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Review

Clinical and genetic features of PEHO and PEHO-Like syndromes: A scoping review

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ABSTRACT

Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome is a genetic neurological condition characterized by extreme cerebellar atrophy. PEHO-Like syndrome is comparable to PEHO syndrome, with the exception that there is no typical neuro-radiologic or neuro-ophthalmic findings. PEHO spectrum disorders are highly clinically and genetically heterogeneous, and this has challenged their diagnosis. This scoping review aims to summarize and discuss common clinical and genetic features of these syndromes to help future researches. This study was performed according to a six-stage methodology structure and PRISMA guideline. A systematic search of seven databases was performed to find eligible publications prior to June 2020. Articles screening and data extraction were independently performed by two reviewers and quantitative and qualitative analyses were conducted. Thirty-eight articles were identified that fulfill the inclusion criteria. Cerebellar atrophy was the main clinical difference between the two groups but data on optic atrophy and infantile spasms/hypsarrhythmia were not consistent with the previously essential diagnostic criteria. Genetic analysis was performed in several studies, leading to identification of pathogenic variants in different genes that caused these conditions due to different mechanisms.

Genetic studies could revolutionize the diagnosis process and our understanding of the etiology of this challenging group of patients by providing targeted sequencing panels and exome- or genome-scale studies in the future.

1. Introduction

PEHO syndrome is a rare neurodegenerative disorder first described by Salonen et al. [1] based on clinical features, neuropathological results, and dysmorphic characteristics of affected cases including progressive encephalopathy, severe hypotonia, seizures with hypsarrhythmia, profound intellectual disability, edema, hyperreflexia, and optic atrophy. Based on the diagnostic criteria refined by Somer (1993) [2], the necessary criteria for this disorder include: 1) Seizure onset at 2–52 weeks of life 2) Infantile spasms/hypsarrhythmia; 3) Early arrest of mental development; 4) Profound hypotonia with no head support or ability to sit unsupported; 5) Poor/absent visual fixation from the first months of life.

Additional supportive criteria include 1) Subcutaneous peripheral and facial edema; 2) Microcephaly developing by 12 months of age; 3) Dysmorphic features (epicanthic folds, midfacial hypoplasia, protruding ear lobes, receding chin, tapering fingers); 4) Pale optic discs.

Prenatal testing is not available for this syndrome, since the earlier diagnosis is crucial for genetic counseling (Orphanet 2836). Treatment solutions are symptomatic only, aimed at relieving symptoms by using antiepileptic medications or adrenocorticotropic hormone (ACTH) treatment and the prognosis is poor [2]. Efforts have also been made to improve quality of life of affected persons by using sleep systems, which are a part of a posture management approach for children with restricted

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movement [3]. The incidence has been estimated to be 1:78,000 in Finland [2], although some patients have been identified from other regions. For instance, the first identified cases out of Finland, have been reported in Japan. These cases had generalized hypotonia, infantile spasms, hypsarrhythmia, abnormal eye movement and visual failure and psychomotor arrest [4]. Somer [2] also described a substantial number of cases who are facially indistinguishable from the true PEHO patients, but typical neuroradiological and ophthalmological findings are not seen in those affected cases [5,6]. This presentation is called PEHO-like syndrome. Some features of these syndromes have overlap with other disorders such as Aicardi syndrome (Orphanet 2836), Joubert syndrome, Norman syndrome, olivopontocerebellar atrophy with spinal muscular atrophy, mevalonic aciduria, infantile Batten disease, carbohydrate-deficient glycoprotein (CGD) syndrome [7], and West syndrome [8]. It is worth mentioning that epilepsy in PEHO and PEHO-like syndrome mostly initiates with infantile spasms. Once infantile spasms are ameliorated, other types of seizures including myoclonic, tonic, clonic and absence seizures are initiated. Notably, these types of seizures do not respond to antiepileptic drugs [9]. In addition to mentioned clinical features, some unusual features including precocious puberty [10] and dyschromatosis [7] have been reported that may help clarify the etiology of these disorders.

The clinical diagnosis of PEHO cases and the clinical heterogeneity in PEHO-Like patients have been challenging and controversial issues [11–14]. Thus, molecular genetic or biochemical diagnostic tests are needed to resolve this problem. A few studies have reported that the PEHO patients have lower levels of IGF-1 than controls and the PEHO-Like patients. Moreover, both PEHO and PEHO-Like cases show increased nitric oxide metabolites, nitrite, and nitrate compared with the controls [9,15]. Nevertheless, these metabolic abnormalities indicate neurodegeneration and therefore are not particular biochemical markers of these disorders. These syndromes have genetically remained unknown until recently. The inheritance patterns are autosomal recessive or dominant (Orphanet 2836). Cytogenetic analysis has shown abnormality in just three cases, including deletion of 2q14.1–q14.2 [16], Xq duplication [17], and inverted duplication of proximal chromosome 15 or isodicentric 15 chromosome [18]. Therefore, the rarity of such abnormalities may indicate merely a coincidence. Recent molecular genetic studies imply heterogeneity in these disorders, a common phenomenon in progressive encephalopathies due to pathogenic variants in various genes which emphasizes the need for more genetic studies for diagnostic purposes [19].

We conduct a scoping review to collect all reported cases with PEHO and PEHO-Like syndromes to summarize and discuss common clinical characteristics and genetic features in these disorders. This paper includes the data obtained from cases with clinical diagnosis of PEHO and PEHO-Like syndromes, even if they do not have the original biallelic *ZNHIT3* gene variants as described in Finnish PEHO cases.

2. Methods

The strategy for this review was according to the scoping review structure recommended by Arksey and O'Malley [20] and later improved by Levac et al. [21]. This includes five distinctive stages: (1) Identifying the research question, (2) Identifying relevant studies, (3) study selection, (4) Charting the data, and (5) collating, summarizing, and reporting results. A sixth optional stage in the scoping review, consultation, was not included in our review. This study was also well guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist [22].

2.1. Identifying the research question

This study aimed to map the existing literature to summarize and discuss reported cases with PEHO and PEHO-Like syndromes. To address these aims, we sought to respond to the subsequent question: What exactly is known from the current literature about the clinical and genetic features of patients with PEHO or PEHO-Like syndromes?

2.2. Identifying relevant studies

To identify all potentially eligible publications, we searched PubMed, Embase, Scopus, Web of Science, Cochrane, ProQuest, and Google Scholar according to specific search tips of each database without any restriction, using the keyword 'PEHO'. Medical Subject Heading (MeSH) term was utilized if available. The last search was performed on 15 June 2020. We also added articles recognized from hand-searching or in the reference lists of the chosen studies. The references were managed using EndNote X9.1.

2.3. Selecting studies

Publications of all types were included if they reported clinical or genetic characteristics of patients diagnosed as PEHO or PEHO-Like syndromes. Non-English language articles with English abstracts were also included. Publication titles and abstracts were first independently screened by two investigators (HS, NKA) for eligibility depending on the above criteria. The full text of the remaining articles were assessed and studies going to fulfill the eligibility criteria were included in the final data analysis. Any discrepancies were solved by agreement with incorporating a third reviewer if required.

2.4. Charting the data

Two investigators (HS, NKA) independently extracted data into a predesigned charting form in Microsoft Excel. It provided details about Authors and publication year, the number of patients, sex, origin, consanguinity, age of onset, age of death and number of deceased, neuroimaging performed, cerebellar atrophy with or without brainstem atrophy, optic atrophy, hypotonia, seizure, infantile spasms or hypsarrhythmia, profound intellectual disability, dysmorphic features, edema, diagnosis, gene, zygosity, pathogenic variant type, pathogenic variant, and protein change.

2.5. Collating, summarizing and reporting the results

Articles fell into clinical features and genetic features categories. We performed quantitative and qualitative analysis. For the quantitative part, we provided a descriptive numerical summary of the characteristics of the included studies. For the qualitative analysis, we presented a narrative review of the existing info addressing our previously mentioned research question with a focus on the significance of findings in the broader context as suggested by Levac et al. [21].

2.6. Bioinformatics analysis

Network analysis were performed by the use of the GeneMANIA Cytoscape plugin [23] using Cytoscape v3.8.0 software [24] to predict functional gene-gene interactions.

Pathway enrichment analysis was conducted according to a protocol recommended by Reimand et al. [25]. Gene list underwent pathway enrichment analysis with parameters FDR Q value < 0.05, using g:Profiler web server [26], to recognize pathways which are enriched in the gene list. The results were visualized and interpreted in Cytoscape v3.8.0 software [24] by the use of EnrichmentMap [27], AutoAnnotate [28], WordCloud [29] and clusterMaker2 [30] plugins.

3. Results

The different steps of finding eligible studies are shown in the flow chart in Fig. 1. A total of 233 articles were found from various sources of

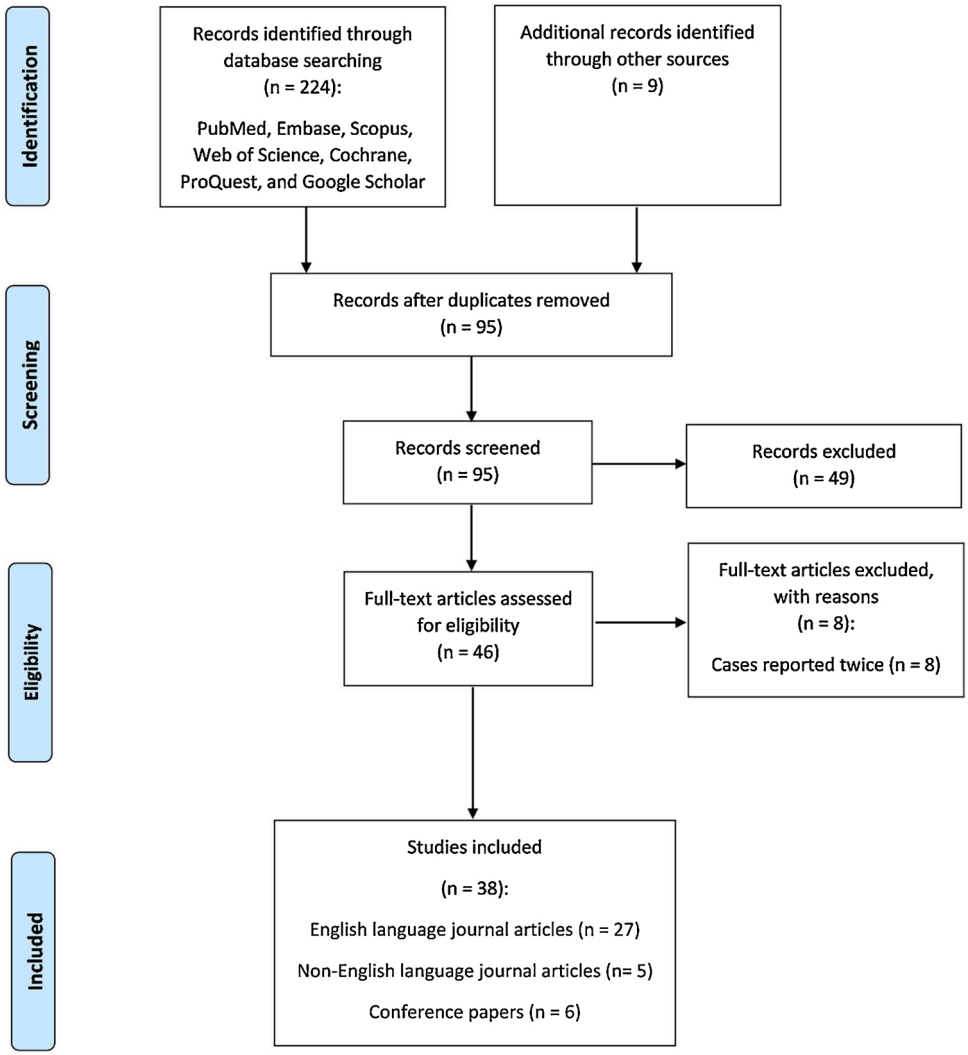

Fig. 1. Search strategy flow chart based on the PRISMA flow diagram.

which 138 were duplicates. Forty-nine articles were excluded according to title or abstract. The full text of the remaining 46 articles were assessed and eight more articles were also excluded because cases were reported twice [5,6,31–36]. Lastly, a total of 38 eligible articles remained, 27 articles were English language journal articles [1,2,4,7,10–14,16,37–53], five articles were non-English language journal articles [54–58], and six articles were conference papers [1,17,18,59–62].

The identified studies were published between 1991 and 2020. One hundred and two patients including 57 PEHO and 46 PEHO-Like cases were reported in 35 publications. Their clinical features are summarized in Table 1. Some features were not reported, and some data were not available in all patients. Clinical information from Antonnen et al. [63] and Antonnen et al. [49] not included because of some cases that overlap with cases reported by other studies described without specific identification, but genetic information of these two articles were included.

Age of onset was from birth to 10 months for PEHO and from birth to 16 months for PEHO-Like and both sexes were involved in both groups. Twenty-four patients were reported to die at the time of publication in a range of age between 18 months and 13 years old for PEHO and between 10 weeks and eight years for PEHO-Like.

Reported cases were from different regions and ethnic groups, including Finland, Japan, Canada (French-Canadian, Filipino/Caucasian, Caucasian/First Nation, Korean), United Kingdom (British, Scottish, Pakistani, Arabic, Sudanese), Hungary, Czech Republic, Turkey, Australia, Netherlands (Dutch), France, Spain, Switzerland, Italy, Poland, South Korea, Germany, Argentina (Spanish and Italian), United States, Saudi Arabia, and Estonia (Fig. 2).

We compared key clinical features of PEHO cases with PEHO-Like cases that are documented in Table 1 (Fig. 3). Cerebellar atrophy with or without brain atrophy was reported in all cases of PEHO except two (95.8 %) that showed brainstem or cerebral atrophy without cerebellar atrophy and 26.2 % of PEHO-Like cases. Optic atrophy was seen in 86 % of PEHO cases and 52.2 % of PEHO-Like cases. All of PEHO and 84.8 % of PEHO-Like patients had hypotonia. The seizure was seen in all of PEHO and 73.9 % of PEHO-Like individuals. Infantile spasms or hypsarrhythmia were found in 91.5 % of PEHO and 83.9 % of PEHO-Like cases. Profound intellectual disability was reported in all of both PEHO and PEHO-like patients. Dysmorphic features were seen in all but one case of PEHO (97.9 %) and all PEHO-Like cases. Furthermore, edema was reported in 84.8 % of PEHO and 86.7 % of PEHO-Like patients.

Thirteen patients came from consanguineous families (four PEHO and nine PEHO-Like). In ten articles, cases were genetically analyzed [46–53,62–64]. The genetic features of reported cases are shown in Table 2. Six heterozygous missense, four homozygous missense, one homozygous biallelic missense, one heterozygous nonsense, one homozygous nonsense, one homozygous frameshift, one duplication, one compound heterozygous biallelic missense, one compound heterozygous no-stop/missense, and one compound heterozygous missense/nonsense pathogenic variants were reported in fifteen genes,

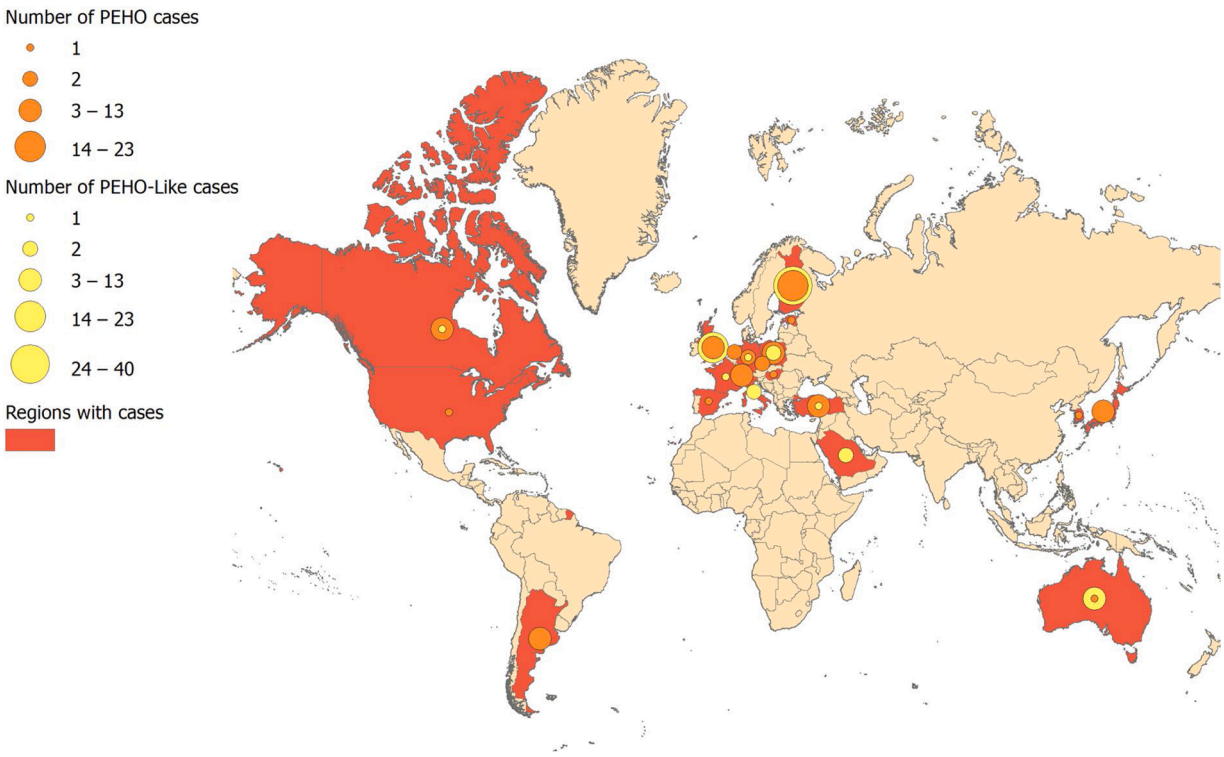

Fig. 2. Geographical distribution of PEHO and PEHO-Like cases. Created using ECDC map maker (EMMa) (https://emma.ecdc.europa.eu). PEHO, progressive encephalopathy, hypsarrhythmia, and optic atrophy.

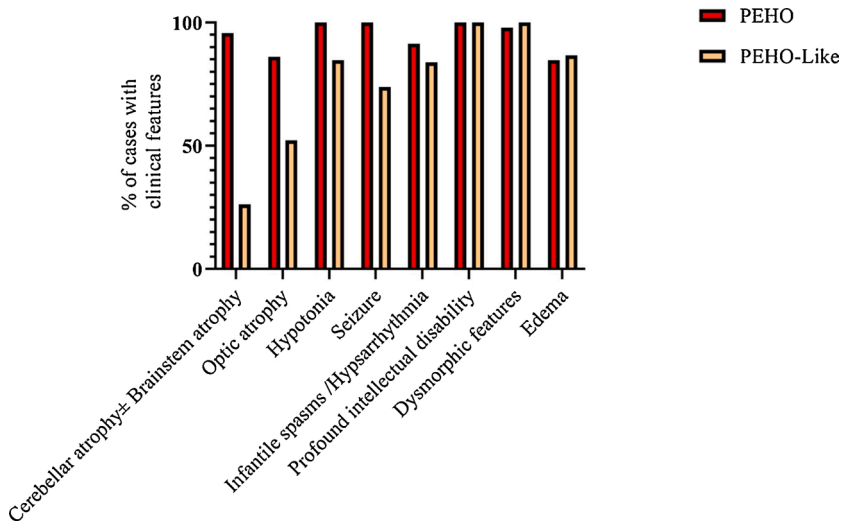

Fig. 3. Column graph showing the variation observed in the key clinical features of PEHO and PEHO-Like cases. Note that some data are not reported or not available and data of PEHO patients from the study by Somer (1993) [2] were not included in the comparison. PEHO, progressive encephalopathy, hypsarrhythmia, and optic atrophy.

including *KIF1A*, *GNAO1*, *HESX1*, *ZNHIT3*, *SCN2A*, *CASK*, *UFM1*, *SPTAN1*, in PEHO cases, *CDKL5*, *UBA5*, *SCN1A*, *SEPSECS*, in PEHO-Like cases and three other genes, *CCDC88A*, *PCLO*, and *PLAA*, in both patients.

4. Discussion

Neuroradiological and ophthalmological findings are two major distinctive features between PEHO and PEHO-Like patients as shown by the comparison between two groups (Fig. 3), but cerebellar atrophy is the main discriminator between them compared with optic atrophy [34, 35]. According to our results, all clinical features assessed in this study proved the credibility of the established diagnostic criteria [2] except for optic atrophy and infantile spasms/hypsarrhythmia. Absence of optic atrophy in all PEHO patients may be because of incomplete data and death of some cases before it was developed [50], but absence of infantile spasms/hypsarrhythmia in some PEHO cases has no special justification and it was previously suggested to remove infantile spasms/hypsarrhythmia from the diagnostic criteria for PEHO syndrome [49].

Age of onset was from birth to 10 and 16 months in PEHO and PEHO-Like groups, respectively that may be important for intervention

approaches [50]. The prognosis is poor and death occurs between the age of 18 months and 13 years old for PEHO and between 10 weeks and eight years for PEHO-Like, so early diagnosis is of particular importance.

Although cases have been reported worldwide, the majority of patients were from Finland. This is because of Finnish disease heritage, i.e., the occurrence of many hereditary disorders in the Finnish population which are rare elsewhere [19,65]. Founder effects, several bottleneck incidents leading to genetic drift may cause higher frequencies of rare in certain populations [19,66,67].

Consanguinity was reported in some families that supports autosomal recessive inheritance and increased risk of progressive encephalopathy and these two syndromes [51,68]. As shown in Table 2, there are different pathogenic variants in several genes that cause PEHO and PEHO-Like syndromes. These data support the notion of the presence of genetic heterogeneity in these syndromes [50]. A homozygous missense variant, c.92C > T (p.S31 L), in *ZNHIT3* gene was considered as a Finnish founder m pathogenic variants not occurring in other populations [64], but one study [53] argues against this issue by reporting a compound heterozygous biallelic missense variants including c.41 G > T (p.C14 F) in an Estonian case for the first time. It is worth mentioning that Estonians and Finns are genetically different [69]. Although the p.S31 L substitution was considered as the Finnish PEHO variant, authors emphasized that the patient has no Finnish origin. *ZNHIT3* encodes a zinc finger protein involved in the assembly of snRNPs and possibly in pre-rRNA processing by interaction with nuclear FMR1 interacting Protein 1 (NUFIP1) [70,71]. A functional study confirmed the role of this gene as a factor in causing PEHO syndrome by proving its essential role in survival and migration of granule neurons and observing similar phenotypes in the model organisms [49].

Recently, pathogenic variants in nine other genes have been reported in PEHO cases. Two different heterozygous missense variants were reported in *KIF1A* which encodes a microtubule motor protein that plays a role in anterograde axonal transports of membranous organelles. The first variant, p.T99 M was reported by one study and was considered as a pathogenic variant due to its impact on the motor domain of the protein, and the literature review by authors showed that some other cases with pathogenic variants in the motor domain of KIF1A meet the PEHO syndrome criteria [47]. The relationship between the second variant, p.E253 K, and reduced mitochondrial respiratory chain complex activity was discussed in another study for the first time [52]. Before this study, Al-Hertani et al. [72] had reported respiratory chain complex deficiency in a child with PEHO-Like features. Further investigations are needed to clarify these relationships. The co-occurrence of two pathogenic variants in *GNAO1* and *HESX1* genes were reported in one PEHO patient [46]. *GNAO1* encodes the alpha subunit of the Go heterotrimeric G-protein signal-transducing complex [73]. Defects in this protein are related to early-onset epileptic encephalopathy type 17 (EIEE17) [74]. *HESX1* encodes a transcriptional repressor of the forebrain and pituitary gland development [73]. Pathogenic variants in this gene are associated with several phenotypes including congenital pituitary abnormalities, optic nerve anomalies, and septo-optic dysplasia [75]. Encephalopathy and optic atrophy, in this case, maybe caused by a merged impact of pathogenic variants at two independent Mendelian loci, thus the patient shows a blended phenotype [46]. *SCN2A*, *CASK*, and *UFM1* are three other genes that have been reported to be involved in the pathogenesis of PEHO syndrome. SCN2A is a voltage-gated sodium channel and is expressed on neurons. Heterozygous pathogenic variants in this gene are reported in association with EIEE type 11 (EIEE11) and benign familial infantile epilepsy (BFIE). A nonsense variant of *CASK* gene, p.E92*, was reported in another PEHO patient [50]. The encoded protein by this gene is a scaffold protein that is located in the brain synapses [73]. A similar variant reported in this patient had previously been shown to be involved in the intellectual disability, axial hypotonia, progressive microcephaly, optic atrophy, and pontine and cerebellar hypoplasia [76]. *UFM1* is another gene that may cause PEHO syndrome. The encoded protein is classified as a ubiquitin-like protein. Further studies are needed to prove the possible role of this gene in the pathogenesis of PEHO [50,77]. *SPTAN1* encodes alpha-II spectrin that is a filamentous cytoskeletal protein and acts as a scaffold protein. It seems that pathogenic variants of *SPTAN1* are related to a wide spectrum of signs ranging from moderate intellectual disability and seizures to intense epileptic encephalopathy with microcephaly and hypoplasia or atrophy of cerebral and cerebellar regions, some of them being common in PEHO patients [62].

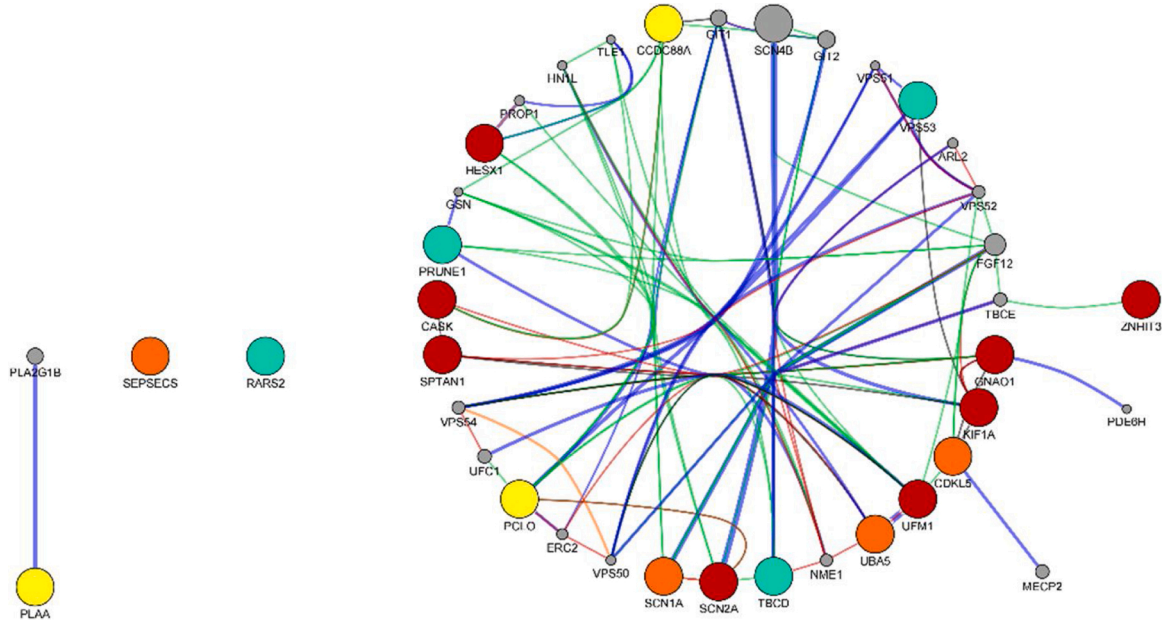

Fig. 4. Interaction network of the 19 genes discussed in the present study. Several functional interactions have been identified between PEHO-associated genes. Network analysis was carried out by the use of the GeneMANIA Cytoscape plugin [23] using Cytoscape v3.8.0 software [24]. Nodes and edges showing interactions between query genes associated with PEHO and PEHO-Like syndromes. Node colors: PEHO syndrome genes (red); PEHO-Like syndrome genes (orange); genes involved in both syndromes (yellow); genes associated with Prune syndrome, PCCA type 2, PCH type 6 (blue-green); related genes predicted by GeneMANIA (gray). Edge colors: physical interactions (blue), co-expression (red), genetic interactions (green), co-localization (black), and shared protein domains (orange).

Table 1
Clinical features of PEHO and PEHO-Like cases.

Author(s) (year)	Number of Patients	Sex (M:F)	Origin	Consanguinity	Age of onset	Age of death (n)	Imaging done	Cerebellar atrophy ± Brainstem atrophy	Optic atrophy	Hypotonia	Seizure	Infantile spasms /Hypsarrhythmia	Profound intellectual disability	Dysmorphic features	Edema	Diagnosed syndrome (n)
Salonen et al. (1991) [1]	14	6:8	Finish	–	2–12 w	18 m-11 y (5)	14/14	14/14	13/14	14/14	14/14	12/14	14/14	14/14	13/14	PEHO
Somer (1993) [2]	21*	?	Finish	–	During the first days of life		21/21	10/10	10/10	10/10	10/10	10/10	10/10	3/10	9/10	PEHO (10)
								2/11	0/11	6/11	1/11	NR	NR	NR	8/11	PEHO-Like (11)
Fujimoto et al. (1995) [4]	2	1:1	Japanese	–	0–4 w	10 y (1)	1/2	0/1	2/2	2/2	2/2	2/2	2/2	2/2	0/2	PEHO
Shevell et al. (1996) [37]	1	F	Canada (French-Canadian)	–	12 w		1/1	1/1	+	+	+	+	+	+	–	PEHO
Chitty et al. (1996) [11]	4	1:3	United Kingdom	–	0–6 w	10 w-2 y 10 m (4)	3/4	0/3	4/4	4/4	4/4	1/4	4/4	4/4	4/4	PEHO-Like
Tanaka et al. (1997) [55]	1	M	Japan	NA	Shortly after birth	NA	1/1	1/1	+	+	+	+	+	+	NA	PEHO
Hollody and Kollar (1997) [54]	1	M	Hungary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PEHO
Zumrová et al. (1999) [56]	2	F	Czech Republic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PEHO
Tekgul and Tutuncuoglu (2000) [39]	1	M	Turkish	NA	Early infancy	NA	1/1	+	+	+	+	+	+	+	+	PEHO
Vanhatalo et al. (2002) [14]	2	1:1	Dutch	–	0–4 w	8 y (1)	2/2	2/2	2/2	2/2	2/2	1/2	2/2	2/2	2/2	PEHO
Longman et al. (2003) [13]	2	F	United Kingdom (Scottish)	–	Shortly after birth	3 y and 8 y (2)	2/2	0/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	PEHO-Like
Goizet et al. (2003) [40]	1	M	French	–	Shortly after birth		1/1	0/1	+	+	+	+	+	+	+	PEHO-Like
Field et al. (2003) [12]	5	2:3	Australian	1/5	0–6 w	3 m-6 y 9 m (4)	5/5	1/1	+	+	+	+	+	+	+	PEHO (1)
								0/4	1/4	4/4	3/4	3/4	4/4	4/4	2/4	PEHO-Like (4)
Nieto-Barrera et al. (2003) [57]	1	M	Spanish	–	From the first month	NA	1/1	1/1	+	+	+	+	+	NA	+	PEHO
Klein et al. (2004) [41]	1	F	Swiss	–	4 m		1/1	1/1	+	+	+	+	+	+	+	PEHO
D'Arrigo et al. (2005) [42]	1	M	Italy	–	16 m		1/1	0/1	–	+	–	+	+	+	+	PEHO-Like
Piotrowski et al. (2005) [17]	1	F	Poland	NA	NA	NA	NA	NA	+	NA	+	+	+	+	+	PEHO
Barber et al. (2006) [16]	1	M	United Kingdom (Pakistani)	+	At birth		1/1	?	–	+	+	NR	+	+	+	PEHO
Kröll et al. (2006) [59]	1	F	Swiss-German	–	During the first weeks of life	NA	1/1	1/1	+	+	+	+	+	NA	NA	PEHO
Sonmez et al. (2007) [43]	1	F	Turkey	NR	NR		1/1	1/1	+	+	+	+	NR	–	–	PEHO
Moon (2007) [58]	1	F	South Korea	NA	NA	NA	1/1	1/1	NA	NA	NA	NA	NA	NA	NA	PEHO
	1	M	Germany	–	3 m		1/1	1/1	+	+	+	+	+	NR	+	PEHO-Like

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Table 1 (*continued*)

Author(s) (year)	Number of Patients	Sex (M:F)	Origin	Consanguinity	Age of onset	Age of death (n)	Imaging done	Cerebellar atrophy ± Brainstem atrophy	Optic atrophy	Hypotonia	Seizure	Infantile spasms /Hypsarrhythmia	Profound intellectual disability	Dysmorphic features	Edema	Diagnosed syndrome (n)
Helbig et al. (2010) [7]																
Paolisso et al. (2010) [60]	1	F	Swiss	–	Neonatal period		1/1	1/1	+	+	+	–	NA	NA	+	PEHO
Iftinca et al. (2011) [61]	1	M	Canada (Korean)	NA	Shortly after birth	NA	1/1	1/1 (At autopsy)	–	+	+	–	+	NA	+	PEHO-Like
Alfadhel et al. (2011) [10]	2	F	Canada (Filipino/ Caucasian and Caucasian/First Nation)	NR	2–4 m	23 m (1)	2/2	1/2	2/2	2/2	2/2	2/2	2/2	2/2	1/2	PEHO
Caraballo et al. (2011) [44]	5	4:1 (2 twin brothers)	Argentina (3 Spanish 2 Italian)	1/5	1–10 m	10–13 y (3)	5/5	5/5	4/5	5/5	5/5	5/5	5/5	5/5	5/5	PEHO
Yiş et al. (2011) [45]	2	F	Turkey	–	first month		2/2	1/1	+	+	+	+	+	+	+	PEHO (1)
								1/1	–	+	+	+	+	+	+	PEHO-Like (1)
Casabianca et al. (2013) [18]	1	NA	Italy	NA	NA	NA	NA	NA	+	+	+	+	+	NA	NA	PEHO-Like
Gawlinski et al. (2016) [46]	4	1:3	Poland	–	Infancy		4/4	2/2	2/2	2/2	2/2	NR	2/2	2/2	2/2	PEHO (2)
								0/2	1/2	2/2	2/2	NR	2/2	2/2	2/2	PEHO-Like (2)
Nahorski et al. (2016) [48]	3	2:1	British (white Caucasians)	+	At birth		3/3	0/3	3/3 (Moderate)	3/3	3/3	3/3	3/3	3/3	3/3	PEHO-like
Harms et al. (2016) [62]	2**	1:1	Germany	NA	NA	NA	2/2	2/2	1/2	2/2	2/2	2/2	2/2	2/2	NA	PEHO
Chitre et al. (2018) [50]	19	NR	United Kingdom (British, Arabic, Sudanese and Pakistani)	5/19	NR	Under 2 y (2)	17/19	7/7	5/7	7/7	7/7	7/7	7/7	7/7	6/7	PEHO (7)
								4/10	8/12	10/12	12/12	12/12	12/12	12/12	11/12	PEHO-Like (12)
Samanta and Gokden (2019) [52]	1	F	United States	–	0–2 m	4 y 2 m	1/1	1/1	+	+	+	+	+	+	+	PEHO
Abdulkareem et al. (2019) [51]	2	1:1	Saudi	+	NR		2/2	2/2	2/2	2/2	2/2	NR	2/2	2/2	2/2	PEHO-like
Ounap et al. (2020) [53]	1	F	Estonian	NR	1 m		1/1	1/1	–	+	+	+	+	+	+	PEHO

M, male; F, female; n, number; -, Not present; +, present; w, week; m, month; y, year; PEHO, Progressive encephalopathy, hypsarrhythmia and optic atrophy;?, Indistinguishable; NR, not reported; NA, not available. Clinical information from Antonnen et al. [63] and Antonnen et al. [49] not included in the table because of some cases that overlap with cases reported by other studies described without specific identification.

* Seven patients from the study by Salonen et al. [1].

** Male patient was identified from a cohort study of 34 PEHO syndrome cases, but information about other cases not available.

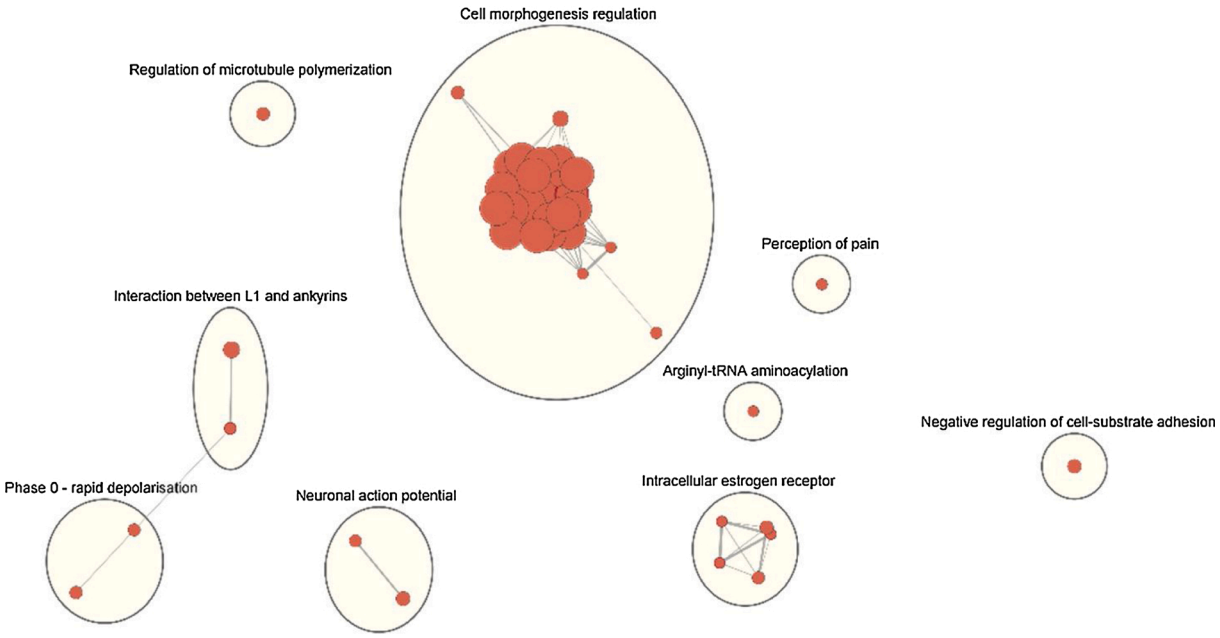

Fig. 5. Pathway enrichment analysis for identification of functional roles of PEHO-associated genes. Enrichment map made with parameters FDR Q value < 0.05 by g: profiler web server [26] and enrichment map Cytoscape plugin [27] using Cytoscape v3.8.0 software [24]. Clusters of nodes were marked by the use of Auto-Annotate [28], WordCloud [29], and clusterMaker2 [30] applications. Each node (red circles) shows a unique pathway, as well as edges (gray lines), represent the number of overlapped genes between pathways, determined by the use of similarity coefficient.

CCDC88A, *PCLO*, and *PLAA* are three genes whose pathogenic variants were reported in both PEHO and PEHO-Like cases [48,50,51]. *CCDC88A* encodes a coiled-coil domain-containing protein being called GIRDIN. GIRDIN has numerous roles related to cell migration and cell polarity, especially in neurons [78,79]. A functional study showed a link between the PEHO-Like syndrome and pathogenic variant in *CCD88A*, suggesting that this gene is important for various parts of human neurodevelopmental processes [48]. *PCLO* and *PLAA* encode proteins that are parts of synapses. *PCLO*, which encodes PICOLLO protein was identified in Drosophila as an important gene for synaptogenesis and function of synapses in the central nervous system (CNS) and this gene also underlies PCH3 [80]. *PLAA* encodes phospholipase A2 activating protein that is highly expressed in the CNS and regulates the endolysosomal pathway of synaptic membrane proteins through the maintenance of ubiquitin amounts [81].

Besides, four other genes have been reported only in PEHO-Like patients: *CDKL5* [46], *UBA5*, *SCN1A* [50] and *SEPSECS* [63,64]. *CDKL5* is a well-known gene related to early-onset epileptic

Table 2
Genetic features of PEHO and PEHO-Like cases.

Gene	Zygosity	Pathogenic variant type	Pathogenic variant	Protein change	Syndrome	Reference(s)
KIF1A	Heterozygous (de novo)	Missense	c.296C > T	p.T99M	PEHO	[47]
KIF1A	Heterozygous (de novo)	Missense	c.757 G > A	p.E253K	PEHO	[52]
GNAO1	Heterozygous (de novo)	Missense	c.134 G > A	p.G45E	PEHO	[46]
HESX1	Homozygous (de novo)	Missense	c.25 G > A	p.A9T	PEHO	[46]
ZNHIT3	Homozygous	Missense	c.92C > T	p.S31L	PEHO	[49]
ZNHIT3	Compound heterozygous	Biallelic missense	c.92C > T c.41 G > T	p.S31L p.C14F	PEHO	[53]
SCN2A	Heterozygous	Missense	c.743 T > C	p.L248P	PEHO	[50]
CASK	Heterozygous (De novo)	Nonsense	c.274C > A	p.E92*	PEHO	[50]
UFM1	Homozygous	Missense	c.241C > T	p.R81C	PEHO	[50]
SPTAN1	Heterozygous (de novo)	Duplication	c.6908-6916dup	p.D2303-L2305dup	PEHO	[62]
PCLO	Homozygous	Biallelic nonsense	c.2703C > T c.7080C > G	p.Q901* p.Y2360*	PEHO and PEHO-Like	[50]
PLAA	Homozygous	Missense	c.68 G > T	p.G23V	PEHO and PEHO-Like	[50]
CCDC88A	Homozygous	Frameshift	c.2313delT	p.L772*	PEHO and PEHO-Like	[48,50]
CCDC88A	Homozygous	Nonsense	c. 1292 G > A	p.W431*	PEHO-Like	[51]
CDKL5	Heterozygous (de novo)	Missense	c.626C > T	p.P209L	PEHO-Like	[46]
UBA5	Compound heterozygous (De novo)	No-stop Missense	c.1214A > T c.1111 G > A	p.*405L+12* p.A371T	PEHO-Like	[50]
SCN1A	Heterozygous	Missense	c.1252A > C	p.I418L	PEHO-Like	[50]
SEPSECS	Compound heterozygous	Missense Nonsense	c.974C > G c.1287C > A	p.T325S p.Y429*	PEHO-Like	[63,64]

encephalopathy. Pathogenic variants in this gene have been seen in cases with Rett-like phenotype that their clinical features overlap with PEHO-Like syndrome [82–84]. *UBA5* encodes a protein from the E1-like ubiquitin-activating enzyme family that activates UFM1, a post-translational modifier protein [73], and forms a dimer with UFM1 and UFC1 [85]. Pathogenic variants in *UBA5* are associated with early-onset encephalopathy [86,87]. SCN1A is involved in neuronal membrane potential regulation. The amino acid change in the reported PEHO-Like case happens in the intracellular part of the domain I-S6 transmembrane region. It is an essential area of the intracellular pore inside the Nav1.7 protein that can permit Na + to get in the cell [50]. A missense and a nonsense pathogenic variants have been reported in the *SEPSECS* gene, which encodes O-phosphoseryl-tRNA(Sec) selenium transferase. This gene has been previously related to progressive cerebello-cerebral atrophy. Functional analysis shows that the pathogenic variants in *SEPSECS* do not eliminate its activity, however, they lead to reduced selenoprotein levels leading to a rise in oxidative protein damage within the brain. These data identify this gene as a candidate for progressive encephalopathies [63,64]. Pathogenic variants in this gene was also associated with the pontocerebellar hypoplasia (PCH) type 2D [88].

PEHO syndrome is clinically similar with Prune syndrome (caused by *PRUNE1* pathogenic variants) [64,89], progressive cerebello-cerebral atrophy (PCCA) type 2 (caused by *VPS53* pathogenic variants) [90], and PCH type 6 (caused by *RARS2* pathogenic variants) [91,92], Moreover, clinical features overlap between PEHO-Like syndrome and encephalopathy related to biallelic pathogenic variants in *TBCD* [93,94] providing further evidence about the role of candidate genes in these two syndromes. So far, several genes have been described with different functions. We performed network analysis to predict functional interactions of the mentioned genes (Fig. 4). The network analysis revealed that the 15 genes reported in PEHO and PEHO-Like syndromes had potential direct or indirect interactions with each other and with the three genes associated with Prune syndrome, PCCA type 2, and PCH type 6 through a complex network. Physical interactions of this network accounted for 61.27 % of the total interactions, co-expression accounted for 26.67 %, co-localization accounted for 6.28 %, shared protein domains accounted for 5.06 %, and genetic interactions accounted for 0.71 %. Since this prediction method is based on a query-dependent weighting to determine how genes in a list are well connected for finding more genes similar to the query, SCN4B and FGF12 were assigned the highest weight due to size which suggests that these two genes may be involved in the pathogenesis of these conditions. We also conducted a pathway enrichment analysis to obtain mechanistic insight into 15 reported PEHO-associated genes (Fig. 5). The overrepresented pathways were involved in cell morphogenesis regulation, intracellular receptor, interaction between L1 and ankyrins, phase 0 - depolarisation, neuronal action potential, regulation of microtubule polymerization, arginyl-tRNA aminoacylation, negative regulation of cell-substrate adhesion, and perception of pain. These predicted gene interactome network and pathway analyses may help provide new insights into the pathogenesis of these syndromes.

5. Conclusion

Diagnosis based on clinical features is still challenging in PEHO spectrum diseases. On the other hand, genetic heterogeneity is clearly seen in this group of patients. These findings highlight the necessity of evaluating several genes by performing whole-exome sequencing or whole-genome sequencing for a comprehensive diagnostic work-up. Future genetic studies could help unravel various dimensions of this challenging group of diseases and a better understanding of the molecular mechanisms associated with these disorders.

Declaration of Competing Interest

The authors report no declarations of interest.

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