

Classification of Pontocerebellar Hypoplasia: Where does it End?

**EDITOR'S
PICK**

Our Editor's Pick for this year's edition of *EMJ Neurology* is the review paper by Appelhof et al. Providing a detailed explanation of the differences between the 12 types of pontocerebellar hypoplasia, this article is essential if improvements in the diagnosis and knowledge of the disease are to be made. The ability to distinguish which disease type the patient is afflicted by and the cause behind it will allow appropriate, type-specific treatments to be developed. Pontocerebellar hypoplasia is a prime example of the positive influence next-generation sequencing is having on such rare, complex diseases.

We hope you enjoy reading this review as much as we did.

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Abstract

Pontocerebellar hypoplasia (PCH) represents a heterogeneous group of congenital neurodegenerative diseases. Patients are afflicted by severe motor and mental impairments and most patients die at a young age. The hallmark of PCH is hypoplasia of the cerebellum and the pons, often in combination with supratentorial involvement. PCH is caused by autosomal recessive mutations in genes, most of which play a role in RNA metabolism. Twelve types (PCH1-12) are described, mainly based on clinical features. Identification of the responsible genes showed that the clinical classification did not match with the genetic classification leading to definition of subtypes. The authors expect that the increasing use of next-generation sequencing will lead to the identification of even more new PCH genes, widening the genetic and phenotypical spectrum. This will expand the classification and make it more complex. Therefore, the authors suggest that a new adjusted classification should be formulated to save the functionality of the PCH group.

INTRODUCTION

Pontocerebellar hypoplasia (PCH) describes a heterogeneous group of rare neurodegenerative diseases. PCH is characterised by hypoplasia of the cerebellum and pons with variable atrophy of supratentorial structures. The first in-depth neuropathological report of a PCH case was published in 1928.¹ PCH was first described as a distinct disease group in 1993 by Barth with the classification of PCH1 and PCH2.² The PCH spectrum was broadened to six PCH types over the following years based on phenotypes. *RARS2*

was the first gene to be associated with PCH and was reported in 2007.³ In the following years, the gene defects for the other five subtypes were reported.^{4,5} It also became clear that mutations in different genes could give a similar clinical PCH phenotype. The number of PCH (sub)types increased rapidly due to the introduction of next-generation sequencing, with a (sub)type classification for each new PCH related gene. Currently, the PCH spectrum describes twelve clinical PCH types with eleven genetic subtypes (MIM PS607596) (Table 1).⁵⁻²⁷ All forms show an autosomal recessive inheritance pattern.

Table 1: Categorisation of the PCH group.

Subtype	MIM number	Gene	Distinctive features	Ref.
PCH1A	#607596	<i>VRK1*</i>	SMA-like, mild motor impairments, normal/very mildly affected cognition, variable microcephaly.	5
PCH1B	#614678	<i>EXOSC3</i>	SMA-like, combined cerebral and spinal motor involvement, microcephaly.	6,7
PCH1C	#616081	<i>EXOSC8</i>	Identical to PCH1B.	8
PCH1D	#618065	<i>EXOSC9</i>	Identical to PCH1B.	9
PCH1E		<i>SL-C25A46*</i>	SMA-like, combined cerebral and spinal motor involvement, optic atrophy.	10,11
PCH2A	#277470	<i>TSEN54</i>	Neonatal onset, clonus, dystonia/chorea, spasticity, swallowing disorder, progressive microcephaly, 'dragonfly' pattern on MRI.	4,12
PCH2B	#612389	<i>TSEN2</i>	Identical to PCH2A.	4,12
PCH2C	#612390	<i>TSEN34</i>	Identical to PCH2A.	4,12
PCH2F	#617026	<i>TSEN15</i>	Milder than PCH2A.	13
PCH2D	#613811	<i>SEPSECS</i>	Cerebral atrophy, spasticity, ataxia, variable pons atrophy.	14,15
PCH2E	#615851	<i>VPS53</i>	Cerebral atrophy, spasticity.	16
PCH4 (PCH5)	#225753 and #610204	<i>TSEN54</i>	Severe form of PCH2A, polyhydramnios, primary hypoventilation, severe generalised clonus neonatal death.	4,12
PCH3	#608027	<i>PCLO</i>	Optic atrophy, dysmorphic facial features.	17
PCH6	#611523	<i>RARS2*</i>	Variable hyperlactataemia, seizures, hypotonia, respiratory chain dysfunction.	3,18
PCH7	#614969	<i>TOE1</i>	DSD, enlarged ventricles, thin corpus callosum, diminished white matter.	19
PCH8	#614961	<i>CHMP1A</i>	Non-progressive, non-degenerative, thin corpus callosum.	20
PCH9	#615809	<i>AMPD2*</i>	Abnormal muscle tone, dysmorphic facial features, 'figure 8' shape of upper brainstem.	21,22
PCH10	#615803	<i>CLP1</i>	Abnormal muscle tone, seizures, mild cerebellar atrophy, motor neuron degeneration.	23,24
PCH11	#617695	<i>TBC1D23</i>	Non-progressive, non-degenerative, dysmorphic facial features.	25,26
PCH12	#618266	<i>COASY*</i>	Severe prenatal symptoms, micrognathia, arthrogryposis.	27

DSD: disorders of sexual development; PCH: pontocerebellar hypoplasia; SMA: spinal muscular atrophy.
*PCH (sub)types in which mutations in the involved gene also can result in another disease.

There is much clinical variability between different types but in general PCH presents as a severe disease with a prenatal onset or an onset of symptoms in the first months of life. Frequently, early symptoms are difficulties swallowing, apnoea, and respiratory difficulties indicating brainstem dysfunction. Prominent other symptoms are severe intellectual disability, epilepsy, and central motor impairment.^{4,12,28} Most PCH subtypes follow a progressive disease course and most patients die at a young age.^{12,29}

Both hypoplasia and atrophy contribute to the reduction of cerebellar volume in PCH. Hypoplasia usually refers to a static state, while atrophy implies a progressive condition. However, it is often difficult to differentiate between the two mechanisms, as follow-up MRI scans are required to determine progression of cerebellar volume loss. PCH patients typically show severe hypoplasia of the cerebellar hemispheres with relative sparing of the vermis resulting in a typical 'dragonfly' pattern on the coronal MRI, as seen in PCH2A patients (Figure 1e and Figure 1h). Another pattern is the 'butterfly'; this reflects a milder form with less atrophy of the hemispheres (Figure 1b).¹² Furthermore, patients display (progressive) supratentorial atrophy which underlies the microcephaly. In contrast to the gross infratentorial abnormalities, typical cerebellar symptoms are absent. This can be explained by the supratentorial involvement which hampers intentional motor skills. Below, this review will discuss the most common disease pathways in PCH, followed by a detailed description of the twelve types of PCH.

MECHANISM OF PONTOCEREBELLAR HYPOPLASIA

Although the pathology of different PCH subtypes is similar, there is no common pathomechanism for all of the PCH types; however, many genes are linked to different aspects of RNA metabolism (Table 1). This review will only focus on the most common pathway: RNA processing. *EXOSC3*, 8, and 9 (PCH1B-C) encode for components of the exosome complex; this complex is responsible for degrading different types of RNA, such as messenger RNA (mRNA) and transfer RNA (tRNA).^{6,8,9} *TOE1* (PCH7) modifies specific RNA types called small nuclear RNA.¹⁹ The four components of the tRNA splicing endonuclease

(TSEN) complex (PCH2A-C,F) together with CLP1 (PCH10) are involved in intron removal from tRNA.^{4,13,23} Mutations in these genes possibly trigger stress pathways caused by accumulation of aberrant RNA fragments in the cells. Activation of stress pathways can suppress protein synthesis leading to neurodegeneration.

Another possible mechanism is shortage of properly processed tRNA, which are responsible for connecting the correct amino acid to the corresponding trinucleotide code on the mRNA in the ribosomes during translation.²³ There are 417 human tRNA genes while there are only 20 different amino acids. Despite the vast redundancy in tRNA genes, the lack of one specific tRNA gene can already cause progressive cerebellar atrophy in mice.³⁰ Almost 7% of the tRNA genes contains an intron;³¹ thus, it is conceivable that tissue-specific expression of intron containing tRNA metabolism genes can result in dependence of the cerebellum on the tRNA splicing machinery. Other tRNA-related PCH genes, such as *RARS2* (PCH6) and *SEPSECS* (PCH2D), are responsible for the production of tRNA coupled to their corresponding amino acids.^{3,14} However, it remains unclear why these aberrations in tRNA metabolism cause a brain specific defect.

The remaining PCH-related genes are thus far not functionally groupable and vary widely in mechanistic functioning.

PONTOCEREBELLAR HYPOPLASIA 1

PCH1 is hallmarked by anterior horn cell degeneration (as seen in spinal muscular atrophy) in addition to PCH. The severity of the disease course of PCH1 in patients is varied. PCH1 is often neonatal lethal because of respiratory insufficiency and severe hypotonia. Congenital contractures and polyhydramnios can also be present at the severe end of the PCH1 spectrum. In milder cases however, the pons is spared, and patients survive into adolescence. So far, five subtypes have been described (PCH1A-E).⁶ PCH1B (MIM #614678), caused by *EXOSC3* mutations, is the most prevalent subtype of PCH1.³² A PCH1B patients' disease course can be mild or severe, depending on the genotype.⁷ A homozygous p.(Asp132Ala) change in *EXOSC3* is associated with sparing of the pons and a mild disease course (Figure 1a-b): patients display some

cognitive development and limited speech. Other *EXOSC3* mutations are associated with a more severe disease course, which is characterised by arthrogryposis and respiratory insufficiency which is often lethal before the first year of life (Figure 1c-d).⁶ *EXOSC8* and its paralogue *EXOSC9*, also components of the exosome complex, underlie PCH1C (MIM #616081) and PCH1D (MIM #618065), respectively. The phenotypes of patients with *EXOSC8* or *EXOSC9* mutations are similar to those of *EXOSC3* patients.^{8,9}in 2016,

Wan et al.³³ reported mutations in *SLC25A46* in patients with PCH1E. Later, the authors of this

present review showed that the PCH1 patients, described by Barth (1993), were compound heterozygous for mutations in *SLC25A46*.^{2,10} The clinical spectrum of patients with *SLC25A46* mutations is very broad, ranging from death within the first postnatal month, to survival into adulthood and with patients becoming symptomatic later in life, presenting with mild cerebellar atrophy and axonal peripheral neuropathy.^{10,11,33} Notably, all patients have optic atrophy in this subtype.³⁴ Mitochondrial disorganisation and enlargement was detected in cells of PCH1E patients, which is in line with the function of *SLC25A46* in mitochondrial fission.¹⁰

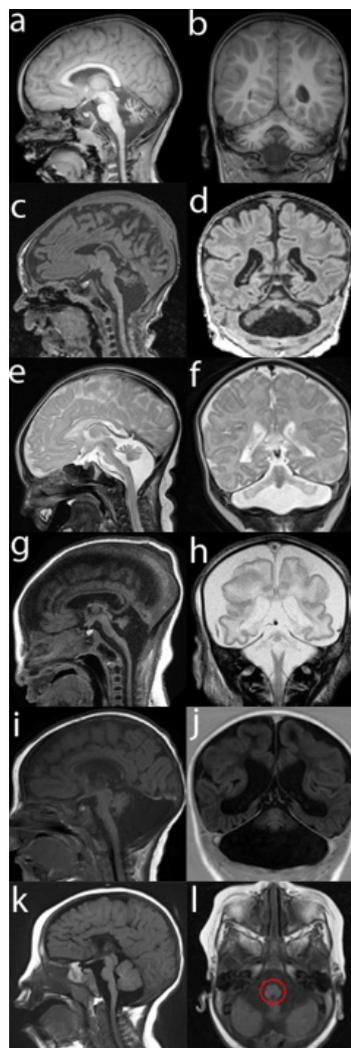


Figure 1: MRI images of PCH patients in sagittal (a, c, e, g, i, k), coronal (b, d, f, h, j), and axial (l) cross sections. MRI 'a' and 'b' display a PCH1B patient with the mild phenotype correlating with the p.(Asp132Ala) change in the *EXOSC3* gene. Other mutations in *EXOSC3* are associated with more severe atrophy of pons and cerebellum ('c', 'd'). PCH2A ('e-f') and PCH4 ('f-h'), both caused by *TSEN54* mutations, display the classical 'dragonfly' pattern seen on the coronal MRI ('f', 'h'); however, in PCH4 more cerebral involvement is seen. *TOE1* mutations cause PCH7 with severely dilated ventricles ('i', 'j'). *AMPD2* mutations cause PCH9 ('k', 'l'), which show a typical 'figure 8' pattern of the midbrain on the axial MRI ('l', red circle).

Lastly, PCH1A (MIM #607596) is caused by mutations in the *VRK1* gene and is sometimes called spinal muscular atrophy with PCH. It is a rare and atypical subtype often reported in patients with an Ashkenazi Jewish origin. Patients seem to present no mental impairments but do display a delayed motor development or only slow, progressive loss of motor functions later in life.³⁵

PONTOCEREBELLAR HYPOPLASIA 2

Of the six PCH2 subtypes (PCH2A-F) that are currently described, PCH2A (MIM #277470) is the most common. Typically, neonates show jitteriness, clonus, poor sucking, and impaired swallowing. Later extrapyramidal movement disorders such as dystonia and chorea, spasticity, and the lack of intentional motor skills become apparent.³⁶ Patients often are afflicted by generalised seizures, sleeping disorders, and chorea which often necessitates institutional care. Respiratory insufficiency and infections are a common cause of death which is generally at an early age, however some patients reach adulthood.²⁹ The neuroradiological hallmark for PCH2A is the 'dragonfly' pattern on MRI of the hypoplastic cerebellum (Figure 1e-f). In patients with a follow-up brain MRI, progressive cerebral atrophy is seen, with apparent ventricular enlargements accentuated by disproportionate affection of the caudate nuclear heads.¹² Neuropathological findings in PCH2A showed stunted folial growth, especially affecting the cerebellar hemispheres, and peculiar fragmentation of the dentate nuclei.³⁷ A breakthrough was achieved in 2008 with the discovery that mutations in the *TSEN54* gene underlie PCH2A. The mutation, p.(Ala307Ser), was initially found in a Dutch genetic isolate and is the most common cause of PCH2.⁴ Patients with the same mutation p.(Ala307Ser) are also found on other continents suggesting that it is a very old mutation. *TSEN54* forms the TSEN complex with three other components: *TSEN34*, *TSEN2*, and *TSEN15*. Mutations in *TSEN2*, *TSEN34*, and *TSEN15* are very rare and result in PCH2B (MIM #612389), PCH2C (MIM #612390), and PCH2F (MIM #617026), respectively.^{4,12,13} One patient with a *TSEN34* mutation and four patients with *TSEN2* mutations have been reported.^{12,38} *TSEN15* mutations are described in three PCH2F patients and have a milder phenotype with no visual

impairments.¹³ The two other PCH2 subtypes are not caused by aberration in the TSEN complex, namely PCH2D (MIM #613811) and PCH2E (MIM #615851). Both were previously described in literature as progressive cerebrotocerebellar atrophies. PCH2D is caused by mutations in the O-phosphoserine tRNA-selenocysteine tRNA synthetase (*SEPSECS*) gene. Reported features of PCH2D are spasticity, optic atrophy, ataxia, and seizures. The MRI shows progressive cerebellocerebral atrophy with variable involvement of the pons.¹⁴ PCH2D disease course is usually severe; however, a mild PCH2D phenotype has been recently reported.¹⁵ PCH2E, caused by *VPS53* mutations, has been reported in twelve Jewish families of Moroccan origin.^{16,39} All cases carried the same mutation, p.(Gln95Arg), suggesting a founder effect. Most patients appear healthy at birth but quickly develop hypotonia and delayed head growth. Subsequently, patients develop tonic-clonic -seizures, progressive spasticity, and progressive cerebrotocerebellar atrophies on brain MRI.¹⁶

PONTOCEREBELLAR HYPOPLASIA 3

Only one family, from Oman, with PCH3 (MIM #608027) has been reported. All four affected children have a homozygous nonsense mutation in the *PCLO* gene.¹⁷ Generalised hypotonia with hyperreflexia, progressive microcephaly, and seizures developed during their first year of life. The patients reported thus far all survived into puberty. MRI shows an atypical pattern with diffuse atrophy of the cerebellum and pons; however, not as drastic as a 'dragonfly' pattern. Supratentorial cerebral reduction of white matter with a thin corpus callosum was reported. *PCLO* is thought to play a role in regulation of proteins in neuronal synapses.¹⁷

PONTOCEREBELLAR HYPOPLASIA 4 AND 5

PCH4 (MIM #225753) describes a severe form of PCH2. Notably, patients present prenatal symptoms such as intrauterine seizures and polyhydramnios resultant of impaired fetal swallowing.^{40,41} Neonates show massive unprovoked myoclonus, hypertonia, hypoventilation, and sometimes seizures.¹² Patients usually require continuous mechanical ventilation and generally

die within the first month of life. Brain MRI shows subtotal destruction of cerebellar hemispheres, which are underdeveloped and atrophied with often mild-to-severe vermal folia atrophy (Figure 1g-h). In addition, cerebral atrophy is more apparent than in PCH2 (Figure 1g-h). Craniocerebral disproportion with a vastly increased subarachnoid space may be seen as the result of progressive loss of cerebral tissue with a prenatal onset (Figure 1h). Post-mortem examination revealed only remnants of the dentate nuclei and the inferior olive nucleus had a horseshoe shape, therefore PCH4 was originally named 'olivo-ponto-cerebellar-hypoplasia'.³⁷ Similar to that seen in PCH2A, *TSEN54* mutations also underlie PCH4 (MIM #225753). PCH4 patients are often compound heterozygous for the common p.(Ala307Ser) mutation in combination with a loss of function mutation. Although patients with homozygous null-alleles of *TSEN54* have not been described, the authors assume that this is incompatible with life. PCH5 (MIM #610204) was initially described as a distinct subtype based on the presence of intrauterine seizure-like activity in one family.⁴¹ In retrospect, PCH2A, PCH4, and PCH5 represent mutations of the same gene where increasingly severe symptoms commensurate with the severity of mutation.⁴²

PONTOCEREBELLAR HYPOPLASIA 6

Mutations in the autosomal gene encoding the mitochondrial argenyl tRNA synthetase (*RARS2*) cause PCH6 (MIM #611523). Characteristics of PCH6 include severe early onset seizures, CSF hyperlactataemia, mitochondrial respiratory chain defects, and later severe developmental delay with rapidly progressive microcephaly.³ Neuroradiologic imaging reveals a global progressive atrophy of the brain with variable hypoplasia/atrophy of the cerebellum.^{18,43} The basal ganglia were spared in some patients with severe cerebral atrophy. Neuropathological reports of two cases reveal an intact olive nucleus and relatively spared dentate nucleus.⁴³

PONTOCEREBELLAR HYPOPLASIA 7

PCH7 (MIM #614969) is characterised by disorders of sexual development in addition to PCH.^{19,44} Clinical symptoms are truncal hypotonia with hypertonic extremities, seizures, and increased

tendon reflexes. Most described patients present with female external genitalia. Ten XY-patients are reported with a small or absent penis and undescended or absent testis. An ultrasound revealed ovaries in two of these patients. In one of the three XX-female patients, no ovaries could be found using ultrasound. Female external genitalia were normal; although one patient showed a prominent clitoris. A brain MRI revealed severely reduced cerebellar and pontine volumes with enlarged ventricles, diminished white matter, and a thin corpus callosum in some patients (Figure 1i-j). Patients carried homozygous or compound heterozygous mutations in the autosomal *TOE1* gene. The function of *TOE1* remains elusive, although current evidence points to a role in snRNA metabolism in the nucleolus.¹⁹

PONTOCEREBELLAR HYPOPLASIA 8

CHMP1A mutations are rare and underlie PCH8 (MIM #614961).²⁰ Only three families and two different pathogenic mutations have been reported. In contrast to the other types of PCH, the disease course of PCH8 appears to be non-progressive. Patients have microcephaly, dystonia, and/or choreiform movements, and sometimes suffer from joint contractures and seizures. Developmental delay is severe, but some patients learn to walk and develop limited speech. Brain MRI shows PCH with reduced cerebral white matter volume and a thin corpus callosum. In patients with follow-up brain MRI, no progression of the atrophy was visible. Mechanistically, it is thought that *CHMP1A* aberrations disrupt the BMI1-regulated proliferation of neuronal progenitor cells.²⁰

PONTOCEREBELLAR HYPOPLASIA 9

PCH9 (MIM #615809) describes a broad disease spectrum with 25 affected individuals reported to date. Clinically, patients have progressive microcephaly, impaired swallowing, brisk tendon reflexes, spasticity, teeth abnormalities, and some patients display dysmorphic facial features.^{21,22,45} While some patients survive into adulthood, most die early in life. In addition to the cerebellar hypoplasia, PCH9 patients displays a distinctive 'figure 8' shape of the midbrain on axial MRI (Figure 1l). Also, a hypoplastic or absent corpus

callosum has been reported. Mutations in the *AMDP2* gene are found in PCH9, but are also identified in one family with hereditary spastic paraplegia 63 (SPG63)⁴⁶ (MIM #615686). Aberrations in *AMDP2*, which regulates GTP levels, is thought to disrupt the initiation of protein translation.

PONTOCEREBELLAR HYPOPLASIA 10

PCH10 (MIM #615803) patients show dysmorphic facial features, cognitive impairment, seizures, and spasticity.^{23,24} Brain MRI showed only mild atrophy of the cerebellum and the pons. Supratentorially, atrophy of the cortex, and a thin hypoplastic corpus callosum are reported. Furthermore, signs of progressive spinal motor loss are seen on electromyography. All PCH10 patients originated from Turkey and carried the same homozygous mutation in the *CLP1* gene, suggesting a founder effect. The *CLP1* protein interacts with the TSEN complex and is involved in tRNA processing.^{23,24}

PONTOCEREBELLAR HYPOPLASIA 11

PCH11 (MIM #617695) is reported in seven families who all carry biallelic mutations in the *TBC1D23* gene. Individuals are relatively mildly affected compared to other PCH types, and so far, a non-progressive nature of PCH11 is noted.^{25,26} Patients present with dysmorphic facial features, microcephaly, hypotonia, and occasional ambulation. Brain MRI shows a reduced cerebellar volume and severe hypoplasia of the pons. The corpus callosum is hypoplastic in most cases. *TBC1D23* is involved in neuronal vesicular trafficking.²⁵

PONTOCEREBELLAR HYPOPLASIA 12

The latest branch of the PCH tree is PCH12 (MIM #618266). PCH12 is a lethal disorder at the severe end of the PCH-spectrum, presenting with severe prenatal onset microcephaly, PCH, and congenital contractures.²⁷ Atrophy of the cerebrum and hypoplasia of the pons, cerebellum, brainstem, spinal cord, and basal ganglia were confirmed on postnatal brain MRI in one of the patients. Genetic analyses identified splice site and frameshift mutations in the *COASY* gene in affected individuals. *COASY* is responsible for the

last two steps of coenzyme A (CoA) synthesis; the CoA synthesis pathway is highly conserved and essential for life. Earlier reports have also linked *COASY* mutations to neurodegeneration with brain iron accumulation 6 (MIM #615643) (NBIA6). Residual function of *COASY* appeared to be higher in NBIA6 patients than in the one tested PCH12 patient, which might explain the more severe phenotype in the latter.⁴⁷

DIFFERENTIAL DIAGNOSIS

Several other diseases should be considered when a patient presents with PCH. The three most common diseases that mimic PCH phenotypes are caused by *CASK* mutations, *PMM2* mutations, and extreme prematurity. Mutations or microdeletions in the *CASK* gene cause mental retardation and microcephaly with pontine and cerebellar hypoplasia (MIM #300749) highly similar to PCH. In addition, neocortical malformations, hearing loss, and facial dysmorphic features can be present.⁴⁸ Overall, development delay is severe, but some patients reach some motor milestones, such as walking. In contrast to all PCH types, *CASK* mutations follow a X-linked dominant inheritance pattern and mutation are generally *de novo*.⁴⁹ Moreover, patients with heredity disorders of glycosylation type 1a (*PMM2*-CDG) (MIM #212065) can mimic PCH. Neuroimaging of *PMM2*-CDG patients reveals cerebellar hypoplasia/atrophy.⁵⁰ Clinically, the phenotype of *PMM2*-CDG patients varies from mild intellectual disability and ataxia to a severe phenotype with antenatal onset multi-organ abnormalities and severe mental and motor impairments. Distinctive dysmorphic features include inverted nipples and abnormal fat distribution. *PMM2*-CDG can be diagnosed by detection of abnormal glycoproteins through isoelectric focussing of transferrin. Additionally, extreme prematurity (gestation age <32 weeks) can occasionally result in PCH.⁵¹ The rapid growth of the cerebellum during the third trimester might increase vulnerability to disruption by very early prematurity.

When lissencephaly is noticed on brain MRI in addition to PCH, mutations in *RELN* (MIM #257320), *VLDLR* (MIM #224050), or α -dystroglycan related dystrophies should be considered.^{52,53} Furthermore, patients at the severe end of the Hoyeraal-Hreidarsson syndrome (MIM #30500) spectrum and spinocerebellar ataxia 29 (SCA29) (MIM #17360) can resemble PCH.

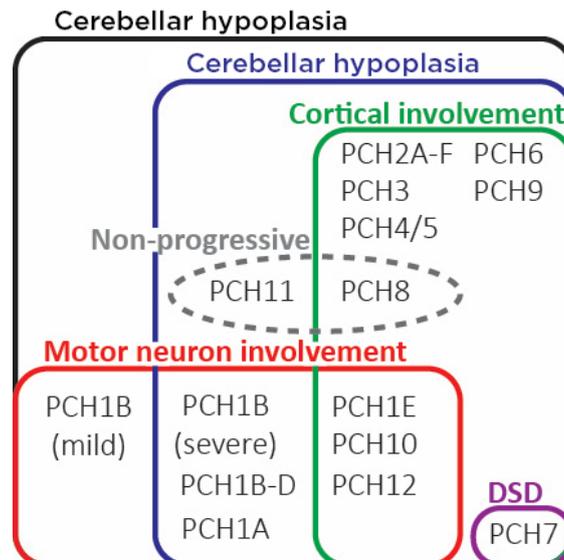


Figure 2: Depiction of pathological overlap between different PCH types.

In PCH2A-C, F, patient cortical involvement is not always present at birth but will always develop postnatally. DSD: disorders of sexual development; PCH: pontocerebellar hypoplasia.

Patients with Hoyeraal-Hreidarsson syndrome usually present with a combination of progressive bone marrow failure and cerebellar hypoplasia.⁵⁴ Furthermore, a patient with an *ITPR1* mutation, normally resulting in SCA29, showed classical PCH on brain MRI.⁵⁵

DIAGNOSIS OF PONTOCEREBELLAR HYPOPLASIA

The diagnoses of PCH is based on careful clinical examination and neuroimaging, followed by genetic testing. Genetic testing is required to confirm the diagnosis because differentiation between subtypes of PCH and other disorders is often not straightforward. Furthermore, for most PCH types the number of patients described is low (e.g., PCH3 or PCH8), and sometimes limited to a single mutation (e.g., PCH10), leading to an incomplete phenotypical characterisation.^{15,56} Therefore, the notion should be taken that PCH phenotypes can deviate from reported descriptions.

PERSPECTIVES

PCH is a clinical diagnosis in patients with atrophy and hypoplasia of the pons and cerebellum. Unlike the suggestion implied by the name PCH,

they represent a group of disorders that affect development of the structure and function of the whole brain. Progressive decline in structure and progressive microcephaly characterise the most common types. Identification of many different PCH genes and types resulted in a rapidly expanding classification. Initially described as a disease associated with defects in (t)RNA metabolism, the identification of *CHMP1A* and *VRK1* mutations challenged this hypothesis.^{5,20} The classification became more complex when cases with milder disease manifestations, such as PCH1B and PCH10, were included.^{7,23} This resulted in the current PCH classification as a collection of disorders that do not always share a common phenotype or affected pathway (Figure 2). Even the criteria of cerebellar and pontine atrophy are not always met; therefore, the authors propose that the classification should be revised, reserving the name PCH for the clinical description of patients with early onset atrophy of the cerebellum and often pons. The most obvious classification is based solely on clinical features, i.e., PCH with disorders of sexual development (PCH7), PCH with dystonia (PCH2), and PCH with spinal muscular atrophy (PCH1). Moreover, the disease course should be considered in the classification because it is important for counselling. The lack of knowledge about pathomechanisms in most forms currently

precludes a classification based on mechanism. The broad phenotypic spectrum within patients with mutations in the same PCH gene also precludes a purely genetic classification; therefore, the clinical symptoms and MRI should be leading in the diagnosis and the genetic diagnosis can be used for counselling and disease course prediction.

CONCLUSION

PCH remains a severe disease for which only symptomatic treatment is available. Preconception carrier screening in high-risk populations is successful and feasible for some subtypes.⁵⁷ It is likely that in the future more genes will be linked to PCH and new mutations in known PCH genes will broaden the phenotype further.

References

- Krauss F. [About a malformation of the cerebellum and some fiber anatomical relations of the organ]. *Neur U Psych.* 1929;119(1):788-815. (In German).
- Barth PG. Pontocerebellar hypoplasias: An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain Dev.* 1993;15(6):411-22.
- Edvardson et al. Deleterious mutation in the mitochondrial arginyl-transfer RNA synthetase gene is associated with pontocerebellar hypoplasia. *Am J Hum Genet.* 2007;81(4):857-62.
- Budde BS et al. tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia. *Nat Genet.* 2008;40(9):1113-8.
- Renbaum P et al. Spinal muscular atrophy with pontocerebellar hypoplasia is caused by a mutation in the *VRK1* gene. *Am J Hum Genet.* 2009;85(2):281-9.
- Rudnik-Schöneborn S et al. Pontocerebellar hypoplasia type 1: Clinical spectrum and relevance of *EXOSC3* mutations. *Neurology.* 2013;80(5):438-46.
- Eggens VR et al. *EXOSC3* mutations in pontocerebellar hypoplasia type 1: Novel mutations and genotype-phenotype correlations. *Orphanet J Rare Dis.* 2014;9:23.
- Boczonadi V et al. *EXOSC8* mutations alter mRNA metabolism and cause hypomyelination with spinal muscular atrophy and cerebellar hypoplasia. *Nat Commun.* 2014;5:4287.
- Burns DT et al. Variants in *EXOSC9* disrupt the RNA exosome and result in cerebellar atrophy with spinal motor neuronopathy. *Am J Hum Genet.* 2018;102(5):858-73.
- Van Dijk T et al. Pontocerebellar hypoplasia with spinal muscular atrophy (PCH1): Identification of *SLC25A46* mutations in the original dutch PCH1 family. *Brain.* 2017;140(8):e46.
- Abrams AJ et al. Mutations in *SLC25A46*, encoding a UGO1-like protein, cause an optic atrophy spectrum disorder. *Nat Genet.* 2015;47(8):926-32.
- Namavar Y et al. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. *Brain.* 2011;134(1):143-56.
- Breuss MW et al. Autosomal-recessive mutations in the tRNA splicing endonuclease subunit *TSEN15* cause pontocerebellar hypoplasia and progressive microcephaly. *Am J Hum Genet.* 2016;99(1):228-35.
- Agamy O et al. Mutations disrupting selenocysteine formation cause progressive cerebello-cerebral atrophy. *Am J Hum Genet.* 2010;87(4):538-44.
- Van Dijk T et al. A *SEPSECS* mutation in a 23-year-old woman with microcephaly and progressive cerebellar ataxia. *J Inher Metab Dis.* 2018;41(5):897-8.
- Feinstein M et al. *VPS53* mutations cause progressive cerebello-cerebral atrophy type 2 (PCCA2). *J Med Genet.* 2014;51(5):303-8.
- Ahmed MY et al. Loss of PCLO function underlies pontocerebellar hypoplasia type III. *Neurology.* 2015;84(17):1745-50.
- Nishri D et al. *RARS2* mutations cause early onset epileptic encephalopathy without ponto-cerebellar hypoplasia. *Eur J Paediatr Neurol.* 2016;20(3):412-7.
- Lardelli RM et al. Biallelic mutations in the 3' exonuclease *TOE1* cause pontocerebellar hypoplasia and uncover a role in snRNA processing. *Nat Genet.* 2017;49(3):457-64.
- Mochida GH et al. *CHMP1A* encodes an essential regulator of BMI1-INK4A in cerebellar development. *Nat Genet.* 2012;44(11):1260-4.
- Marsh APL et al. Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to *AMPD2* loss. *Neurol Genet.* 2015;1(2).
- Accogli A et al. Novel *AMPD2* mutation in pontocerebellar hypoplasia, dysmorphisms, and teeth abnormalities. *Neurol Genet.* 2017;3(5):e179.
- Schaffer AE et al. *CLP1* founder mutation links tRNA splicing and maturation to cerebellar development and neurodegeneration. *Cell.* 2014;157(3):651-63.
- Karaca E et al. Human *CLP1* mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function. *Cell.* 2014;157(3):636-50.
- Ivanova EL et al. Homozygous truncating variants in *TBC1D23* cause pontocerebellar hypoplasia and alter cortical development. *Am J Hum Genet.* 2017;101(3):428-40.
- Marin-Valencia I et al. Homozygous mutations in *TBC1D23* lead to a non-degenerative form of pontocerebellar hypoplasia. *Am J Hum Genet.* 2017;101(3):441-50.
- Van Dijk T et al. Biallelic loss of function variants in *COASY* cause prenatal onset pontocerebellar hypoplasia, microcephaly, and arthrogryposis. *Eur J Hum Genet.* 2018;26(12):1752-8.
- Namavar Y et al. Classification, diagnosis and potential mechanisms in pontocerebellar hypoplasia. *Orphanet J Rare Dis.* 2011;6:50.
- Sanchez-Albisua I. Natural course of pontocerebellar hypoplasia type 2A. *Orphanet J Rare Dis.* 2014;9:70.
- Ishimura R et al. RNA function. Ribosome stalling induced by mutation of a CNS-specific tRNA causes neurodegeneration. *Science.* 2014;345(6195):455-9.
- Chan PP, Lowe TM. GtRNAdb 2.0: An expanded database of transfer RNA genes identified in complete and draft genomes (2016). Available at: <http://gtRNAdb.ucsc.edu/citation.html>. Last accessed: 29 July 2019.
- Wan J et al. Mutations in the RNA exosome component gene *EXOSC3* cause pontocerebellar hypoplasia and spinal motor neuron degeneration. *Nat Genet.* 2012;44(6):704-8.
- Wan J et al. Loss of function of *SLC25A46* causes lethal congenital pontocerebellar hypoplasia. *Brain.*

- 2016;139(11):2877-90.
34. Sulaiman RA et al. A novel mutation in *SLC25A46* causes optic atrophy and progressive limb spasticity, with no cerebellar atrophy or axonal neuropathy. *Clin Genet*. 2017;92(2):230-1.
 35. Vinograd-Byk H et al. The spinal muscular atrophy with pontocerebellar hypoplasia gene *VRK1* regulates neuronal migration through an amyloid- β precursor protein-dependent mechanism. *J Neurosci*. 2015;35(3):936-42.
 36. Barth PG et al. The syndrome of autosomal recessive pontocerebellar hypoplasia, microcephaly, and extrapyramidal dyskinesia (pontocerebellar hypoplasia type 2): Compiled data from 10 pedigrees. *Neurology*. 1995;45(2):311-7.
 37. Barth PG et al. Pontocerebellar hypoplasia type 2: A neuropathological update. *Acta Neuropathol*. 2007;114(4):373-86.
 38. Bierhals T et al. Pontocerebellar hypoplasia type 2 and *TSEN2*: Review of the literature and two novel mutations. *Eur J Med Genet*. 2013;56(6):325-30.
 39. Hady-Cohen R et al. Progressive cerebello-cerebral atrophy and progressive encephalopathy with edema, hypersarrhythmia and optic atrophy may be allelic syndromes. *Eur J Paediatr Neurol*. 2018;22(6):1133-8.
 40. Albrecht S et al. Fatal infantile encephalopathy with olivopontocerebellar hypoplasia and micrencephaly. *Acta Neuropathologica*. 1993;85(4):394-9.
 41. Patel MS et al. Severe, fetal-onset form of olivopontocerebellar hypoplasia in three sibs: PCH type 5? *Am J Med Genet A*. 2006;140(6):594-603.
 42. Namavar Y et al. *TSEN54* mutations cause pontocerebellar hypoplasia type 5. *Eur J Hum Genet*. 2011;19(6):724-6.
 43. Lax NZ et al. Neuropathologic characterization of pontocerebellar hypoplasia type 6 associated with cardiomyopathy and hydrops fetalis and severe multisystem respiratory chain deficiency due to novel *RARS2* mutations. *J Neuropathol Exp Neurol*. 2015;74(7):688-703.
 44. Anderson C. Early pontocerebellar hypoplasia with vanishing testes: A new syndrome? *Am J Med Genet A*. 2011;155A(4):667-72.
 45. Akizu N et al. *AMPD2* regulates GTP synthesis and is mutated in a potentially treatable neurodegenerative brainstem disorder. *Cell*. 2013;154(3):505-17.
 46. Novarino G et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science*. 2014;343(6170):506-11.
 47. Dusi S et al. Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. *Am J Hum Genet*. 2014;94(1):11-22.
 48. Moog U et al. Phenotypic spectrum associated with *CASK* loss-of-function mutations. *Journal of Medical Genetics*. 2011;48(11):741-51.
 49. Burglen L et al. Spectrum of pontocerebellar hypoplasia in 13 girls and boys with *CASK* mutations: Confirmation of a recognizable phenotype and first description of a male mosaic patient. *Orphanet J Rare Dis*. 2012;7:18.
 50. Schiff M et al. Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation) and review of the literature. *J Med Genet*. 2017;54(12):843-51.
 51. Zafeiriou DI et al. Pontocerebellar hypoplasia in extreme prematurity: Clinical and neuroimaging findings. *Pediatr Neurol*. 2013;48(1):48-51.
 52. Valence S, Garel C, Barth M, Toutain A, Paris C, Amsellem D, et al. *RELN* and *VLDLR* mutations underlie two distinguishable clinico-radiological phenotypes. *Clin Genet*. 2016;90(6):545-9.
 53. Schorling DC et al. Congenital muscular dystrophies and myopathies: An overview and update. *neuropediatrics*. 2017;48(4):247-61.
 54. Dehmel M et al. Novel mutation in the *DKC1* gene: Neonatal hoyeraal-hreidarsson syndrome as a rare differential diagnosis in pontocerebellar hypoplasia, primary microcephaly, and progressive bone marrow failure. *Neuropediatrics*. 2016;47(3):182-6.
 55. Van Dijk T et al. A *de novo* missense mutation in the inositol 1,4,5-triphosphate receptor type 1 gene causing severe pontine and cerebellar hypoplasia: Expanding the phenotype of *ITPR1*-related spinocerebellar ataxia's. *Am J Med Genet A*. 2017;173(1):207-12.
 56. Li N et al. A novel mutation in *VRK1* associated with distal spinal muscular atrophy. *J Hum Genet*. 2019;64(3):215-9.
 57. Mathijssen IB et al. Targeted carrier screening for four recessive disorders: High detection rate within a founder population. *Eur J Med Genet*. 2015;58(3):123-8.