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Review

Orofacial Lymphedema in Phelan–McDermid Syndrome: A Case of Hemifacial Involvement and a Scoping Review

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Abstract: Phelan–McDermid syndrome (PMS) is a rare genetic disorder primarily caused by deletions or structural alterations of chromosome 22q13, often involving the SHANK3 gene. However, mutations in other genes, such as CELSR1, or deletions in the interstitial regions of 22q13 contribute to the phenotypic variability of PMS. The syndrome is characterized by developmental delay, cognitive impairment, absent or significant impairment speech, autism spectrum disorder (ASD), and distinctive craniofacial features. Lymphedema, present in 10–25% of cases, typically affects peripheral regions, while facial involvement has not been documented to date. Orofacial manifestations frequently include dolichocephaly, widely spaced eyes, prominent ears, and dysmorphic features, such as a bulbous nose and arched palate. This scoping review analyzed seven studies on orofacial features associated with PMS, highlighting a higher phenotypic variability, with frequent findings of intellectual disability, hypotonia, and craniofacial dysmorphisms. Genomic analyses identified consistent deletions in 22q13.31–q13.33 and complex genomic rearrangements. This review, through the report of the first documented case of hemifacial lymphedema in the literature, analyzes the facial features of patients with PMS and their genetic origins. It also highlights the importance of interdisciplinary collaboration and inclusive genetic testing to better define the phenotypic spectrum of this syndrome. A deeper understanding of the genetic and clinical characteristics of PMS can facilitate early diagnosis and personalized management for these patients.

Keywords: Phelan–McDermid syndrome; lymphedema; orofacial lymphedema

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1. Introduction

Phelan–McDermid syndrome (PMS) or 22q13.3 deletion syndrome is a rare genetic disorder, characterized by a complex neurological and psychiatric phenotype, along with additional features that can vary widely among affected individuals and across the patient's lifespan [1–7]. Although individual case reports have been published, Phelan and McDermid were the first to comprehensively describe and consolidate the clinical features observed in larger cohorts of individuals with PMS [1]. Current estimates suggest that PMS accounts for approximately 1% of autism spectrum disorder cases. This means that between 1/8000 and 15,000 individuals (including those with 22q13.3 deletions and SHANK3 gene variants) have PMS [1,4,8]. However, this may be an underestimate, since not all patients with PMS will present with autism. As of the end of September 2024, the membership

and patient registry of the Phelan–McDermid Syndrome Foundation (PMSF) include over 3216 individuals diagnosed with PMS worldwide (https://pmsf.org) [1,2,4,9].

PMS is predominantly attributed to de novo deletions of chromosome 22, frequently of paternal origin, or to unbalanced chromosomal rearrangements inherited from a parent with a balanced translocation [2,10,11]. The SHANK3 gene is believed to underpin the syndrome's key neurological features, such as speech delay, intellectual disability, and autistic traits [2,11–16]. Genotype–phenotype correlation studies revealed an association between deletion size and specific clinical features, such as developmental delay, dysmorphic traits, medical comorbidities, hypotonia, and communication impairment, with larger deletions generally resulting in more severe phenotypic outcomes [17–22]. The contribution of genes beyond SHANK3 was emphasized by the identification of PMS-compatible phenotypes in individuals with interstitial 22q13 deletions that preserve SHANK3, thereby distinguishing SHANK3-related and SHANK3-unrelated forms of PMS [17,23–26].

Evidence suggests that multiple additional genes contribute to the pathogenesis of PMS [8,14]. The deletion of multiple interstitial genes, including MMPED1 and CYB5R3 in 22q13.2, as well as FBLN1, NUP50, C22orf9, KIAA1644, PARVB, TRMU, WNT7B, ATXN10, and microRNAs, such as hsa-mir-1249, hsa-let-7a-3, and hsa-let7 in 22q13.31, may result in consequences comparable to the haploinsufficiency of SHANK3 and other terminal genes [27].

PMS presents with neonatal hypotonia, significantly delayed or absent speech, developmental delay, and mild dysmorphic facial features. The majority of affected individuals present with moderate to profound intellectual disability [7,24,25,28,29]. Additional clinical features include large fleshy hands, dysplastic toenails, and decreased perspiration, leading to a predisposition to overheating [24]. Unlike other autosomal chromosome disorders, individuals with PMS typically exhibit normal stature and head circumference. Behavioral manifestations often include mouthing or chewing non-food items, reduced pain sensitivity, and the presence of autism spectrum disorder or autistic-like affect and behavior [24,25]. The comparative analysis of larger deletions (>5 Mb) and smaller deletions ($\leq$0.5 Mb) involving the SHANK3 gene has demonstrated notable differences in facial morphology. Facial features were observed in approximately 35–80% of individuals [30]. Conversely, individuals with SHANK3 gene variants tend to exhibit fewer dysmorphic features compared to those with microdeletions [30]. Craniofacial features of PMS are often subtle and heterogeneous [11,31]. Cranial morphology is often characterized by an elongated or dolichocephalic shape. Facial features commonly include a broad forehead, deep-set eyes, puffy eyelids, a bulbous nose, and long, thick eyelashes. The midface may appear flattened, accompanied by a broad nasal bridge and full cheeks [11,31]. The chin is frequently pointed and may become more prominent with age [11,31]. The ears are typically large and may be appear prominent or malformed. Less frequently observed features include ptosis, epicanthal folds, strabismus, an elongated philtrum, and a high-arched palate [11,31]. The subtlety of the craniofacial features and the variability in manifestations, likely influenced by the size of the deletion, make it challenging to establish a diagnosis of this syndrome based exclusively on craniofacial characteristics [11].

Dental overcrowding and malocclusion are among the most commonly observed dental issues. These conditions are frequently linked to contributing factors, such as reduced muscle tone, habitual chewing, tongue thrusting, and bruxism. Malocclusion is often associated with difficulties in swallowing and salivation, which may further complicate speech impairments [32,33].

Facial lymphedema is a rare condition commonly associated with prior surgery in the head and neck region, infection, radiation therapy, or local tumor growth. Lymphedema increases the risk of infection due to lymphatic system impairment. The most common

infection is cellulitis, which can affect the edematous area [34]. Only a few cases of isolated facial lymphedema have been reported in the literature, and none of them are associated with PMS. However, lymphedema, beyond facial locations, is associated with PMS in 10 to 25% of cases, becoming a relatively common manifestation in PMS [2,35]. Furthermore, lymphedema in PMS appears to be attributable to deletions of the 22q13 gene without alterations in SHANK3, as reported in Table 1 [14]. CELSR1 has recently been identified as a likely cause of lymphedema observed in PMS [13,24].

Table 1. Modified classification of the clinical features of Phelan–McDermid syndrome, as described by Scön et al., in patients with 22q13 deletions without SHANK3 haploinsufficiency and in individuals with SHANK3 variants.

Signs/Symptoms	PMS Individuals with 22q13 Deletions (%) (Without SHANK3 Haploinsufficiency)	PMS Individuals with SHANK3 Variants (%)
Development		
Global developmental delay	98%	96%
Marked speech impairment	88%	31%
Neurology		
Seizures (one or more)	27%	26%
Hypotonia	74%	82%
Structural brain anomalies	53%	29%
Senses		
Vision disturbances	22%	26%
Strabismus	24%	14%
Hearing loss	8%	10%
Increased pain tolerance	65%	79%
Behaviour		
ASD	57%	79%
Hyperactivity	29%	72%
Aggression	19%	37%
Self-injury	13%	30%
Sleep disorder	26%	52%
Internal Organs		
Gastro-oesophageal reflux	25%	17%
Cardiac anomalies	13%	7%
Frequent airway infections	27%	32%
Urogenital problems	15%	0%
Renal abnormalities	15%	0%
Growth		
Short stature	9%	10%
Tall stature	21%	7%
Craniofacial features		
Dolichocephaly	26%	7%
Long eyelashes	48%	49%
Down-slanting palpebral fissures	22%	30%
Periorbital fullness	29%	18%
Ptosis	22%	7%
Epicanthal folds	32%	21%
Ear anomalies	47%	39%
Wide nasal bridge	45%	36%
Broad nose	48%	38%
Short philtrum	16%	0%
Thin upper vermillion	27%	27%
Thick lower vermillion	9%	24%
Malocclusion	37%	34%

Table 1. *Cont.*

Signs/Symptoms	PMS Individuals with 22q13 Deletions (%) (Without SHANK3 Haploinsufficiency)	PMS Individuals with SHANK3 Variants (%)
Retrognathia	25%	0%
Macrocephaly	17%	15%
Microcephaly	16%	10%
Facial Lymphedema		
Physical and dermatological anomalies		
Clinodactyly 5th finger	20%	35%
2–3 syndactyly of toes	28%	45%
Sandal gap	54%	7%
Lymphedema	11%	0%
Eczema	21%	30%
Hypohidrosis	37%	8%
Hyper-extensible joints	22%	60%
Small/malformed nails [14]	32%	45%

No clinical diagnostic criteria have been definitively established for SHANK3-related PMS [26]. The diagnosis of PMS relies on the identification of a 22q13 chromosomal deletion involving the SHANK3 gene or a pathogenic variant within the gene itself. Genetic testing methods include exome or genome sequencing, chromosomal microarray, single-gene testing, and multigene panels [26,36].

The diagnostic process begins with the detection of SHANK3 deletions or duplications, followed, if necessary, by gene sequencing. SHANK3-unrelated PMS is rare and requires a complex analysis: patients must have a 22q13 deletion that does not involve SHANK3 but still exhibits the typical clinical features of the syndrome [26,37].

The differential diagnosis includes several conditions, such as autism, cerebral palsy, and syndromes like Angelman, Prader–Willi, fragile X, Williams–Beuren, and Smith–Magenis, as well as other rare genetic syndromes [23,38–43].

The aim of this scoping review, focusing on the analysis of a unique case in the literature (hemifacial lymphedema in a patient with PMS), was to explore and map the existing scientific literature on the orofacial manifestations of PMS. This review analyzes patients with orofacial manifestations associated with PMS, evaluating them based on sex/age, general characteristics, orofacial traits, and genetic panel. Only studies in English with data on human patients were included, while studies on animal models and reviews were excluded.

2. Case Report

We present the case of a 6-year-old girl who was referred to the Department of Odontostomatology at the Polyclinic of Bari (University of Bari Aldo Moro) due to hemifacial swelling (Figure 1). Her primary dentist had advised urgent consultation at the emergency department of the Polyclinic of Bari, suspecting a maxillary phlegmon. The patient did not exhibit any tenderness upon palpation. At the intraoral examination, no necrotic dental elements were observed that could account for an infectious–inflammatory process. The patient had a confirmed diagnosis of PMS, established through genetic testing in 2020. Given the clinical presentation, hemifacial lymphedema was suspected, which is an atypical manifestation within the spectrum of PMS. The patient, born to non-consanguineous parents, had been referred for evaluation due to developmental delays and prominent swelling on the right side of her face.

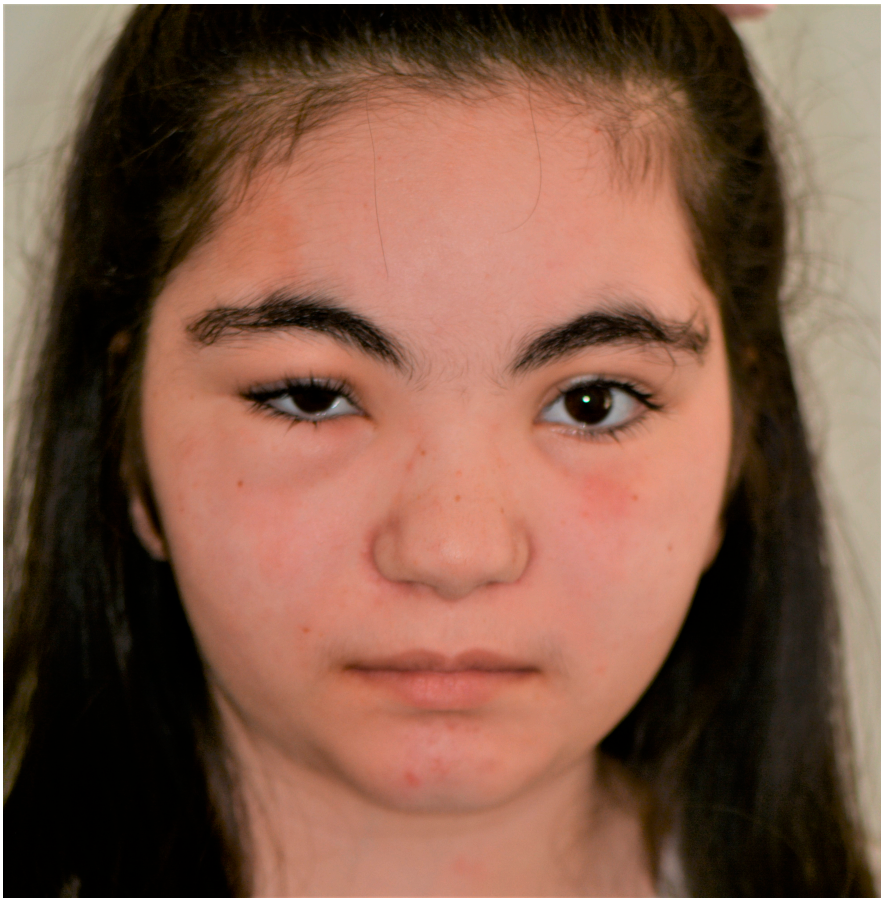

Figure 1. Patient diagnosed with Phelan–McDermid syndrome. Notable features of this syndrome include a bulbous nose and a broad nasal bridge, along with hemifacial lymphedema.

The child's history revealed global developmental delay, the absence of verbal communication, and mild hypotonia. Behavioral assessments indicated traits consistent with autism spectrum disorder (ASD), including limited social interaction and repetitive behaviors. Further diagnostic evaluation included chromosomal microarray analysis, which confirmed a deletion in the 22q13.3 region encompassing the SHANK3 gene. Facial MRI revealed diffuse soft tissue swelling consistent with lymphedema, without evidence of vascular anomalies. Indocyanine green lymphangiography demonstrated delayed lymphatic drainage in the affected hemiface. Laboratory tests excluded infectious or autoimmune causes. The patient was managed through a multidisciplinary approach. A lymphedema specialist initiated manual lymphatic drainage therapy and recommended facial compression garments. Developmental interventions included speech and occupational therapies, while structured behavioral therapy was implemented to address ASD-related symptoms. Six months into treatment, the hemifacial lymphedema remained stable with improved cosmetic outcomes; however, developmental progress was gradual, and verbal communication remained absent. This case highlights hemifacial lymphedema as a novel manifestation of PMS, expanding the phenotypic understanding of the syndrome. It emphasizes the importance of comprehensive, multidisciplinary management to address the complex needs of patients with PMS.

3. Methods

3.1. Study Registration

This study has been registered on the Open Science Framework (OSF) portal, accessible as of 4 December 2024 (https://osf.io/kugf2). The scoping review was carried out in

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews (Table S1).

3.2. Objective

The objective of this scoping review was to examine and map the current scientific literature on the orofacial manifestations of Phelan–McDermid syndrome (PMS), while also presenting an orofacial manifestation that has not been previously reported in the literature.

3.3. Eligibility Criteria

For this scoping review, we included case reports, clinical conferences, clinical studies, clinical trials, controlled clinical trials, letters, multicenter studies, observational studies, randomized controlled trials, and human-based studies, while excluding book chapters, systematic reviews, reviews, in vitro studies, and animal models. Furthermore, only studies published in English were considered. The review encompassed all patients exhibiting orofacial manifestations of Phelan–McDermid syndrome.

3.4. Search Strategy

The search was performed using MEDLINE/PubMed, Ovid, and Scopus, applying search filters, such as "Phelan–McDermid Syndrome 'Facial'", "Phelan–McDermid Syndrome 'Face'", and "22q13.3 Deletion Syndrome 'Facial'". Articles published between 1990 and December 2024 were included in the analysis.

3.5. Study Selection and Data Extraction

A total of 19 articles were identified, of which 2 were excluded, as they did not include a diagnosis of Phelan–McDermid syndrome, and 12 were excluded for falling into categories of excluded study types. Data from the remaining 5 articles were compiled into a data table, with patients selected based on age, sex, general clinical characteristics, orofacial features, and genetic traits (Table S2).

3.6. Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the CASP (Critical Appraisal Skills Programme) tools. CASP was selected for its capacity to systematically assess methodological quality and potential bias across different study designs, ensuring a standardized evaluation of methodological rigor.

4. Results

This scoping review was carried out by analyzing the literature from the MEDLINE/PubMed, Ovid, and Scopus databases using the keywords "Phelan–McDermid Syndrome 'Facial'", "Phelan–McDermid Syndrome 'Face'", and "22q13.3 Deletion Syndrome 'Facial'", covering the period from 1990 to December 2024. Through the analysis of these studies, a database was created in which patients were recorded based on gender/age, general characteristics, orofacial traits, and genetic features. The analysis of the data presented in Table 2 reveals a greater involvement of females compared to males, with the age at diagnosis for patients typically occurring within the first decade of life. All patients included in the review exhibited general alterations, such as intellectual disability, speech delay, joint abnormalities, and changes in the hands and feet. In some cases, additional general alterations were present, including hypoplasia of the thyroid cartilage, infantile hypotonia, white matter hypoplasia, torticollis, a waddling gait, and hirsutism. There are no documented cases of lymphedema.

Orofacial manifestations are also well documented, being widely reported in all described cases. Facial dysmorphism is characterized by major features, such as dolichocephaly, prominent ears and forehead, widely spaced eyes, strabismus, ptosis, a bulbous nose, and a wide nasal bridge, and minor features, including a round face, epicanthic folds, macroglossia, microcephaly, mild hypoplasia of the central part of the face, frontal hairiness, an arched palate, and an expressionless face. The deletions of the cases examined are predominantly large deletions. An analysis of the mutated genetic sequences reveals that Del(22)(q13.31–q13.33) has been consistently detected, indicating a deletion within this region (chr22: 46,285,592–51,244,566, hg19). Additional variations included del(22)(q13.31q13.33) and del(22)(q13.3), with multiple cases suggesting a potential hotspot for alterations. Some cases also presented del(22)(qter) and del(22)(q13.3-ACR), highlighting a broader spectrum of deletions affecting chromosome 22. Dup(9)(q34.3) was observed in both 46, XX and 46, XY karyotypes, with sequence data showing an increased copy number for the respective genomic regions (139,372,567–140,950,541 for XX and 139,367,413–141,077,092 for XY). There were also instances of combined deletions and duplications, such as del(22)(q13.33) coupled with dup(8)(p23.3p23.2), indicating complex genomic rearrangements.

Table 2. Characteristics of patients included in this scoping review, categorized by age/gender, general clinical manifestations, orofacial abnormalities, and genetic mutations.

Study ID	Type	Patients	Gender/Age	General Characteristics	Orofacial Traits	Genetic Features
Xia S, Liu Z et al. Medicine (Baltimore). 2021 Jun. doi: 10.1097/MD.0000000000026307. [44]	Case Report	1		Intellectual disability Absent speech Abnormal hands and toenails	Tooth grinding Dysmorphic face	Del(22)(q13.31–q13.33)
Li S, Xi KW, et al. BMC Med Genomics. 2020, doi: 10.1186/s12920-020-00802-0. [45]	Case Series	1	M/7	Hypoplasia of the thyroid cartilage Infantile hypotonia and hypoplasia of white matter and external hydrocephalus Severe language disability Large and fleshy hands and feet Clinodactyly of the fifth finger of the right hand Dysplastic nails	Dolichocephaly Large and prominent ears Prominent forehead Widely spaced eyes Bilateral ptosis Bulbous nasal tip Wide nasal bridge Long philtrum	Del(22)(q13.31q13.33)
		1	F/7	Infantile hypotonia and hypoplasia of white matter and external hydrocephalus Severe language disability Large and fleshy hands and feet Clinodactyly of the fifth finger of the right hand Dysplastic nails	Dolichocephaly Large and prominent ears Prominent forehead Widely spaced eyes Bilateral ptosis Bulbous nasal tip Wide nasal bridge Long philtrum	Del(22)(q13.31q13.33)
Görker I, Gürkan, et al. Balkan J Med Genet. 2017 Mar, doi: 10.1515/bjmg-2016-0041. [46]	Case Report	1	F/9	Mild clinical intellectual disability Neonatal hypotonia Aggressive behavior and irritability	Rounded face Pointed chin	Del(22)(q13.33), Dup(8)(p23.3p23.2)

Table 2. *Cont.*

Study ID	Type	Patients	Gender/Age	General Characteristics	Orofacial Traits	Genetic Features
Lei D, Li S, Banerjee S, et al. Oncotarget. 2016 Dec, doi: 10.18632/oncotarget.12552. [47]	Case Series	1	F/6	Intellectual disability Absence of speech Unable to understand a few words Wryneck Wadding gait, Single transverse palmar crease	Strabismus	46, XX, Dup(9q34.3). 46,XX, Del(22q13.31q13.33).
		1	M/3	Intellectual disability Absence of speech Unable to understand a few words Wryneck Wadding gait Single transverse palmar crease	Strabismus	46, XY, Dup(9q34.3); 46, XY, Del(22q13.31q13.33).
Delahaye A, Toutain A, et al. Eur J Med Genet. 2009 Sep-Oct. doi: 10.1016/j.ejmg.2009.05.004. [48]	Case Report	1	F	Delayed motor development Severe dysarthria Hollow feet	Epicanthic fold Mild ptosis Prominent cupped ears	del(22)(q13.3q13.3)
Bonaglia MC, Giorda R, et al. J Med Genet. 2006 Oct;43(10):822-8. doi: 10.1136/jmg.2005.038604. [49]	Case Report	1	F/17	Syndactyly of the second and third toes with toenail hypoplasia Severe intellectual disability Absent language Autistic traits	Mild facial dysmorphisms Long, flat face Brachycephaly Deep-set eyes Short philtrum Mild prognathism Hypoplastic ear lobes Macrostomia	del(22)(qter), del(22)(q13.3q13.3), del(22)(q13.3-ACR), del(22)(q13.3-22-3:22-7)

Table 2. *Cont.*

Study ID	Type	Patients	Gender/Age	General Characteristics	Orofacial Traits	Genetic Features
Battini R, Battaglia, et Al. Am J Med Genet A. 2004 Oct 1;130A(2):196-9. doi: 10.1002/ajmg.a.30276. [50]	Case Report	1	M/3	Hirsutism Sacral dimple Broad toes Lax joints Axial hypotonia Lower limb hypertonia with increased deep tendon reflexes	Dolichocephaly Microcephaly Frontal hair upsweep Mild prominence of the metopic suture Bilateral epicanthal folds Mildly dysplastic ears Saddle nose with bulbous tip Mild midface hypoplasia Long philtrum Highly arched palate Expressionless face	del(22q13.31q13.33).

5. Discussion

PMS is a rare, heterogeneous, and complex neurological developmental disorder, with a phenotype that can vary widely and often manifests clinically without typical features [14,41,51]. The management of these patients requires an interdisciplinary approach, involving neonatologists, pediatricians, neurologists, psychiatrists, endocrinologists, immunologists, cardiologists, gastroenterologists, nephrologists, and oral pathologists [41]. Supervision should be led by a geneticist or neuropsychiatrist, responsible for coordinating clinical follow-up and providing genetic counseling to families. A comprehensive understanding of developmental characteristics in children is essential for effectively supporting families, identifying specific challenges, and formulating personalized care plans [41].

This study presents the first documented case of hemifacial lymphedema associated with PMS. Clinically, hemifacial lymphedema closely mimics phlegmonous swelling of odontogenic origin [52,53]. Therefore, a comprehensive intraoral and radiological examination, alongside a detailed assessment of the symptomatology, should be performed by the clinician before proceeding with further diagnostic investigations [52,54]. Differential diagnosis is crucial to exclude odontogenic inflammatory processes, as misdiagnosis could lead to significant delays in recognizing PMS [52–54].

Angioneurotic edema should be included in the differential diagnosis, as it presents with rapid, localized swelling of subcutaneous or submucosal tissues, often triggered by allergens, hereditary factors, medications, or physical stimuli, such as cold exposure. Differentiating it from hemifacial lymphedema is essential, as timely recognition and treatment are necessary to prevent complications. Diagnosis relies on a comprehensive medical history, the absence of identifiable triggers or episodic patterns, and targeted laboratory investigations when appropriate [55,56].

The association between lymphedema and PMS was first described by Nesslinger et al. in 1994 [57]. In PMS, lymphedema may manifest at birth or in early childhood and can progressively worsen if left untreated, leading to significant clinical complications [35]. Lymphedema arises from a dysfunctional lymphatic system, which may result from anatomical or functional abnormalities or an increased lymphatic load, ultimately leading to fluid accumulation [35]. In PMS, lymphedema is classified as primary and is likely attributable to an inadequate lymphatic system. However, the precise mechanisms underlying this lymphatic insufficiency remain unknown, and an as-yet-unidentified gene is suspected to play a causal role [2]. Yin et al. reported a higher prevalence of lymphedema, along with kidney abnormalities, congenital heart defects, abnormal brain imaging, hypotonia, feeding difficulties, and distinct dysmorphic features, in individuals with larger class II deletions [58]. Evidence suggests that alterations in CELSR1 and, to a lesser extent, SHANK3 may contribute to lymphedema pathogenesis [14,35]. Smith et al. found that CELSR1 haploinsufficiency increased the risk of lymphedema 12-fold [59]. However, while lymphedema has been observed in individuals with SHANK3 variants, its correlation with SHANK3 mutations appears weak, leading researchers to consider these cases incidental [59]. Further studies consistently demonstrated that lymphedema was present in 10.6–23.3% of individuals with 22q13 deletions but absent in those with isolated SHANK3 variants, reinforcing CELSR1 as the more likely candidate gene [30,36]. Palumbo et al., in a study on 22q13.31 interstitial deletions, identified CELSR1 as a gene of interest. In a case report of a 20-year-old woman with PMS due to a large deletion and concurrent lymphedema, the authors attributed the condition to the loss of CELSR1 [44,60]. Beyond PMS, the role of CELSR1 in lymphedema pathogenesis is further supported by findings that loss-of-function variants in CELSR1 are linked to primary and hereditary forms of lymphedema [40,61]. Collectively, these findings strongly suggest that CELSR1 haploinsufficiency plays a causal role in the development of lymphedema [62].

Orofacial dysmorphic features associated with larger deletions, including enamel defects, supernumerary teeth, thick eyebrows, and the presence of diastema, are well-recognized characteristics of PMS [58,63]. Furthermore, as highlighted by Sarasua et al., larger deletions are associated with more severe clinical manifestations [64]. The study by Soorya et al. further underscores the considerable heterogeneity in dysmorphic traits among affected individuals, making it challenging to define a consistent phenotypic pattern [18]. The authors describe 32 dysmorphic features, including numerous orofacial abnormalities, such as a bulbous nose, long eyelashes, ear anomalies, full lips, macrocephaly, dolichocephaly, prominent cheekbones, periorbital fullness, a pointed chin, a broad nasal bridge, a long philtrum, malocclusion or widely spaced teeth, micrognathia, deep-set eyes, ptosis, and low-set ears [18]. These findings align with our study, where the significant variability in craniofacial manifestations complicates the identification of consistent facial features in PMS. An observational study by Nevado et al. further supports this, indicating that facial features in PMS are neither pathognomonic nor specific, as patients exhibit substantial phenotypic variability, even among those with similar deletion sizes [30]. According to these authors, the only consistent clinical hallmarks of PMS are severe global developmental delay—particularly evident in profound speech impairment—and muscular hypotonia [18]. Nevertheless, certain facial characteristics, including a bulbous nose, pointed chin, ear anomalies, thick eyebrows, long eyelashes, and a broad nasal bridge, have been observed in 35–80% of cases [30]. These traits, along with the features outlined in Table 1, should, therefore, be considered core phenotypic markers of PMS [65–67].

Several authors have reported craniofacial dysmorphisms in patients carrying mutations in the genes TCF20, ALG12, NAGA, CELSR1, and SCUBE1, which are also involved in early craniofacial development in rodents (Table 3) [31,68]. Mutations in CELSR1 contributed to both the development of primary lymphedema and neural tube defects, resulting in cranio-cerebral abnormalities [31,69]. Therefore, in the reported case, CELSR1 may have represented a potential geno-phenotypic link between lymphedema and certain craniofacial abnormalities.

Table 3. Genetic characteristics of craniofacial dysmorphisms in PMS.

Gene	Function	Clinical Phenotypes	Associated Syndromes/Conditions
TCF20	Coactivator of several transcription factors	Severe neurodevelopmental phenotypes, cognitive and motor impairment, autistic features, and ADHD Craniofacial dysmorphisms, macrocephaly, scoliosis, seizures, excessive body growth, muscle hypotonia, strabismus, myopia, keratoconus, and constipation. Recurrent infections	Smith–Magenis syndrome-like phenotype Potocki–Lupski syndrome
ALG12	Encodes for α6-mannosyltransferase	Neurodevelopmental delay Muscle hypotonia, progressive microcephaly, failure to thrive, brain MRI alterations Reduced coagulation factors, and cardiac defects Craniofacial and skeletal abnormalities, strabismus, retinitis pigmentosa	Congenital disorder of glycosylation, type Ig (ALG12-CDG)

Table 3. *Cont.*

Gene	Function	Clinical Phenotypes	Associated Syndromes/Conditions
NAGA	Lysosomal exoglycosidase	Facial dysmorphisms Brain malformations, behavioral dysfunctions, ASD, hyperactivity, delayed speech, and ID	Schindler disease
CELSR1	Cadherin involved in Wnt/PCP pathway	Primary non-syndromic lymphedema Congenital heart defects Neural tube defects Kidney and ureter development issues Arterial thrombosis Kidney injury	
SCUBE1	Expressed in endothelial cells, platelets, liver, kidney, and CNS	Renal tubular cell proliferation Re-epithelialization Obsessive–compulsive disorder Early craniofacial development defects	
PARVB	Codifies for a protein that interacts with ARHGEF6 resulting in the activation of Rho GTPases PARVB have also been associated with overactivation of the AKT-PTEN pathway (macrocephaly)	Macrosomy and macrocephaly	Non-alcoholic fatty liver disease (NAFLD)
SHANK3	Scaffold protein of the postsynaptic density	Craniofacial dysmorphisms Hypotonia, global developmental delay, delayed motor development, absent or delayed speech, and compromised expressive language development Severe intellectual disability, seizures, inappropriate chewing behavior, autistic features, and aggressive behavior	
MLC1	Encodes for a membrane protein similar to voltage-dependent potassium (K^+) channel subunits	Macrocephaly	Megalencephalic leucoencephalophathy with subcortical cysts (MLC1)
SBF1	Involved in phosphoinositide-mediated signaling and membrane trafficking	Microcephaly Neuropathy Strabism Skeletal deformities	Charcot–Marie–Tooth neuropathy type 4 (CMT4B3) Autosomal recessive axonal Charcot–Marie–Tooth disease (AR-CMT2) [31,68]
CHKB	Encodes for choline kinase beta	Muscle wasting Motor and speech delay, severe ID Microcephaly	Congenital muscular dystrophy (CMD), megaconial type

Table 3. *Cont.*

Gene	Function	Clinical Phenotypes	Associated Syndromes/Conditions
TUBGCP6	Encodes for an integral constituent of the centriole, interacts with PLK4 kinase	Abnormalities in neocortical growth and microcephaly Severe ID, retinopathy, brain MRI malformations, and additional neurological deficits	
TRMU	Synthesis of mitochondrial thiouridylase	Infantile-onset liver failure Growth retardation Muscle hypotonia Sensorineural hearing loss	
CYB5R3	Encodes for a cytochrome b5 reductase	Failure to thrive, progressive microcephaly up to, in some cases, hypertonia, and opisthotonus	Recessive congenital methemoglobinemia (RCM)

In a review by Vitrac et al., eight genes within the 22q13 region were associated with microcephaly: CHKB, CYB5R3, SBF1, TUBGCP6, RRP7A, ALG12, ACO2, and NDUFA6. One gene, MLC1, was linked to macrocephaly, while two genes, SHANK3 and TCF20, were associated with both conditions [37]. In-depth studies on individuals with point mutations in SHANK3 documented cases of both microcephaly and macrocephaly [36]. Homozygous recessive mutations in CHKB caused microcephaly without evident structural brain abnormalities [70]. According to Ricciardello et al., the study of interstitial deletions suggests that PARVB haploinsufficiency contributes to macrocephaly and overgrowth, likely through the activation of the PI3K-AKT signaling pathway [31]. Other genomic regions may have been associated with gastrointestinal disorders, ophthalmic features, and epilepsy; although, results across studies were inconsistent [33,71,72].

The diagnostic process for these patients should involve an evaluation by a clinical geneticist, who will perform genetic assessments and dysmorphology examinations to monitor growth, pubertal development, craniofacial features, head size, digits, limbs, skin, spine, and chest and to identify any organ malformations [63]. Additionally, dental anomalies, including malocclusion, are common and may be especially severe in certain cases. Orthodontic or surgical intervention may be necessary to correct malocclusion, helping to reduce the risk of dental caries and periodontal disease, as well as alleviate strain on the temporomandibular joint [32,33,63]. PMS is often subtle at birth and should be considered in cases of unexplained neonatal hypotonia. As a result, prenatal diagnosis has been recommended for healthy parents with affected children, due to the potential for parental germline mosaicism [10].

6. Conclusions

PMS is a rare genetic disorder characterized by highly heterogeneous clinical manifestations. The prevalence of this syndrome is globally underestimated due to the absence of a distinctive phenotype in the lack of significant dysmorphic features. Moreover, in most cases, individuals carrying SHANK3 variants or small deletions do not exhibit specific facial characteristics. Finally, the high genetic and clinical variability complicates the diagnostic process and highlights the current limitations in the genetic mapping of this syndrome. Therefore, diagnostic genetic testing for PMS should be as comprehensive as possible to accurately delineate the full phenotypic spectrum of this disorder. Future studies would benefit from the systematic collection of phenotypic data from patients with a well-characterized genotype, including precise breakpoint positions and exome or

genome sequencing to identify contributory variants elsewhere in the genome or on the preserved copy of 22q13.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app15042195/s1, Table S1: Prisma checklist; Table S2: Prisma flow diagram. References [73,74] are cited in the Supplementary Materials.

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