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# Definition and clinical variability of *SHANK3*-related Phelan-McDermid syndrome

Michael Schön [a,*], Pablo Lapunzina [b], Julián Nevado [b], Teresa Mattina [c], Cecilia Gunnarsson [d], Kinga Hadzsiev [e], Chiara Verpelli [f], Thomas Bourgeron [g], Sarah Jesse [h], Conny M.A. van Ravenswaaij-Arts [i], the European Phelan-McDermid syndrome consortium [i,1], Raoul C. Hennekam [j]

[a] *Institute for Anatomy and Cell Biology, Ulm University, Ulm, Germany*
[b] *Instituto de Genética Médica y Molecular (INGEMM)-IdiPAZ, Hospital Universitario La Paz; CIBERER, Centro de Investigación Biomédica en Red de Enfermedades Raras, ISCIII; ITHACA-European Reference Network, Hospital La Paz, Madrid, Spain*
[c] *Department of Biomedical and Biotechnological Sciences, Medical Genetics, University of Catania, Catania, Italy*
[d] *Department of Clinical Genetics and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Centre for Rare Diseases in South East Region of Sweden, Linköping University, Linköping, Sweden*
[e] *Department of Medical Genetics, Medical School, University of Pécs, Pécs, Hungary*
[f] *CNR Neuroscience Institute, Milano, Italy*
[g] *Génétique Humaine et Fonctions Cognitives, Institut Pasteur, UMR3571 CNRS, Université de Paris Cité, IUF, Paris, France*
[h] *Department of Neurology, Ulm University, Ulm, Germany*
[i] *University of Groningen, University Medical Centre Groningen, Dept Genetics, Groningen, Netherlands*
[j] *Department of Pediatrics, Amsterdam University Medical Center, Amsterdam, Netherlands*

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ABSTRACT

Phelan-McDermid syndrome (PMS) is an infrequently described syndrome that presents with a disturbed development, neurological and psychiatric characteristics, and sometimes other comorbidities. As part of the development of European medical guidelines we studied the definition, phenotype, genotype-phenotype characteristics, and natural history of the syndrome. The number of confirmed diagnoses of PMS in different European countries was also assessed and it could be concluded that PMS is underdiagnosed. The incidence of PMS in European countries is estimated to be at least 1 in 30,000. Next generation sequencing, including analysis of copy number variations, as first tier in diagnostics of individuals with intellectual disability will likely yield a larger number of individuals with PMS than presently known. A definition of PMS by its phenotype is at the present not possible, and therefore PMS-*SHANK3* related is defined by the presence of *SHANK3* haploinsufficiency, either by a deletion involving region 22q13.2–33 or a pathogenic/likely pathogenic variant in *SHANK3*. In summarizing the phenotype, we subdivided it into that of individuals with a 22q13 deletion and that of those with a pathogenic/likely pathogenic *SHANK3* variant. The phenotype of individuals with PMS is variable, depending in part on the deletion size or whether only a variant of *SHANK3* is present. The core phenotype in the domains development, neurology, and senses are similar in those with deletions and *SHANK3* variants, but individuals with a *SHANK3* variant more often are reported to have behavioural disorders and less often urogenital malformations and lymphedema. The behavioural disorders may, however, be a less outstanding feature in individuals with deletions accompanied by more severe intellectual disability. Data available on the natural history are limited. Results of clinical trials using IGF-1, intranasal insulin, and oxytocin are available, other trials are in progress. The present guidelines for PMS aim at offering tools to caregivers and families to provide optimal care to individuals with PMS.

* Corresponding author. Institute for Anatomy and Cell Biology, Ulm University, Albert-Einstein-Allee 11, 89081, Ulm, Germany.
*E-mail address:* michael.schoen@uni-ulm.de (M. Schön).
[1] All members of the consortium are listed in the editorial of this special issue.

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## 1. Introduction

The present study was performed as part of the development of consensus guidelines for Phelan-McDermid syndrome (PMS) (Van Ravenswaaij-Arts et al., 2023, this issue). The consensus guidelines aimed to integrate knowledge from literature with the experience of medical doctors and scientists as well as social science experts, and particularly the experience of family representatives (Landlust et al., 2023, this issue), in order to provide an optimal basis for the diagnosis and treatment of affected individuals. This review summarizes the definition of the syndrome, epidemiology, phenotype, associations between genotype and phenotype, natural history, and an overview of clinical trials and other preclinical treatment studies.

### 1.1. Definition

PMS is a neurodevelopmental disorder (NDD) with a neurological and psychiatric phenotype and diverse additional characteristics, which can vary widely between affected individuals and across life. Although individual case reports have been published earlier on, Phelan and McDermid were the first to describe and summarize the characteristics of larger cohorts of individuals with PMS (predominantly children) (Phelan et al. 1992, 2001). Further cohort studies including those on adults and on the natural history of PMS were published subsequently.

Thus far, the diagnosis of PMS has been based on the presence of genetic alterations on chromosome 22q13 (Koza et al., 2023, this issue). The most common cause is a deletion of varying size ranging from 22q13.2 to 22q13.33 (hereafter indicated as 22q13) although complex rearrangements such as ring chromosome 22 (Jeffries et al., 2005) or other chromosome alterations (Kurtas et al., 2018) exist. These additional anomalies may influence the phenotype (Koza et al., 2023, this issue). Some symptoms correlate with deletion size, but the phenotype, i.e. the presence and severity of the various features, varies widely in the affected individuals, even with similar deletion sizes (see chapter 3.2.). *SHANK3*, encoding the synaptic scaffolding protein SHANK3, has been considered one of the main genes causative for the phenotype and variants in *SHANK3* have been described as cause for PMS as well. *SHANK3* has a prominent role as: 1) It codes for an abundantly expressed protein in the brain and localizes to the postsynaptic compartment of glutamatergic synapses; 2) Laboratory and animal studies show its central role in synaptic integrity and plasticity, and the phenotypes of animal models carrying *Shank3* deletions or variants show phenotypes compatible with PMS (Delling and Boeckers 2021); 3) Most individuals with PMS with a 22q13 deletion are haploinsufficient for *SHANK3*; 4) Balanced translocations with a breakpoint in *SHANK3* (Bonaglia et al., 2001), and intragenic variants, here termed *SHANK3* variants (Durand et al., 2006), exhibit some of the common features and severe manifestations (including language impairment, intellectual disability (ID), behavioural abnormalities) as described for deletion cases (Nevado et al., 2022); 5.) Individuals carrying variants in the other *SHANK* genes, *SHANK1* and *2,* also display developmental delay, ID and/or autism spectrum disorders (ASD), but with less severe symptoms compared to carriers of *SHANK3* variants (Leblond et al., 2014). A more comprehensive analysis of the contribution of *SHANK3* and other genes in the chromosomal region 22q13 is discussed elsewhere in this issue (Vitrac et al., 2023, this issue).

For the present guidelines, we considered first to define PMS by its phenotype. Such definition would allow grouping of parents and caregivers with similar experiences and emotions to share these. This would also facilitate studies in individuals with similar signs, symptoms, and clinical trajectories. It would also allow diagnostics (and treatments) at clinical sites or in circumstances at which cytogenetic or molecular facilities are not available. We realized, however, that the main features of PMS (developmental delay, muscular hypotonia, speech impairment) are non-specific compared to other genetically determined NDD. The external physical phenotype is typically also non-specific, and a combination of signs and symptoms would not allow us to distinguish PMS from other disorders. Therefore, a firm diagnosis based on the phenotype and the clinical history of individuals with PMS is at present not possible. We concluded that PMS should be defined by its genetic cause, i.e. *SHANK3* haploinsufficiency (loss of one functional copy of *SHANK3*) either caused by a deletion of the region 22q13.2–33 or by the presence of a pathogenic/likely pathogenic variant in *SHANK3*. It has been suggested to indicate this group as PMS-*SHANK3* related (Phelan et al., 2022). There is a limited number of individuals reported with interstitial deletions on chromosome 22q13 without loss of *SHANK3* (Disciglio et al., 2014; Mitz et al., 2018; Wilson et al., 2008), in whom the phenotype shows some overlap with PMS. These individuals have been suggested to be indicated as PMS-*SHANK3* unrelated. Elements of this guideline describing this overlap may also be valid for them. This may change if data from cohort studies of sufficient size will become available. We recommend including individuals with PMS-*SHANK3* unrelated at the request of parents or caregivers in patient organizations and in PMS expert centres for medical care. It is justifiable from the caregiver's perspective, scientifically correct, and likely the fastest way to gather data on the phenotype. In the present guideline we use the term PMS for the group of individuals with PMS-*SHANK3* related and indicate specifically if the group with PMS-*SHANK3* unrelated is meant.

## 2. Methods

The focus of the guidelines was mainly based on the results of an international parental survey conducted prior to the guidelines development (Landlust et al., 2023, this issue). The fundamental questions to be addressed by the guidelines were subsequently discussed and developed by a consortium including experts from multiple European countries, again in collaboration with parents of individuals with PMS. The AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010) was used to develop the guidelines.

A comprehensive search was performed using Pubmed and Google as search machines. Keywords were "Phelan-McDermid syndrome" or "22q13 deletion syndrome" as separate terms and combined with the terms "characterization", "epidemiology", "genotype-phenotype correlation", or "natural history". We searched for clinical trials using the site ClinicalTrials.gov. Publications were carefully studied and discussed repeatedly during online conferences. Preliminary drafts were reviewed by all consortium members including patient representatives and discussed in person at a final guidelines consortium conference in Groningen, Netherlands in June 2022.

The guideline will be updated whenever new information becomes available and as long as the Guideline Consortium exists. The most up-to date version will be available on the ERN-ITHACA website (Guidelines - ERN ITHACA (ern-ithaca.eu)). An official revision of the guideline will take place upon request and under the responsibility of the Guideline working group of ERN-ITHACA.

## 3. Results

### 3.1. Epidemiology

Figures on incidence and prevalence are currently limited. There are no reliable long-term population studies to indicate the birth rate for PMS, and nation-wide diagnosis rates depend largely on their health care systems. The recent data on prevalence and incidence are more accurate for children born today than in the past due to an increased awareness of the genetic cause for most developmental disorders and the wide availability of cytogenetic and molecular analyses. However, it can also be assumed that large deletions are detected more frequently, followed by smaller deletions and intragenic *SHANK3* variants the least frequent. A diagnostic algorithm is described elsewhere in this issue (Koza et al., 2023, this issue).

Indirect estimates of the frequency of PMS can be made using figures

on population-based prevalence of ID and ASD if adequate techniques have been used to detect microdeletions and/or *SHANK3* variants. In cohorts with unspecified developmental delay/ID, 0.25–3.33% were identified with PMS (Gong et al., 2012; Ravnan 2006; Tabet et al., 2017; Utine et al., 2009; Xu et al., 2016). In a study of individuals with mild ID, the proportion was 0.69%, and in those with moderate to severe ID 2.1% (Leblond et al., 2014). Detection frequency of *SHANK3* haploinsufficiency in individuals with ASD is variable: 0.19–4.48% (Betancur and Buxbaum 2013; Chen et al., 2017; Cooper et al., 2011; Leblond et al., 2014; Nair-Miranda et al., 2004; Samogy-Costa et al., 2019; Waga et al., 2011). This is due to variable acquisitions, definitions, inclusion criteria, and molecular techniques used, and it is not possible to derive a reliable, widely applicable incidence from these.

We gathered the information from various European countries. Some of the sources are indicated by the last names of consortium members (listed in Van Ravenswaaij-Arts et al., 2023, this issue). The Dutch national data include 65 children and 40 adults known to the single Dutch expert centre in 2022. Stratification of the number of affected individuals detected by all Dutch cytogenetic laboratories with a deletion 22q13.3 in a 5-year period from 2010 to 2014 during which microarray was used as first tier test in children with NDD and ID, allowed an estimate of the incidence of 1 in 30,000 (Van Ravenswaaij, unpublished). This number represents an underestimate because not all individuals with an NDD were examined and PMS could not be identified by microarray due to a *SHANK3* variant. In Spain around 220 patients, mostly below 18 years of age, are known in 2022 (Nevado et al., 2022). In the German expert centre at Ulm university clinic 125 individuals (of whom 22 are adults) have attended from Austria, Switzerland, and Germany until January 2022 (Jesse and Schön, personal communication). The PMS association representing families from Austria, Germany, and Switzerland encompasses approximately 140 families until December 2022 (including 9 from Austria, 9 from Switzerland, 1 from Belgium, and 1 from the Netherlands; Board of the PMS association, personal communication). A French family organization represents 180 families and nearly 100 individuals with PMS have been registered until September 2022 at the Hôpital Robert-Debré and Institut Pasteur in Paris (Tabet and Bourgeron, personal communication). Over 300 families originating from the UK and Ireland are registered with the American PMSF or the partner organization PMSF UK. In Portugal, at least 30 affected individuals are known in October 2022 (Guedes, personal communication) and four individuals with PMS are known in Lithuania in October 2022 (Matulevičienė, personal communication). In Hungary, there are at least six patients diagnosed with PMS (Hadzsiev, personal communication). In Sweden, a survey in October 2022 among medical genetic institutes yielded approximately 50 individuals with PMS, likely representing the prevalence in two-thirds of the total population (Anderlid, personal communication). In Italy, 106 individuals with PMS have been registered until November 2022 at the Scientific Institute IRCCS E. Medea, of whom at least 50 were referred by the Italian PMS family organization (Bonaglia, Mattina, and Verpelli, personal communication). There are currently 26 patients (children and adults) with PMS followed up at the multidisciplinary PMS clinic at the Centre for Human Genetics, University Hospital of Leuven, Belgium. The consortium has no data on the numbers of patients with PMS followed up at the other genetic centres in Belgium (Van Buggenhout, Swillen, and Vogels, personal communication). In summary, well over 1000 individuals with PMS are known in Europe. Based on the frequency in the Netherlands the incidence is estimated to be at least 1:30,000. In most countries the organisation differs from the Dutch way of acting, and reliable country-wide data are lacking. Most likely many individuals with PMS are therefore unrecognized. The use of next generation sequencing techniques, including analysis of copy number variations, as first tier in diagnostics of individuals with ID will likely allow diagnostics to be more complete.

### 3.2. Phenotype and genotype-phenotype correlation

The phenotype in individuals with PMS is very variable, a typical phenotype cannot be discerned. We have summarized the frequencies of phenotypes of the pertinent literature on larger cohort studies in individuals with 22q13 deletions, including those with ring chromosome 22 formation and those with *SHANK3* variants, and excluding case reports (Table 1). Very rarely reported phenotypes are not mentioned in this chapter. There are some less frequently occurring comorbidities that need further research in order to proof a non-coincidental association, and to lead to evidence-based recommendations. An example is the incidentally reported autoimmune hepatitis in PMS. The consortium will study these in the near future and any conclusions arising will be added to the clinical surveillance scheme (Van Eeghen et al., 2023, this issue). New recommendations will be added to the guideline whenever consensus is reached by the consortium. Otherwise they will only be mentioned as “points of attention”. The reliability of the tabulated figures is limited due to small numbers of individuals, and despite efforts not to use potentially biased publications, a bias can still not be excluded. A subdivision based on sex did not show differences (data not shown) (Nevado et al., 2022; Sarasua et al., 2014a; Soorya et al., 2013). The external phenotype typically shows only limited unusual morphological characteristics, and a common pattern of features cannot be discerned (Soorya et al., 2013). The only common characteristics are a marked global developmental delay, especially evident in a marked speech impairment, and muscular hypotonia. Psychiatric disorders or behavioural symptoms, i.e. ASD and to a lesser extent hyperactivity, are common. We realize that, frequently, terminology in various publications is not well defined and that the methodology to diagnose psychiatric disorders is incorrect or not mentioned at all. This hampers comparing results of studies markedly. Next to the differences in terminology, definitions and methodology in diagnostics, we suggest to use continuous scales in symptomatology in ASD as suggested by others (Gillberg, 2010) as this might help in explaining differences in genotype – phenotype as well. Issues regarding psychiatric disorders and behaviour are discussed in more detail elsewhere (Van Balkom et al., 2023, this issue). The data on the various organ-specific characteristics are discussed in the other articles of this issue.

The significance of the various individual genes in region 22q13 is discussed in detail elsewhere in this issue (Vitrac et al., 2023, this issue); here we limit ourselves to the effects of the various genes in genotype-phenotype correlations. In large deletions up to 108 genes may be lost, but the median loss in 22q13 deletions contains approximately 50 genes (Mitz et al., 2018). The key gene is *SHANK3*, which is deleted in most affected individuals. Individuals with interstitial deletions not involving *SHANK3* (PMS-*SHANK3* unrelated) may exhibit a phenotype similar to those involving *SHANK3* (Phelan et al., 2022), which may point either to involvement of genes with a function similar to *SHANK3* or decreased functioning of *SHANK3* due to position effects of the deletion on neighbouring genes. However, we also acknowledge that some parts of the phenotype may not be gene-specific as these are observed in many other entities that go along with NDD. A single study showed that individuals with PMS-*SHANK3* related were more likely to have seizures if the gene alteration was of maternal origin (Sarasua et al., 2014a). Several genes involved in larger deletions (*ACO2*, *NDUFA6*, *TRMU*, *SCO2*, *TYMP*, *CPT1B*) are associated with mitochondrial functioning and have been suggested to be associated with ASD, regression, failure-to-thrive, and exercise intolerance/fatigue (Frye et al., 2016). SHANK3 is not only expressed in the brain, but also in the intestine (James et al., 2019; Wei et al., 2017), skeletal muscle (Lutz et al., 2020), liver, kidney, spleen, thymus (Lim et al., 1999; Redecker et al., 2006), and in neurons of the dorsal root ganglia, which are involved in pain processing (Han et al., 2016).

Several studies found correlations between deletion size and the phenotype (Bonaglia et al., 2011; Jeffries et al., 2005; Levy et al., 2021; Luciani et al., 2003; Sarasua et al., 2011 & 2014a & b; Soorya et al.,

**Table 1**
Main phenotypic findings with frequencies in patients with PMS caused by a deletion of segment 22q13 (irrespective of the mechanism) and those caused by a *SHANK3* variant.

| Sign/Symptom/Diagnosis | HPO | PMS individuals with 22q13 deletions *(%)* | PMS individuals with *SHANK3* variants *(%)* |
|---|---|---|---|
| **Development** | | | |
| Global developmental delay | 0001263 | 493/504 (98%)[2,4,6,7,9,11,12,13,14,15,16,19,20,21] | 48/50 (96%)[5,10,15,20] |
| Marked speech impairment | 0000750 | 507/572 (88%)[2,4,6,7,9,11,12,13,14,15,16,17,18,19,20,21] | 31/44 (70%)[5,10,15,20] |
| **Neurology** | | | |
| Seizures (one or more) | 0001250 | 148/542 (27%)[2,3,4,6,8,9,11,12,13,14,15,16,18,19,20] | 14/53 (26%)[5,8,10,15,20] |
| Hypotonia | 0001252 | 333/451 (74%)[2,4,6,7,9,11,12,13,14,15,16,18,20] | 42/51 (82%)[5,10,15,20] |
| Structural brain anomalies | 0012443 | 118/223 (53%)[1,4,7,8,11,13,15,19,20] | 12/42 (29%)[1,5,8,15,20] |
| **Senses** | | | |
| Vision disturbances | 0000504 | 70/316 (22%)[3,15,17,19] | 9/34 (26%)[5,15] |
| Strabismus | 0000486 | 59/243 (24%)[4,7,9,15,20] | 4/28 (14%)[15,20] |
| Hearing loss | 0000365 | 32/372 (8%)[3,7,11,15,17,18,19,20] | 3/29 (10%)[15,20] |
| Increased pain tolerance | 0010832 | 204/314 (65%)[2,9,15,16,18,20] | 38/48 (79%)[5,15,20] |
| **Behaviour** | | | |
| ASD | 0000729 | 162/282 (57%)[2,3,4,6,9,13,15,17,18,19,20] | 26/33 (79%)[5,10,15,20] |
| Hyperactivity | 0000752 | 33/112 (29%)[4,9,19,20] | 21/29 (72%)[5,20] |
| Aggression | 0000718 | 50/267 (19%)[15,19,20] | 18/49 (37%)[5,10,15,20] |
| Self-injury | 0100716 | 10/80 (13%)[19,20] | 8/27 (30%)[5,20] |
| Sleep disorder | 0002360 | 62/237 (26%)[15,18,20] | 24/46 (52%)[5,15,20] |
| **Internal organs** | | | |
| Gastro-oesophageal reflux | 0002020 | 31/122 (25%)[4,11,18,19,20] | 5/29 (17%)[5,20] |
| Cardiac anomalies | 0001627 | 49/387 (13%)[2,9,11,15,18,19,20] | 3/46 (7%)[5,15,20] |
| Frequent airway infections | 0002205 | 75/280 (27%)[6,9,15,18,20] | 15/47 (32%)[5,15,20] |
| Urogenital problems | 0000119 | 9/62 (15%)[9,11,13,20] | 0/24 (0%)[5,20] |
| Renal abnormalities | 0000079 | 20/137 (15%)[2,18,19] | 0/17 (0%)[5] |
| **Growth** | | | |
| Short stature (height $\leq$ P3) | 0004322 | 37/392 (9%)[2,4,6,7,11,12,14,15,19,20] | 4/41 (10%)[5,15,20] |
| Tall stature (height $\geq$ P98) | 0011407 | 84/392 (21%)[2,4,6,7,11,12,14,15,19,20] | 3/41 (7%)[5,15,20] |
| Macrocephaly (skull circumference $\geq$ P98) | 0000256 | 55/329 (17%)[4,7,9,13,14,15,19,20] | 6/39 (15%)[5,15,20] |
| Microcephaly (skull circumference $\leq$ P3) | 0000252 | 53/329 (16%)[4,7,9,11,13,14,15,19] | 5/52 (10%)[5,15,20] |
| **External phenotype** | | | |
| Dolichocephaly | 0000268 | 84/319 (26%)[2,9,14,15,16] | 2/28 (7%)[5,15] |
| Long eyelashes | 0000527 | 149/312 (48%)[2,7,9,13,15,18,20] | 19/39 (49%)[5,15,20] |
| Down-slanting palpebral fissures | 0000494 | 16/74 (22%)[9,14,18,20] | 3/10 (30%)[20] |
| Periorbital fullness | 0000629 | 69/239 (29%)[9,13,20] | 7/39 (18%)[5,15,20] |
| Ptosis | 0000508 | 62/286 (22%)[2,14,15,16] | 2/28 (7%)[5,15] |
| Epicanthal folds | 0000286 | 122/378 (32%)[2,6,9,13,14,15,16,18,20] | 8/39 (21%)[5,15,20] |
| Ear anomalies | 0000356 | 232/492 (47%)[2,4,6,9,12,13,14,15,16,18,19,20] | 16/41 (39%)[5,10,15,20] |
| Wide nasal bridge | 0000431 | 156/349 (45%)[2,9,13,15,19,20] | 15/42 (36%)[5,10,15,20] |
| Broad nose | 0000445 | 169/349 (48%)[6,9,13,15,18,19,20] | 15/40 (38%)[5,10,15,20] |
| Short philtrum | 0000322 | 22/138 (16%)[9,18,19,20] | 0/21 (0%)[5,20] |
| Thin upper vermillion | 0000219 | 15/56 (27%)[9,18] | 3/11 (27%)[5] |
| Thick lower vermillion | 0000129 | 4/44 (9%)[4,18,20] | 5/21 (24%)[5,20] |
| Malocclusion | 0009102 | 109/297 (37%)[2,15,19] | 10/29 (34%)[5,15] |
| Retrognathia | 0000278 | 29/115 (25%)[7,9,11,19] | 0/31 (0%)[5,20] |
| Pointed chin | 0000307 | 154/309 (50%)[2,6,15,16,18] | 18/29 (62%)[5,15] |
| Large fleshy hands | 0001126 | 180/392 (46%)[2,6,9,14,15,16,19] | 11/28 (39%)[5,15] |
| Clinodactyly 5th finger | 0030084 | 79/405 (20%)[2,9,15,16,18,19] | 10/28 (35%)[5,15] |
| 2-3 Syndactyly of toes | 0001270 | 65/232 (28%)[2,9,13,16,18,19] | 5/11 (45%)[5] |
| Sandal gap | 0001852 | 30/56 (54%)[9,18] | 6/9 (7%)[5] |
| Small/malformed nails | 0001292 | 138/438 (32%)[2,6,9,13,15,16,18,19] | 13/29 (45%)[5,15] |
| Lymphedema | 0001004 | 29/270 (11%)[3,6,7,14,15,18] | 0/34 (0%)[5,15] |
| Eczema | 0000964 | 48/225 (21%)[4,7,15,20] | 14/46 (30%)[5,15,20] |
| Hypohidrosis | 0000966 | 31/84 (37%)[16,18,20] | 2/24 (8%)[5,20] |
| Hyper-extensible joints | 0001382 | 4/18 (22%)[4,13] | 6/10 (60%)[5] |

Only original publications describing earlier unpublished patients have been used (or by excluding those patients), in whom it was clear whether the study participants had a deletion (including those in a ring 22 formation) or a *SHANK3* variant. If participants of a study were (in part) from a patient support group in a country, from which also publications from clinics are available, that study was not used to avoid double counting; in addition, in individuals originating from support groups typically the cause of the PMS was not indicated in detail. Infrequently or rarely described phenotypes are not mentioned. The reported percentages should be considered as the minimal frequencies as signs and symptoms may arise after publication or were not present at the time of examination. Used references are: 1: Aldinger et al., 2012; 2: Bonaglia et al., 2011; 3: Brignell et al., 2020; 4: Denayer et al., 2012; 5: De Rubeis et al., 2018; 6: Dhar et al., 2010; 7: Droogmans et al., 2019; 8: Holder and Quach, 2016; 9: Jeffries et al., 2005; 10: Li et al., 2018; 11: Lindquist et al., 2005; 12: Luciani et al., 2003; 13: Manning et al., 2004; 14: Nesslinger et al., 1993; 15: Nevado et al., 2022; 16: Phelan et al., 2001; 17: Richards et al., 2017; 18: Samogy-Costa et al., 2019; 19: Tabet et al., 2017; 20: Xu et al., 2020; 21: Zwanenburg et al., 2016b. ASD = autism spectrum disorder, HPO = Human Phenotype Ontology, P = percentile, PMS = Phelan-McDermid syndrome.

2013; Tabet et al., 2017) but results are conflicting. In a study of 18 individuals with PMS, a correlation of the deletion size with language impairment but not ASD was described (Ponson et al., 2018). Two other cohort studies also identified a positive association between deletion size and language impairment (Sarasua et al., 2014a & b; Tabet et al., 2017). Tabet et al. (2017) identified a negative association between deletion size and the occurrence of ASD, and reported on an association between particular genomic regions within 22q13 and speech impairment, eye and heart anomalies, gastro-oesophageal reflux, and seizures (Tabet et al., 2017). In a Brazilian cohort, a correlation was found between deletion size and renal abnormalities, lymphedema, and language impairment, but not with ASD (Samogy-Costa et al., 2019). Still others found a correlation between deletion size with hypotonia and developmental delay, but not with language impairment, behavioural problems, and seizures (Luciani et al., 2003). A further study showed a correlation between deletion size and comorbidities including ASD but not with motor skills, language, and repetitive and restrictive behaviours. Lymphedema, asthma, cardiac and renal malformations were only found in large deletions (Soorya et al., 2013). Several candidate genes have been discussed for renal malformations, including *CELSR1*, *FBLN1*, *UPK3A*, and *WNT7B*. In a review study, it was found that larger deletions are significantly more often associated with such abnormalities, especially for deletions with >4 megabases of loss at 22q13 region (McCoy et al., 2022). However, others did not find a correlation between deletion size and organ anomalies nor with ID (Wilson, 2003). Two recent large cohort studies also addressed genotype and phenotype correlations (Levy et al., 2021; Nevado et al., 2022). The latter is one of the largest study to date (n = 210 individuals with PMS, including 21 individuals with a *SHANK3* variant) from Spain. Levy and co-workers (2021) studied data on a series of 170 patients combined from several centres. Both studies showed similar genotype-phenotype correlations. In the Spanish study (Nevado et al., 2022), it was observed that there was a positive correlation of deletion size with brain MRI findings, ear abnormalities, toe syndactyly, while abnormal behaviour correlated negatively. Furthermore, individuals with large deletions were more likely to have macrocephaly, while small deletions were associated with microcephaly. Some individuals also had an interstitial deletion without *SHANK3* involvement (PMS-*SHANK3* unrelated) and still resembled the PMS phenotype indicating again either effects of other dosage-sensitive genes or positional effects on *SHANK3*. Interestingly, some characteristics were more frequent in individuals with *SHANK3* variants, such as sleep disturbances or incontinence. The US study (Levy et al., 2021) subdivided 22q13 deletions in two classes: Class I included small deletions containing *SHANK3* (*SHANK3* in combination with *ARSA* and/or *ACR* and *RABL2B*) – to which the authors added those with *SHANK3* variants; Class II contained all other deletions, so those with a loss of larger regions of chromosome 22. Class I individuals had a less pronounced delay in development and higher cognitive abilities but were more prone to regression of skills and psychiatric disorders. Class II individuals had more often abnormalities of the kidneys, eyes, and spine. Ataxia and muscular hypotonia were also more common. In a study of 22 individuals with PMS (Schenkel et al., 2021), the epigenetic profile was compared between individuals with large deletions (2–5.8 Mb, which includes *BRD1*) and those with small deletions (<1 Mb) or *SHANK3* variants. The group with larger deletion demonstrated a genome-wide hypermethylation, the other group had an unaltered DNA methylation. Individuals with larger deletions were found to have an altered metabolic profile. Further studies in larger groups of individuals are needed to confirm the findings and to study whether the results can be useful in clinical care (Schenkel et al., 2021).

### 3.3. Natural history

The natural history has been documented in only a limited manner in literature, and especially data on older individuals are missing. The latter can be explained by the relative recent availability of genetic techniques allowing reliable molecular genetic diagnostics in PMS individuals. We added data available through (Unique), and experience of the present consortium members. Some descriptions also refer to mainly non-structured descriptions of experts who conducted cohort studies or descriptions of parents or caregivers (Bonaglia et al., 2011; Phelan and McDermid 2011; Zwanenburg et al., 2016b). The descriptions are classified by age level. Problems of one stage can persist in later ages or appear for the first time at these ages, but also in younger ages as well.

#### 3.3.1. Global observations

Female and male individuals display similar phenotypes (Nevado et al., 2022; Sarasua et al., 2014a). Sarasua et al. (2014a) described in a large cohort study that several physical characteristics decrease with age, such as kidney problems, large fleshy hands, full or puffy eyelids, muscular hypotonia, and lax ligaments. Behavioural problems may also subside with increasing age, however, it is unknown whether this is influenced by the consequence of specific psychiatric medications. Other characteristics worsened over time, such as ASD, seizures, abnormal reflexes, cellulitis, and lymphedema (Sarasua et al., 2014a). The decrease of hypotonia over time has been reported by others as well (Levy et al., 2021; Sarasua et al., 2014a). Another study reported that behavioural problems clustered at younger ages, while regression dominated later (Droogmans et al., 2019). Regression, particularly of language skills, is repeatedly reported. However, there is no consensus on this. Children benefit from communication support and language therapy, but limitations usually persist throughout their lives (Burdeus-Olavarrieta et al., 2023, this issue). The main phenotypes discussed hereinafter are described in detail in the other publications of this issue. Frequencies reported in literature on large cohort studies are summarized in Table 1.

#### 3.3.2. Pregnancy

Pregnancies and births of children with PMS are usually uneventful, malformations are only infrequently detected by ultrasound or present at birth. In case of an organ malformation the further work-up may allow detection of a 22q13 microdeletion or *SHANK3* variant and PMS may be diagnosed this way.

#### 3.3.3. Newborn period

Newborns usually look healthy and have growth parameters within normal values. The limited facial morphological signs are non-specific and typically the child resembles the parents. The main symptom that can be present is muscular hypotonia, sometimes recognizable as a so-called floppy infant. This may go along with feeding problems.

#### 3.3.4. Infancy and childhood

The hypotonia remains present in most cases and may lead to delayed achievement of motor milestones, although others may reach these at a normal age. Balance and gait may be disturbed, and also the fine motor skills are commonly affected. Later on, this will influence self-care such as dressing and feeding independently. Growth is disturbed (decrease or increase) in only a small minority of affected children. Upper airway infections are frequent in some patients. Gastrointestinal problems such as swallowing, gastro-intestinal reflux, and constipation or diarrhoea are commonly present in the children (Matuleviciene et al., 2023, this issue). Toilet training is often delayed and usually only partially successful.

Almost invariably marked delay of cognitive, language, social and emotional development is noted, with progress in these developmental domains remaining slow (Zwanenburg et al., 2016b). Usually children are unable to attend mainstream schools but do benefit from schools for children with special needs and constant support. In particular, expressive language development is and remains delayed. Receptive language can function at a higher level (Burdeus-Olavarrieta et al., 2023, this issue). Limited abilities to express their needs may lead to frustration, but in general the children are described by their parents as happy, sociable, friendly, and affectionate. Sensory processing

difficulties may be prominent, such as altered reactivity to tactile stimuli, panic reactions to loud noises or rapid movements, and increased pain tolerance (Walinga et al., 2023, this issue). Hypo- or hyperreactivity or increased interest to sensory stimuli is also found in ASD. A fraction of the infants and children may show clinical symptoms, such as repetitive behaviour, sensory issues, poor eye contact, and reduced social communication, that may fit for a diagnosis of ASD (Van Balkom et al., 2023, this issue).

#### 3.3.5. Puberty and adolescence

Puberty usually starts at a normal age, but can also be precocious or delayed. At this age, seizures become more frequent (De Coo et al., 2023, this issue), as does lymphedema (Damstra et al., 2023, this issue), although both occur in a minority of affected individuals. Onset of sleep disturbances (Cáceres San José et al., 2023, this issue), psychiatric disorders such as bipolar disorder or catatonia have also been described in some cases (Van Balkom et al., 2023, this issue). Major physical problems are uncommon.

#### 3.3.6. Adulthood

Adults with PMS have typically a normal height and limited physical problems, but remain commonly markedly globally delayed in their cognitive development. Mood disorders such as bipolar disorders have been reported at this age (Denayer et al., 2012; Egger et al., 2016; Van Balkom et al., 2023, this issue) but due to small numbers in studies and diagnostic difficulties especially in patients with global developmental delay, the true frequency of some psychiatric disorders remains uncertain. No firm data on fertility are available but the occurrence of several couples of affected (mosaic) parent and child seemingly indicate that fertility can be present (Tabet et al., 2017; Wilson et al., 2008). Data on the disorders that are common in the general population such as cardiovascular problems and cancer, and on disorders common in aged individuals in general, are not available. An exception is the increased frequency of NF2-related tumours in individuals with a ring chromosome 22 (Koza et al., 2023, this issue; Nevado et al., 2022; Ziats et al., 2020). There are no data on life expectancy in PMS. However, it can be assumed that it can be diminished, as generally observed in ID. This is partly due to a lack of awareness of health-related behaviour, including healthy diet and physical exercise, and consequences of the drug treatment (often polypharmacy in individuals with ID).

### 3.4. Note on COVID-19 in PMS

There are only limited data on the consequences of COVID-19 infections and vaccination in individuals with PMS, but no aggregated data. Individuals with developmental problems, cognitive impairment, and some syndromic disorders have been reported to be more prone to a severe course of a COVID-19 infection (WHO SAGE roadmap for prioritizing use of COVID-19 vaccines, updated 21st January 2022; Dutch COPP LUMC study). The cause for this is likely the combined consequences of behaviour, altered anatomy, impaired immunity, and altered reactions on management. Risks vary between individuals, and usually it is not possible to determine the exact risk of an individual. Therefore, it is prudent to classify an individual with PMS having an increased risk for a severe course of a COVID-19 infection, as was done in some countries (Dutch Health Council; German epidemic surveillance authority Robert Koch Institute with the advisory vaccination expert committee STIKO). There is no indication that vaccination is less effective in an individual with PMS. Obviously, situations differ in various countries, and vaccination guidelines of the national vaccination and epidemic protection authorities should be followed.

### 3.5. Clinical trials in Phelan-McDermid syndrome

There is currently no standard policy to use specific drugs in PMS for the main characteristics developmental delay, ID, behavioural problems, and psychiatric disorders (Van Balkom et al., 2023, this issue). At the present pharmacologic treatment should be considered on the basis of individual presentation and considerations. Individuals with PMS ideally receive PMS-specific multidisciplinary care, especially in a centre of expertise for PMS (Van Eeghen et al., 2023, this issue). Three randomized controlled clinical trials (RCT) in humans with PMS have been reported in the literature that investigated the effect of intranasally administered insulin Zwanenburg, subcutaneously administered insulin-like growth factor 1 (IGF-1), and intranasal oxytocin on development and/or behaviour (Fastman et al., 2021; Kolevzon et al., 2014; Zwanenburg et al., 2016a), respectively. Insulin and IGF-1, in addition to their function as hormones in the systemic circulation, function as neurotrophic factors in the brain. Both bind to the same receptors, but with a different affinity. Amongst a number of functions, the insulin/IGF-1 pathway is involved in the formation of dendritic spines and synaptic connections (Lee et al., 2011). Synapse formation is impaired in PMS due to reduced expression of SHANK3. Oxytocin is a hormone that influences social behaviour presumably through involvement of the dopaminergic pathway (DeMayo et al., 2017).

#### 3.5.1. IGF-1

The first clinical pilot study of testing the efficacy of subcutaneous IGF-1 injections included nine children (5–15 years) with PMS and showed a positive effect on social and restrictive behaviour in daily life (Kolevzon et al., 2014). The intervention consisted of twice-daily subcutaneous IGF-1 injections or saline (as placebo) for a period of 12 weeks, followed by 4 weeks without treatment (wash out), and then another 12 weeks of treatment. Using the Aberrant Behaviour Checklist (ABC) and the Repetitive Behaviour Scale (RBS), treatment with IGF-1 showed a significant decrease on the subscale of socially withdrawn behaviour and on the subscale of restrictive behaviour (Kolevzon et al., 2014).

An RCT was completed in 2016 (ClinicalTrials.gov, NCT01525901; Kolevzon et al., 2022). Ten children (5–9 years) with PMS were randomized to receive IGF-1 or placebo (saline) using a 12-week, double-blind, crossover design. Results measured by the Aberrant Behaviour Checklist - Social Withdrawal (ABC-SW) subscale and core symptoms of ASD were analysed together with the results of the previous study described above (combined n = 19). Results on the ABC-SW did not reach statistical significance, however, significant improvements in sensory reactivity symptoms were observed. IGF-1 treatment also led to significant improvements in repetitive behaviours and hyperactivity (Kolevzon et al., 2022).

#### 3.5.2. Intranasally administered insulin

The first clinical pilot study testing the efficacy of intranasal administered insulin included six children with PMS and showed positive effects on motor activity, cognitive function, non-verbal communication, and autonomy (Schmidt et al., 2008). However, this study was not blinded or placebo-controlled. An RCT in 25 children (1–16 years) using a daily dose of intranasal insulin or intranasal albumin (as placebo) in a stepped wedge design, measured 6-monthly the increase in developmental age in terms of development and development of behaviour, using various instruments: Bayley–III–NL or WPPSI-III-NL, Vineland screener 0–6, and the Experimental Scale for the assessment of the Social - Emotional Development Level (ESSEON) (EU Clinical Trials Register, 2012-002873-77; Zwanenburg et al., 2016a). During intranasal insulin use a significant increase in developmental age was seen for most developmental domains, while without insulin this was only significant in three domains. The effect on cognition and social skills was more prominent in the subgroup of children older than 3 years (Zwanenburg et al., 2016a). Currently, intranasal insulin is offered as treatment under specific conditions via the centres of expertise for PMS in the Netherlands and in Germany.

#### 3.5.3. Oxytocin

In an RCT in 18 children (5–17 years) with PMS (ClinicalTrials.gov, NCT02710084; Fastman et al., 2021), participants were randomized to receive intranasal oxytocin or placebo (intranasal saline) and underwent treatment during a 12-week double-blind, parallel group phase, followed by a 12-week open-label extension phase, during which all participants received oxytocin. Efficacy was assessed using the primary outcome of the ABC-SW subscale as well as a number of secondary outcome measures related to the core symptoms of ASD (Fastman et al., 2021). The study revealed no statistically significant improvement with oxytocin as compared to placebo.

#### 3.5.4. Future studies

Currently, approximately ten treatment studies are outlined at ClinicalTrials.gov including three trials (December 2022) actively recruiting participants (drugs: growth hormone, lithium, and NNZ-2591). Based on the preliminary effects of the IGF-1 study, a new pilot study has been performed with recombinant human growth hormone (rhGH), which is known to stimulate IGF-1 release (Sethuram et al., 2022; ClinicalTrials.gov, NCT04003207). Daily rhGH administration for 12 weeks in six children with PMS resulted in an increase of IGF-1 levels by two standard deviations and was associated by a clinical improvement in social withdrawal, hyperactivity, and sensory symptoms. Larger and placebo-controlled studies with rhGH are needed to confirm the positive clinical effects.

Based on preclinical research, there are a number of other drugs that are applied for developmental and behavioural problems. Valproic acid is prescribed for certain types of epilepsy or bipolar disorder and research in the brains of zebrafish has shown that valproic acid increases certain isoforms of *Shank3* mRNA (Liu et al., 2016). Valproic acid and lithium – the latter being a compound to treat mood disorders – have been shown to increase *SHANK3* mRNA expression in neurons derived from human stem cells (Darville et al., 2016; Lutz et al., 2020). Treatment with lithium reduced the excess of grooming in *Shank3* mutant mice (Tatavarty et al., 2020), and also the severity of the autism traits in an individual with PMS (Darville et al., 2016). Another case series (n = 18) also showed that mood stabilizers, such as lithium or valproic acid, supplemented with an antipsychotic (e.g. quetiapine), had a positive effect on functioning and mood when there was a bipolar disorder in addition to PMS (Egger et al., 2016). In 2022, an RCT with lithium started in France (ClinicalTrials.gov, Lisphem NCT04623398).

Currently, several studies are exploring gene therapy approaches addressing *SHANK3*. To the consortium's knowledge, all studies are still in the preclinical stage.

#### 3.5.5. Considerations

Insulin nasal spray treatment showed an improvement in development, but the statistical significance could not be demonstrated for all domains in the small study group (n = 25) (Zwanenburg et al., 2016a). Since any increase in skills is of interest to the person with PMS and their environment, a trial treatment within a centre of expertise is offered in the Netherlands according to the Dutch guideline (Dutch guideline on PMS, 2018). The results of the trial treatment are continuously monitored by the centre of expertise. The administration of insulin through the nose is safe, non-invasive, and has no adverse systemic effects, while potential local side effects are limited (nose bleeds).

The European consortium is of the opinion that there is currently insufficient evidence for a positive effect of IGF-1 on development and behaviour in individuals with PMS to recommend it outside a research environment, so in clinical practice, also taking into account the burden of the invasive administration.

## 4. Discussion: considerations and conclusions

- Almost invariably, the diagnosis of PMS is clinically not possible.
- PMS is defined in this guideline by the involvement of *SHANK3* on chromosome 22q13 (PMS-*SHANK3* related).
- Available data on the frequency of PMS are limited but the incidence can be estimated to be at least 1:30,000.
- PMS is underdiagnosed. We advocate to perform next generation sequencing, including analysis of copy number variations, in all individuals with ID and/or ASD.
- The phenotype in individuals with PMS is variable. The most commonly present symptom is a marked global developmental delay.
- Several associations between the size of the deletion and patient characteristics have been reported in individuals with PMS, but inconsistency of study results does not allow to draw firm conclusions.
- The available data on signs and symptoms of PMS is still limited, and participation of individuals with PMS, their families, and other caregivers in gathering such data should be encouraged.
- There are limited reliable data on natural history. Life expectancy does not seem to be limited if comorbidities are controlled. Some phenotypes occur age-specifically, but may also appear or disappear at other ages.
- To improve our knowledge on PMS, longitudinal cohort studies with a centralized registration would be beneficiary. This registration should not only include follow-up data, but also data on participation in trials and data on the effect of clinical treatments allowing to optimize clinical care.
- The current state of studies on therapies for PMS should be reviewed regularly by the centres of expertise in order to allow individuals to benefit from new treatments or to participate in new trials.

## 5. Recommendations as agreed upon by the European Phelan-McDermid syndrome consortium

Enrolment in a clinical treatment trial may be considered and discussed with individuals with PMS (if possible) or their representatives.

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## Disclosure of conflict of interest

The authors declare no conflict of interest.

## CRediT authorship contribution statement

**Michael Schön:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Pablo Lapunzina:** Writing – review & editing. **Julián Nevado:** Writing – review & editing. **Teresa Mattina:** Writing – review & editing. **Cecilia Gunnarsson:** Writing – review & editing. **Kinga Hadzsiev:** Writing – review & editing. **Chiara Verpelli:** Writing – review & editing. **Thomas Bourgeron:** Writing – review & editing. **Sarah Jesse:** Conceptualization, Writing – review & editing. **Conny M.A. van Ravenswaaij-Arts:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Raoul C. Hennekam:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

## Data availability

No data was used for the research described in the article.

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