, intellectual disability and Hirschsprung's disease. Besides these main characteristics, affected individuals present with blepharophimosis and -spasms, short stature and primary axonal neuropathy with secondary progression. GOSHS is caused by bi-allelic variants in *KIAA1279* [27]. Other less common causes of a combination of polymicrogyria and polyneuropathy can be found in Table 1 and 2.

In other genetically defined MCDs, polyneuropathy is exceedingly rarely or not at all described in the literature (Table 1 and 2).

### 3.2 MYOPATHY

Myopathies are a heterogeneous group of disorders affecting the skeletal muscle structure, metabolism, or channel function [28]. Myopathies can be subdivided into inherited and acquired myopathies. Inherited myopathies include mitochondrial, metabolic and congenital myopathies as well as muscular dystrophies and channelopathies. Myopathies can also be causes by auto-immune-mediated processes, and environmental causes such as infections and effects of certain drugs [28, 29].

Timing of onset of symptoms is variable and depends on the underlying cause. Individuals affected by a congenital myopathy often present in the neonatal period as floppy infants, but mildly affected individuals can come to clinical attention only later during childhood. Acquired myopathies often present with muscle weakness during adulthood. Other common symptoms include muscle stiffness and spasms, and muscle pain. In severe cases, myopathies can be associated with rhabdomyolysis [28].

MCDs are only rarely associated with inherited myopathies, except for microcephaly (Table 1 and 2).

Pathogenic variants in *EPG5* are responsible for the Vici syndrome, a severe congenital multisystem disorder [30]. Pathological features demonstrate a pattern of vacuolar myopathy with glycogen storage and immature, hypoplastic and atrophic muscle fibers. Principal features include agenesis of the corpus callosum, cataracts, oculocutaneous hypopigmentation, cardiomyopathy and a combined immunodeficiency. Besides these main characteristics, profound developmental delay, acquired microcephaly and marked failure to thrive are frequent clinical findings, but virtually every organ system can be affected [30, 31].

Individuals with pathogenic variants in *MORC2* present with developmental delay, impaired growth, dysmorphic facies, axonal neuropathy (DIGFAN), hyporeflexia and microcephaly. In some individuals MRI shows characteristic Leigh-like changes, which are symmetrical necrotic lesions in the basal ganglia and/or brainstem which appear as hyperintense lesions on T2 images [32].

Heterozygous variants in *MORC2* have also been reported in individuals with autosomal-dominant Charcot-Marie-Tooth disease type 2Z (CMT2Z) and spinal muscular atrophy [32].

Homozygous variants in *MYO18B* are responsible for Klippel-Feil anomaly with associated myopathy, microcephaly, mild short stature and facial dysmorphisms [33]. In Klippel-Feil anomaly vertebral development is affected. Affected individuals are born with abnormal fusion of at least two vertebrae (most frequently level C2/C3). Other clinical features are short neck, low hair line, restricted movement of the upper spine, Sprengel deformity and central nervous system anomalies (including Chairi malformation and spina bifida) [34].

Recessive pathogenic variants in *EXOSC3* and *PRUNE1* can lead to microcephaly co-occurring with both neuropathy and myopathy [19–21, 26]. Several other genes primarily linked to MCD (microcephaly, megalencephaly, subcortical band heterotopia, polymicrogyria, schizencephaly and focal cortical dysplasia) have been reported to cause myopathy (Table 1 and 2).

### 3.3 MUSCULAR DYSTROPHIES

As a subgroup of inherited myopathies, muscular dystrophies account for a group of degenerative disorders characterized by progressive muscle weakness of either limbs, axial skeleton, facial muscles, respiratory muscles, cardiac smooth muscles or a combination of these. Age at onset of symptoms and rate of disease progression, together with the distribution of affected muscles and histological features of muscle biopsies allow further classification of muscular dystrophies[35, 36]. To date, pathogenic variants in more than 40 genes have been reported in individuals with muscular dystrophies. These genes encore for, for example, extracellular matrix proteins, basement membrane proteins, and proteins with enzymatic function in glycosylation or other enzymatic steps necessary for muscular function, and sarcomeric proteins, leading to impaired function of the muscle cells [35].A subset of muscular dystrophies is caused by defects in genes involved in the O-glycoslysation of α-dystroglycan, including *POMGNT1*, *POMT1*, *POMT2*, *FKRP*, *FKTN* and *LARGE*, collectively referred to as dystroglycanopathies [37]. Dystroglycan is a protein of the cell membrane that is important for the formation of the pial basement membrane and involved in signal transduction from the extracellular matrix [38]. Impaired glycoslysation results in defects in the pial basement membrane, resulting in overmigration of neurons and formation of an extracortical layer [37]. Unlike for other muscular dystrophies, involvement of other organs, especially the brain and eyes, is common in dystrogylcanopathies. Abnormalities of the eyes include glaucoma, optic nerve hypoplasia, congenital cataract, retinal dysplasia and coloboma amongst others.

The combination of severe brain malformations, muscular dystrophy and ocular symptoms are

pathognomonic for several autosomal recessive syndromes, including Fukuyama congenital muscular dystrophy, muscle-eye-brain disease and Walker-Warburg syndrome. Affected individuals have microcephaly, eye abnormalities, muscular dystrophy with elevated levels of creatine kinase, and diffuse cobblestone malformation, white matter changes, dilated ventricles, hypoplasia and/or dysplasia of the brainstem and cerebellum with cerebellar cysts on brain MRI. These individuals are usually non-ambulatory and present with hypotonia, contractures, severe global developmental delay and epilepsy shortly after birth [36, 39]. Progressive cardiac involvement with decreased left ventricular systolic function occurs in some individuals [40]. Survival is variable and reduced to three years in severely affected individuals with Walker-Warburg syndrome, whereas survival into the third decade has been reported for individuals with muscle-eye-brain disease [41]. The different clinical features can depend both on the location of a pathogenic variants in the affected gene as well as on the combination of different variants on the two alleles. For example, variants in *FKTN* can cause either limb gridle muscular dystrophy, Fukuyama congenital muscular dystrophy or Walker-Warburg syndrome [42].

Pathogenic variants in *TMEM5* and *ISPD* have been reported in individuals with either polymicrogyria or cobblestone malformations, with clinical features similar to those seen in dystroglycanopathies [43].

Recessive variants in *LAMA2* are associated with congenital muscular dystrophy type 1, presentation occurs at birth or during the first months of life. Affected individuals present with central and peripheral hypotonia, motor development is delayed and limited. MRI reveals diffuse abnormalities in brain white matter, typically sparing the corpus callosum, internal capsule and cerebellum. In the initial phase of the disease, creatine kinase levels can increase up to four-fold of normal values [44].

Pathogenic variants in *INPP5K* have been reported in individuals with overlapping phenotypes of dystroglycanopathies and Marinesco-Sjögren syndrome. Affected individuals present with short stature, eye abnormalities such as cataracts and strabismus, myopathy and muscular dystrophy, and microcephaly. Cobblestone malformations and hypoplasia of the cerebellum and brainstem are usually absent [45].

Muscular dystrophy has also been reported in several individuals with isolated microcephaly, periventricular nodular heterotopia and polymicrogyria (Table 1 and 2).

### 3.4 HEREDITARY SPASTIC PARAPLEGIA

Hereditary spastic paraplegia (HSP) comprises a group of neurodegenerative disorders causing bilateral spasticity and/or weakness of the lower limbs, often associated with hyperreflexia and impaired sensitivity. Timing of the onset of disease is variable and can be early in childhood, clinically resembling cerebral palsy, or in adolescence or adulthood with a slowly progressive disease course.

HSP can occur isolated or in association with other neurological symptoms such as intellectual disability or peripheral neuropathy [46].

Pathogenic variants in genes encoding for the adaptor protein complex 4 (AP-4), including *AP4B1*, *AP4E1*, *AP4M1* and *AP4S1*, have been described in individuals with MCDs. While microcephaly is common and has been described for pathogenic variants in all subunits, polymicrogyria has only been reported in a subset of individuals with pathogenic variants in *AP4S1* and *AP4E1*. In addition, pathogenic loss of function variants in either of the genes encoding for the AP-4 subunits has been linked to complex HSP [47].

Typical clinical features associated with AP4-related HSP include global developmental delay, hypotonia progressing to spastic di/tetraplegia, epilepsy. Brain MRI shows can show additional brain malformations, such as cerebral atrophy and white matter loss, ventriculomegaly and hypoplasia of the corpus callosum in the majority of patients [47].

HSP is also associated with microcephaly, periventricular white matter lesions and a thinned corpus callosum in individuals with heterozygous pathogenic variants in *KIF1A*. These individuals also present with complex HSP with intellectual disability, language delay, epilepsy and optic nerve atrophy [48]. Other rare causes of HSP with microcephaly include pathogenic variants in *ACO2*, *AARS*, *ARL6IP1* and *COL4A1* [49–52].

## 4. DISCUSSION – CLINICAL TIPS

This review highlights that genetic variants underlying MCDs can also cause a broad spectrum of disorders affecting the peripheral nervous system. As MCDs are rare disorders, it is difficult for clinicians to be familiar and keep up to date with all clinical and molecular features. Nevertheless, clinical examination is of key importance for optimal care and diagnostic assessment. This raises several important aspects to keep in mind when evaluating individuals affected by MCDs.

Although PNS manifestations can be of high diagnostic value, they are easily overlooked during clinical examination in severely affected individuals, and additional testing such as electromyography or nerve conduction velocity studies for detecting and stratifying these symptoms might not be performed routinely. The work-up of MCD therefore calls for detailed clinical evaluation including the peripheral nervous system. As per international recommendations, clinical evaluation should also include measurement of head circumference, dysmorphology examination, skin inspection and, where relevant, ophthalmological examination and hearing evaluation [4].
We show that there are several specific phenotype-genotype correlations that might offer diagnostic clues in a subset of MCD patients. Further diagnostic work-up of MCD should include microarray-based comparative genomic hybridization as a first step. Second line next-generation sequencing has become common clinical practice and has significantly improved our understanding of the underlying pathogenic mechanisms of MCD during the last years [4]. Although novel techniques such as whole-exome or whole-genome sequencing, have proven very useful tools for the detection of pathogenic variants in individuals with MCD, extensive genetic testing also leads to the detection of unexpected findings, the significance of which might be challenging to interpret. Providing extensive clinical information when referring a patient for genetic testing can be of immense assistance for the geneticists. This is also true for clinical signs that might not seem significant at first sight as other clinical features may predominate [1]. The combination of features can help delineate a specific clinical syndrome, ultimately helping to narrow the differential diagnosis or be useful for variant interpretation.

Whenever a causal diagnosis is established in an individual with MCD, patient data including clinical, imaging, molecular and where relevant pathology data should be correlated with data available in the literature. This includes re-examination of the patient for eventual clinical features that have been described in other individuals in the literature. Re-evaluation of brain MRI can also lead to the identification of subtle abnormalities that have not been reported on first evaluation. This process is referred to as reverse phenotyping.

The identification of PNS involvement in individuals with MCD is also of clinical relevance since it potentially adds to disease-related morbidity and targeted treatment options might stabilize or improve clinical features.

Individuals presenting with a combination of central and peripheral central nervous system involvement, especially in the presence of multiple organ involvement, should be evaluated for inborn errors of metabolism (IEM) such as congenital disorders of glycosylation or mitochondrial disorders [53]. These disorders can have a variable age of onset but often present with neonatal or infantile failure to thrive, developmental delay, hypotonia and seizures. Neuroimaging commonly reveals cerebral and cerebellar atrophy as well as involvement of white matter or basal ganglia [54]. MCDs can also occur in these disorders, causing an overlapping syndrome of IEM and MCD. The most common MCD type associated with either of these disorders is microcephaly. To date, more than 800 genes are associated with microcephaly [55]. Despite this vast molecular spectrum, the molecular differential diagnosis can be limited when taking associated clinical clues into consideration. It is important to make a difference between individuals with MCD and IEM, as the disease course of IEMs can in many cases be less severe if they are diagnosed soon after onset of symptoms and appropriate treatment is initiated [56].

Importantly, clinical symptoms can evolve over time or be progressive in nature in patients with MCD. Regular follow-up and reassessment of neurological status of MCD patients is therefore of value to detect degradation of the clinical status as early as possible to maintain or improve patient (and family) comfort and avoid complications.

## CONCLUSION

When evaluating individuals with MCD, care should be taken to perform a detailed clinical assessment including examination of the peripheral nervous system. The presence of polyneuropathy, myopathy, muscular dystrophy or progressive spastic paraplegia might assist with genetic work-up and variant interpretation. Reversely, when pathogenic variants are identified in genes which result in MCD with potential co-occurring PNS involvement, careful clinical evaluation might lead to more appropriate management.

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## Figures and tables

### Box 1. Currently defined malformations of cortical development

| Pathogenesis | MCD subtype |
|---|---|
| Abnormal neuronal and glial cell proliferation and apoptosis | • Microcephaly<br>• Macrocephaly - Megalencephaly |
| Neuronal migration disorders | • Periventricular nodular heterotopia<br>• Subcortical band heterotopia<br>• Lissencephaly<br>• Cobblestone malformation<br>• Dysgyria |
| Malformations of postmigrational cortical organization and connectivity | • Polymicrogyria<br>• Schizencephaly<br>• Focal cortical dysplasia |

**Table 1. Reported clinical features per gene**

| MCD SUBTYPE | GENE | NEUROPATHY | MYOPATHY | MUSCULAR DYSTROPHY | SPASTIC PARAPLEGIA |
|---|---|---|---|---|---|
| **MICROCEPHALY** | | | | | |
| | AARS | x | | | |
| | ACO2 | x | | | x |
| | ADAT3 | x | | | |
| | AFG3L2 | x | x | | |
| | AIMP1 | x | | | |
| | AMPD2 | x | | | |
| | AP4S1 | | | | x |
| | AP4B1 | | | | x |
| | ARL6IP1 | x | | | x |
| | BICD2 | | x | | |
| | CARS | x | | | |
| | CHKB | | | x | |
| | COL4A1 | | x | | |
| | COL4A2 | | x | | |
| | CTDP1 | x | | | |
| | DPM1 | | | x | |
| | DPM2 | | | x | |
| | EPG5 | | x | | |
| | ERCC6 | x | | | |
| | ERCC8 | x | | | |
| | EXOSC3 | x | x | | |
| | EXOSC3 | | x | | |
| | FKTN | | x | x | |
| | GOLGA2 | | | x | |
| | GPT2 | | | | x |
| | GTPBP2 | x | | | |
| | IBA57 | | x | | |
| | IGHMBP2 | x | | | |
| | INPP5K | x | x | x | |
| | KARS | x | x | | |
| | KIAA1279 | x | | | |
| | KIF1A | x | | | x |
| | MCT8 | | x | | |
| | MFF | x | | | |
| | MORC2 | x | x | | |
| | MPV17 | x | | | |
| | MTATP6 | x | x | | |
| | MYO18B | | x | | |
| | NARS1 | x | | | |
| | PGK1 | x | | | |
| | PGM1 | | x | | |
| | PNKP | x | | | |
| | POMT1 | | x | x | |
| | POMT2 | | x | x | |
| | PRTH2 | x | | | |
| | PRUNE1 | x | x | | |
| | PTRH2 | x | | | |
| | RAB3GAP1 | x | | | |
| | SBF1 | x | | | |
| | SCYL2 | | x | | |
| | SLC35A3 | | x | | |
| | SNAP29 | x | | | |
| | TBCD | x | | | |
| | TOR1AIP1 | | x | | |

| | | | | | |
|---|---|---|---|---|---|
| | VRK1 | x | | | |
| **MEGALENCEPHALY** | | | | | |
| | CACNA1E | | x | | |
| | MTM1 | | x | | |
| **PERIVENTRICULAR NODULAR HETEROTOPIA** | | | | | |
| | FKRP | | | x | |
| **LISSENCEPHALY** | | | | | |
| | DYNC1H1 | | x | | |
| **SUBCORTICAL BAND HETEROTOPIA** | | | | | |
| | DCX | | x | | |
| **POLYMICROGYRIA** | | | | | |
| | A3243G | | x | | |
| | AP4E1 | | | | x |
| | AP4S1 | | | | x |
| | BICD2 | | x | | |
| | COL4A1 | | x | | x |
| | FIG4 | x | | | |
| | KIAA1279 | x | | | |
| | MICU1 | | x | | |
| | PI4KA | | x | | |
| | PIGB | x | | | |
| | RAB3GAP1 | x | | | |
| | TMEM5 | | | x | |
| | TUB8A | x | | | |
| **COBBLESTONE MALFORMATION** | | | | | |
| | B3GALNT2 | | | x | |
| | CRPPA | | | x | |
| | FKNT | | | x | |
| | FKRP | | | x | |
| | ISPD | | | x | |
| | LAMA2 | | x | x | |
| | LARGE | | | x | |
| | POMGNT1 | | x | x | |
| | POMT1 | | x | x | |
| | | | | | |
| **DYSGYRIA** | | | | | |
| | TUBB3 | x | | | |
| **SCHIZENCEPHALY** | | | | | |
| | COL4A1 | | x | | x |
| **FOCAL CORTICAL DYSPLASIA** | | | | | |
| | COL4A1 | | x | | x |
| | DEPDC5 | | x | | |
| | KMT2A | | x | | |
| | NPRL2 | | x | | |
| | SMPD4 | | x | | |

Table 2. Overview clinical PNS clues associated with molecularly defined MCD

| Frequent correlation MCD | | | Occasional correlation MCD | |
|---|---|---|---|---|
| **MCD subtype** | **Gene** | **Phenotype** | **MCD subtype** | **Genes** |
| **Polyneuropathy** | | | | |
| **Microcephaly** | PRTH2 | Infantile multisystem neurologic-endocrine-pancreatic disease (IMNEPD) | Microcephaly | AARS, ACO2, ADAT3, AFG3L2, AIMP1, AMPD2, ARL6IP1, CARS, CASK, CTDP1, GPR126, GTPBP2, IGHMBP2, KARS, MFF, MORC2, MPV17, MTATP6, NARS1, PGK1, RAB3GAP1, SBF1, SNAP29, TBCD |
| **Microcephaly** | PNKP | Microcephaly with seizures (MCSZ) and Ataxia with oculomotor apraxia type 4 (AOA4) | Lissencephaly | DYNC1H1 |
| **Microcephaly** | VRK1 | Pontocerebellar hypoplasia type 1A (PCH1A) | PMG | DYNC1H1, LAMA2, PIGB, RAB3GAP1, TUB8A |
| **Microcephaly** | EXOSC3 | Pontocerebellar hypoplasia type 1B (PCH1B) | Dysgyria | TUBB3 |
| **Microcephaly** | ERCC6 | Cockayne syndrome type B and cerebro-oculo-facio-skeletal (COFS) syndrome 1 | | |
| **Microcephaly** | ERCC8 | Cockayne syndrome type A | | |
| **Microcephaly** | PRUNE1 | Neurodevelopmental disorder with microcephaly, hypotonia and variable brain anomalies (NMIHBA) | | |
| **Microcephaly - PMG** | KIAA1279 | Goldenberg-Shprintzen Megacolon syndrome | | |
| **MYOPATHY** | | | | |
| **Microcephaly** | EPG5 | Vici syndrome | Microcephaly | AFG3L2, COL4A1, COL4A2, FKTN, IBA57, INPP5K, KARS, MCT8, MTATP6, PGM1, POMT1, POMT2, SCYL2, SLC35A3, TOR1AIP1 |
| **Microcephaly** | EXOSC3 | Pontocerebellar hypoplasia type 1B (PCH1B) | Megalencephaly | CACNA1E, MTM1 |
| **Microcephaly** | MORC2 | Developmental delay, impaired growth, dysmorphic facies, axonal neuropathy (DIGFAN), hyporeflexia | SBH | DCX |
| **Microcephaly** | MYO18B | Klippel-Feil anomaly with associated myopathy | PMG | A3243G, BICD2, MICU1, PI4KA |

| | | | | |
|---|---|---|---|---|
| **Microcephaly** | PRUNE1 | Neurodevelopmental disorder with microcephaly, hypotonia and variable brain anomalies (NMIHBA) | Schizencephaly | COL4A1 |
| | | | FCD | COL4A1, DEPDC5, KMT2A, NPRL2, SMPD4 |
| **MUSCULAR DYSTROPHY** | | | | |
| **Microcephaly – cobblestone - PMG** | POMT1, POMT2 | Dystroglycanopathy: Walker-Warburg syndrome | Microcephaly | CHKB, DPM1, DPM2, GOLGA2, INPP5K |
| **Microcephaly - cobblestone - PMG** | FKTN, FKRP | Dystroglycanopathy: limb gridle muscular dystrophy, Fukuyama congenital muscular dystrophy or Walker-Warburg syndrome | PVNH | FKRP |
| **Microcephaly - cobblestone - PMG** | POMGNT1 | Dystroglycanopathy: muscle-eye-brain disease | PMG | FKRP, LARGE, POMGNT1, TMEM5 |
| **PMG** | LAMA2 | Congenital muscular dystrophy type 1A | Cobblestone | B3GALNT2, CRPPA, ISPD, LAMA2, LARGE, POMT1 |
| **SPASTIC PARAPLEGIA** | | | | |
| **Microcephaly** | AP4B1, AP4E1, AP4M1, AP4S1 | AP-4 deficiency syndrome | Microcephaly | ACO2, ARL6IP1, GOLGA2 |
| **Microcephaly** | GPT2 | Intellectual and developmental disability (IDD), postnatal microcephaly. | PMG | AP4E1, AP4S1, COL4A1, COL4A2 |
| **Microcephaly** | KIF1A | Speech delay, mild intellectual disability, a slowly progressive pyramidal syndrome, bilateral optic subatrophy, sensory axonal polyneuropathy, cerebellar atrophy | Schizencephaly | COL4A1 |