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Landlust, Annemiek M.; Koza, Sylvia A.; Carbin, Maya; Walinga, Margreet; Robert, Sandra; Cooke, Jennifer; Vyshka, Klea; the European Phelan-McDermid syndrome consortium; van Balkom, Ingrid D.C.; van Ravenswaaij-Arts, Conny

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Parental perspectives on Phelan-McDermid syndrome: Results of a worldwide survey

Annemiek M. Landlust [a,b,1,*], Sylvia A. Koza [b,1], Maya Carbin [c], Margreet Walinga [b], Sandra Robert [d], Jennifer Cooke [e], Klea Vyshka [f], the European Phelan-McDermid syndrome consortium, Ingrid D.C. van Balkom [a,g], Conny van Ravenswaaij-Arts [a,b]

[a] Autism Team Northern-Netherlands, Jonx, Department of (Youth) Mental Health and Autism, Lentis Psychiatric Institute, Groningen, the Netherlands
[b] University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, the Netherlands
[c] Phelan-McDermid Association, the Netherlands
[d] (Swiss Representative of) Phelan-McDermid-Gesellschaft e.V. Geschäftsstelle Universitätsklinikum Ulm, Sekretariat Neurologie, Ulm, Germany
[e] Forensic and Neurodevelopmental Sciences Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, United Kingdom
[f] ERN ITHACA Guideline Working Group, ERN ITHACA Project Management & Legal Office, Clinical Genetics Department, Robert Debré University Hospital, Paris, France
[g] Rob Giel Research Centre, Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

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ABSTRACT

Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder characterised by hypotonia, speech problems, intellectual disability and mental health issues like regression, autism and mood disorders. In the development, implementation and dissemination of a new clinical guideline for a rare genetic disorder like PMS, the parental experienced perspective is essential. As information from literature is scarce and often conflicting the European Phelan-McDermid syndrome guideline consortium created a multi-lingual survey for parents of individuals with PMS to collect their lived experiences with care needs, genotypes, somatic issues, mental health issues and parental stress. In total, we analysed 587 completed surveys from 35 countries worldwide. Based on parental reporting, PMS appeared to be caused by a deletion of chromosome 22q13.3 in 78% (379/486) of individuals and by a variant in the *SHANK3* gene in 22% (107/486) of the individuals. Parents reported a wide variety of developmental, neurological, and other clinical issues in individuals with PMS. The most frequently experienced issues were related to speech and communication, learning disabilities/intellectual disability, and behaviour. While most reported issues were present across all age groups and genotypes, the prevalence of epilepsy, lymphoedema, and mental health issues do appear to vary with age. Developmental regression also appeared to begin earlier in this cohort than described in literature. Individuals with PMS due to a 22q13.3 deletion had a higher rate of kidney issues and lymphoedema compared to individuals with *SHANK3* variants. Parental stress was high, with specific contributing factors being child and context related in accordance with the PMS phenotype. The survey results led to various validated recommendations in the European PMS guideline including an age specific surveillance scheme, specific genetic counselling, structured healthcare evaluations on sleep and communication and a focus on family well-being.

1. Introduction

This paper presents the results of a worldwide parental survey and is part of the series of papers that make up the European consensus guideline for Phelan-McDermid syndrome (van Ravenswaaij-Arts et al., 2023; this issue). Phelan-McDermid syndrome (PMS), also known as 22q13.3 deletion syndrome (OMIM #606232), is a rare neurodevelopmental disorder characterised by hypotonia, absent or delayed speech and moderate to severe intellectual disability (ID). Approximately 65% of individuals with PMS are also diagnosed with Autism Spectrum Disorder (ASD) (Oberman et al., 2015; Schön et al., 2023, this issue) and other mental health issues such as mood disorders (van

* Corresponding author. Autism Team Northern-Netherlands, Jonx, Lentis, Laan Corpus den Hoorn 102-2, 9728, JR Groningen, the Netherlands.
E-mail address: a.landlust@lentis.nl (A.M. Landlust).
[1] These authors contributed equally to this manuscript.

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Balkom et al., 2023, this issue). PMS can be caused by a deletion in 22q13.3, containing the *SHANK3* gene, or by a pathogenic variant in *SHANK3* (Koza et al., 2023, this issue; Vitrac et al., 2023, this issue). Following a recent proposal on nomenclature, the European guideline focuses on "PMS-*SHANK*3 related", which refers to the subgroup of PMS individuals with either a deletion 22q13.3 including the *SHANK3* gene or a pathogenic variant in *SHANK3* (Phelan et al., 2022).

Information on care needs, genotype-phenotype relationships, somatic issues, mental health issues and parental stress in PMS is scarce and often conflicting, with earlier studies hampered by methodological issues such as limited participant numbers (Vogels et al., 2021; Kohlenberg et al., 2020 & Droogmans et al., 2019). Nevertheless, this information is indispensable in rare disorders, where lack of expert knowledge can cause diagnostic delay, improper and inconsistent care, and patient disempowerment. Parents (i.e. caretakers) are the experts regarding the specific needs of their child in day-to-day and clinical care (Droogmans et al., 2019). The European consensus guideline is a best clinical practice guideline for individuals with PMS and their families based on the AGREE II methodology (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010) that aims to improve the quality of practice guidelines. In developing a clinical guideline for a rare genetic disorder, the parental experience perspective is essential (Brouwers et al., 2010; Armstrong et al., 2018). Armstrong et al. (2018), in particular, describe the positive impact of patient and public involvement (PPI) in the development, implementation and dissemination of clinical practical guidelines. To ensure a validated guideline for clinical practice, the European PMS guideline consortium created a multi-lingual survey for parents of individuals with PMS to obtain information based on their lived experience (Frechette et al., 2020, Armstrong et al., 2017; Shippee et al., 2015 & Tong et al., 2012) on care needs, genotypes, somatic issues, mental health issues and parental stress. In this research report we describe the results of the survey, based on 587 responses, which formed the starting point for the recommendations for clinical care in individuals with PMS and their families, that are described elsewhere in this special issue.

2. Methods

2.1. Procedure

A parental survey was created by members of the European PMS guideline consortium (van Ravenswaaij-Arts et al., 2023; this issue) and reviewed by all consortium members, including lived-experience representatives from 12 European countries. The survey was developed in English and forward-backward translated in nine additional languages: French, German, Italian, Dutch, Spanish, Portuguese, Swedish, Lithuanian, and Hungarian. The languages chosen were influenced by the active involvement of native speaking patient and professional representatives with those languages within the consortium, allowing for access to patient organizations and/or active support groups in those countries for distribution of the survey.

In May 2021, links to and instructions for the survey were sent to various European PMS parent support groups as known to Orphanet (https://www.orpha.net/consor/cgi-bin/index.php) and Unique (https://rarechromo.org/), as well as the PMSFoundation located in the US (https://pmsf.org/) and all groups were asked to distribute the survey. The survey was also promoted by consortium members and on the websites of support groups, and social media (Facebook parent groups). The survey was open from 1 May2021, until 29 November2021.

2.2. Content of the survey

As no validated questionnaires specific for PMS were available the survey was specifically designed for this project (See supplements). It consisted of 35 questions divided into four sections: general, diagnosis, clinical features & support, and the Genetic Syndrome Stressors Scale (GSSS). The GSSS consists of 14 four-point Likert scales that measure parental stress factors related to their child's genetic syndrome (0 = Not stressful, 1 = A little stressful, 2 = Moderately stressful and 4 = Extremely stressful). It has good face validity and internal consistency and moderately good concurrent validity (Griffith et al., 2011). The consortium also added an extra question about stress due to specific communication problems in PMS. The first three sections of the survey included multiple-choice questions and open questions, and the survey closed with a comment field on which topic was most crucial to include in a PMS guideline. Some questions required obligatory answers to complete the survey. The survey was anonymous; parents had to fill in their country of residence and their child's sex, and year of birth. The survey in English can be found in the Supplements.

2.3. Participants and data analysis

The survey was completed by 587 participants from 35 countries representing all continents except Antarctica. Surveys were included in the analysis if they were completed by parents and caretakers of individuals with PMS (all possible ages and genetic backgrounds: simple deletion, unbalanced translocation, ring 22, and *SHANK3* pathogenic variant). Duplicate surveys, defined as >95% match in answers, if sex, country, year of birth, and age at diagnosis matched 100%, were excluded. Survey information was given by parents and answers were not cross-referenced with for instance databases with genetic information. Blanks were registered as missing values. Statistical analysis was performed using SPSS 11.0 for Windows with Chi-square test and post-hoc analysis.

3. Results

3.1. Participants

For 98% of the individuals, parents completed the survey based on their experiences and observations of their children (577/587). The remaining surveys were completed by a grandparent, sibling, or someone else. Table 1 provides an overview of the characteristics of the individuals with PMS.

3.2. Access/level of care

Regarding level of care, 171 (29%) individuals received care at a local or regional hospital, 150 (26%) at an academic or university hospital, 55 (9%) at a centre of expertise for PMS, and 22 (4%) at a centre of expertise for rare syndromes. "Other" was the answer chosen for 185 individuals (32%). Significantly fewer individuals in South America (2%) received care in an academic/university hospital as compared to North America (25%), Northern & Western Europe (36%), and Southern & Eastern Europe (39%) ($p < 0.000$ for all pairwise comparisons). Significantly more individuals in South America (71%) received care outside of a hospital ("other") compared to North America (34%), Northern & Western Europe (28%), and Southern & Eastern Europe (24%) ($p < 0.000$ for all pairwise comparisons) (Fig. 1.). The percentage of individuals who received treatment at a local/regional hospital or a centre of expertise for PMS/rare syndromes did not differ significantly among the continents ($p = 0.41$, $p = 0.13$).

At a local/regional level of care, 12% of parents reported always experiencing timely and adequate communication among healthcare providers. This was 15% at academic/university hospitals, 17% at centres of expertise for PMS/rare syndromes, and 7% when care was not at a hospital ("other"). The level of care did not influence timely and adequate communication ($p = 0.17$). Significantly fewer parents from South America (2%) reported experiencing timely and adequate communication among healthcare providers, compared to parents from North America (17%), Northern & Western Europe (16%), and Southern & Eastern Europe (14%) ($p = 0.001$, for all pairwise comparisons). The

Table 1
Characteristics of the individuals with PMS.

	N (%) Total N: 587	Median age in years (Range)
Age at completion survey		12 (0–60)
Age at diagnosis		3 (0–59)
Sex (n = 585)		
Male	256 (44%)	
Female	329 (56%)	
Reported Intellectual Quotients of individuals >2 years (n = 302):	N (%)	
>90	14 (5%)	
70–90	16 (5%)	
50–70	57 (19%)	
<50	215 (71%)	
Continents (Fig. S1):		
North America	196 (33%)	
-United States[a]	174 (30%)	
Northern & Western Europe	187 (32%)	
-Germany[a]	67 (11%)	
Southern and Eastern Europe	96 (16%)	
South America	68 (12%)	
-Brazil[a]	62 (11%)	
Oceania	26 (4%)	
Asia	10 (2%)	
Africa	4 (<1%)	

Note: N, sample size.
[a] = Country with the most completed surveys for that continent.

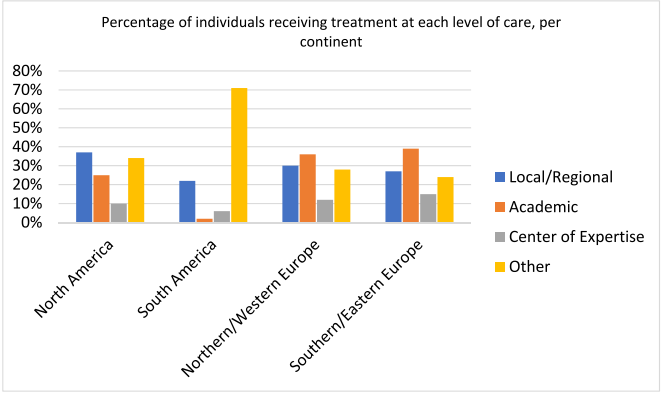

Fig. 1. Percentage of individuals receiving treatment at each level of care, per continent.

rest of the comparisons were not statistically significant (Fig. 2).

3.3. Genotype

Significantly fewer parents from South America (51%) were well-informed regarding the genotype of their child as compared to parents from North America (79%), Northern & Western Europe (75%), and Southern & Eastern Europe (76%) ($p < 0.000$, for all pairwise comparisons). Other comparisons did not show any statistically significant results.

The genotype was known by parents in 486/587 individuals (83%). Deletions were more common (379/486; 78%) than *SHANK3* pathogenic variants (107/486; 22%). In 328/379 individuals (87%), the underlying cause of the 22q13.3 deletion was known. A simple 22q13.3 deletion not caused by a translocation or a ring chromosome 22 was present in 245/379 (65%), while 43/379 had a ring chromosome 22 (11%), and 40/379 had an unbalanced translocation (11%) (Fig. 3).

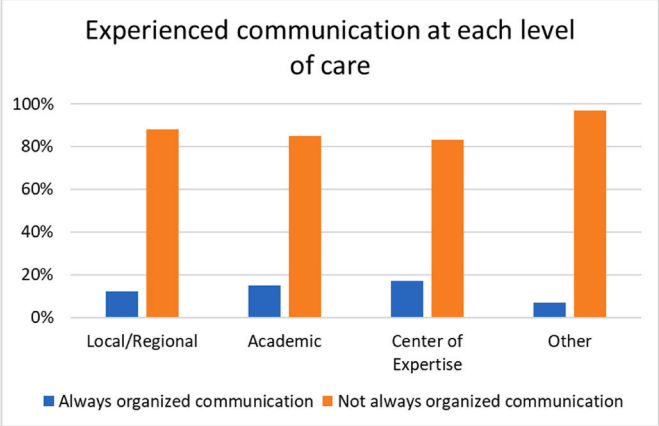

Fig. 2. Percentage of respondents reporting that the communication they experienced at each level of care was always organised or not always organised.

Most parents received genetic testing (404/587; 69%), which found an abnormal result in 20/404 parents (5%). Out of the 32 individuals with an unbalanced translocation whose parents were tested, 16 had a parent who was carrier of a balanced translocation (50%). Three individuals with a *SHANK3* variant had a parent who was a carrier of a mosaic *SHANK3* variant (3/79; 4%). One individual with a simple 22q13.3 deletion had a parent who was a carrier of a mosaic 22q13.3 deletion (1/243; <1%).

3.4. Phenotype

The most frequently reported issues in individuals with 22q13.3 deletions and *SHANK3* variants were divided into six categories (development, neurology, senses, behaviour, gastrointestinal issues, and other), that are presented in Table 2, ranked from most frequent to least frequent. Table 2 also shows the prevalence described in literature and delineated by Schön et al. (2023, this issue). Approximately two-thirds of individuals (64%) had at least one issue occurring in adulthood (later in life in the survey), most frequently loss of previously acquired skills (regression) (49%), and mood issues (e.g., catatonia) (34%). Neuro Fibromatosis tumours type 2 (NF2) which are a known complication of ring chromosome 22, were seen in 2/43 (5%) individuals with PMS due to a ring chromosome 22. Significant differences between individuals with deletions and *SHANK3* variants are marked in Table 2. The column total in Table 2 is referring to all respondents; deletions, *SHANK3* variants and unknown aetiology.

3.5. Influence of genotype on the phenotype

Parents of individuals with 22q13.3 deletions reported hypotonia, issues with gross motor skills, heart issues, kidney issues, issues with feet, and lymphoedema significantly more often than parents of individuals with *SHANK3* variants (Table 2). Parents of individuals with *SHANK3* variants reported a higher prevalence of issues in speech and communication and regulating body temperature than is reported in literature. Parents of individuals with 22q13.3 deletions reported a higher prevalence of sleeping issues than reported in literature. Results from parental report indicate individuals with SHANK3 variants had significantly higher rates of anxious and aggressive behaviour than individuals with a deletion. *Influence of age on phenotype.*

The sample was divided into four age groups according to calendar age at the time of the survey (see Table 3). The prevalence of hypotonia decreased with age, while the prevalence of epilepsy, sleeping issues,

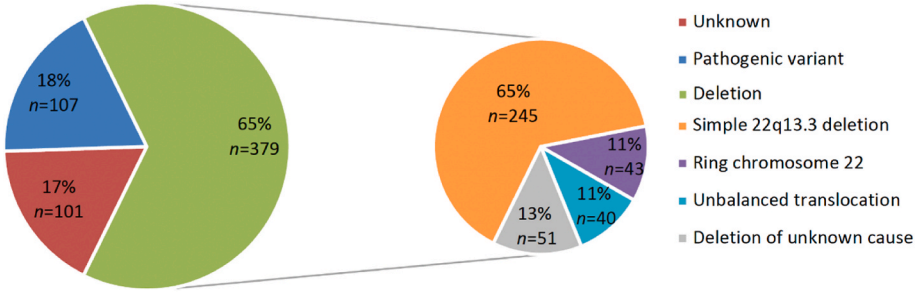

Fig. 3. Genotype of individuals with PMS. Pie chart at left shows the genotype of all individuals, the right chart specifies the cause of deletions.

Table 2
Problems and symptoms reported in individuals with PMS.

(Somatic) problem/symptom	Prevalence, 22q13.3 deletions (n = 377, 2 missing)	Prevalence 22q13.3 deletions Schön et al.	Prevalence *SHANK3* variants (n = 107)	Prevalence, *SHANK3* variants Schön et al.	Prevalence all genotypes (n = 584, 3 missing)	Chi^2 p-value
Development						
Problems with speech and communication	97%	88%	94%	70%	97%	n.r.
Learning difficulties or intellectual disability	94%	98%	96%	96%	95%	n.r.
Neurology						
Problems with fine motor skills (including hand movements)	84%	n.r.	79%	n.r.	83%	n.r.
Low muscle tone (hypotonia)	81%*	74%	66%*	82%	77%	0.002*
Problems with gross motor skills (such as clumsy walking)	77%*	n.r.	63%*	n.r.	74%	0.003*
Epilepsy	25%	27%	33%	26%	25%	n.s.
Senses						
Low pain perception/high pain threshold	76%	65%	82%	79%	78%	n.s.
Problems with regulating body temperature	49%	37%	49%	8%	47%	n.s.
Problems with eyes and vision	30%	22%/8%	24%	26/10%	28%	n.s.
Gastrointestinal problems						
Constipation	46%	n.r.	41%	n.r.	48%	n.r.
Swallowing difficulties	33%	n.r.	33%	n.r.	33%	n.r.
Problems with teeth	31%	37%	24%	34%	30%	n.s.
Vomiting	17%	25% GERD	15%	17% GERD	16%	n.s.
Other						
Behavioural problems (generally)	70%	n.r.	78%	n.r.	71%	n.r.
Sleeping problems	57%	26%	64%	52%	59%	n.s.
Problems with feet	37%*		20%*		34%	0.001*
Problems with the kidneys and urinary tract	17%*	15%	9%*	0%	16%	0.048*
Heart problems	9%*	13%	2%*	7%	7%	0.015*
Lymphoedema	13%* (n = 371)	11%	3%* (n = 101)	0%	11%	0.004*
Behavioural problems (Median age 12, 0–60)	**Prevalence, 22q13.3 deletions (n = 376)**		**Prevalence *SHANK3* variants (n = 106)**		**Prevalence (n = 583, 4 missing)**	
Problems with attention and concentration	82%	57% (ASD)	80%	79% (ASD)	80%	n.s.
Problems with flexibility and adapting to changes	52%	57% (ASD)	45%	79% (ASD)	50%	n.s.
Hyperactivity	44%	29%	49%	72%	46%	n.s.
Anxious behaviour	37%*	n.r.	54%*	n.r.	41%	0.001*
Obsessions	33%	n.r.	42%	n.r.	35%	n.r.
Aggression	18%*	19%	34%*	37%	22%	0.001*
Self-injurious behaviour	16%	13%	19%	30%	17%	n.s.
Depressed behaviour	12%	n.r.	18%	n.r.	12%	n.r.
Other behavioural problems	10%	n.r.	15%	n.r.	12%	n.r.
No behavioural problems	10%	n.r.	8%	n.r.	10%	n.r.

Note: n, sample size; * = variables that show a significant difference with $p < 0.005$ according to Chi^2,/ = separate problems; GERD = gastroesophageal reflux disease; ASD = Autism Spectrum Disorder; n.r. = not reported; n.s. = not significant.

Table 3
Phenotypes that differ significantly per age group.

Problem/ symptom	0–4 years (n = 86)	5–12 years (n = 227)	13–18 years (n = 119)	>18 years (n = 156)	Chi^2 P value
Hypotonia	90%	77%	73%	70%	p = 0.000
Epilepsy	9%	19%	23%	43%	p < 0.000
Sleeping problems	41%	55%	62%	73%	p = 0.000
Loss of skills (regression)	30%	44%	51%	64%	p < 0.000
Mood problems	16%	23%	42%	54%	p < 0.000
Lymphedema	6%	5%	13%	15%	p = 0.001
Severe psychiatric problems	0%	2%	7%	13%	p < 0.000

Note: n, sample size.

regression, mood issues, lymphoedema, and severe psychiatric issues increased with age. The prevalence of the characteristics not included in this table did not differ significantly among the age groups (data not shown).

3.6. Associations between different clinical issues

There was a significant association between level of ID and epilepsy (See Table 1 for reported intellectual levels), 34% of individuals with severe ID (IQ < 50) had epilepsy compared to 11% of individuals with less severe ID (p = 0.000). There was also a significant association between epilepsy and sleeping issues, 73% of individuals with epilepsy had sleeping issues compared to 54% of individuals without epilepsy (p = 0.000). There was no significant association between ID and behavioural issues, 72% of individuals with severe ID had behavioural issues compared to 67% of individuals with less severe ID (p = 0.422). No difference was found in terms of sleeping issues (65% vs. 55%, p = 0.101).

3.7. Parental stress

Questions on parental stress were completed by 86.4% (507/587) of the respondents, and the results are summarised in Table 4. Mean level of parental stress was 1.8 on a 0–3 point Likert scale. Very strong contributors to parental stress (mean > 2.4) were "worrying about adulthood care" and "not knowing what is bothering the child due to limited communication possibilities". The percentages of parents who scored the items as "extremely stressful" are included in Table 4. Ten items (10/15) were scored as "extremely stressful" by more than 30% of parents. Two items "worrying about services in adulthood" and "not knowing what is bothering the child due to limited communication possibilities" were scored as "extremely stressful" by more than 60% of parents.

3.8. Child-related factors

Regarding child-related factors there was a significant association between age and the item on amount of effort to reach milestones (p = 0.016). Parents of children under 12 years of age scored the amount of effort it takes to reach milestones significantly higher. Stress due to limited communication possibilities was also significantly higher for parents of younger children (p = 0.017). There was also a significant association between the level of parental stress and behavioural issues in general (p= <0.00). No significant associations were found regarding sex and level of ID.

Table 4
Mean scores (0–3 Likert scale) and percentage extremely stressful scores on items GSSS (n = 507) and extra added item 15.

	Topic item	Mean (0–3 Likert scale)	Percentage (%) "extremely stressful"
1.10	A genetic diagnosis causing tension within the immediate and extended family	0.94	11.1
2.	People staring when I go out in public with my child	1.12	9.9
3.	Having to make extensive preparations for my child before leaving the house	1.39	16.2
4.	Having to explain my child's condition to new people I meet	1.42	13.8
5.	Sleep deprivation, due to my child's sleeping patterns	1.58	29.8
6.	Getting my child's complex needs met through social services	1.81	30.5
7.	Not having access to professionals who have knowledge about child's condition	1.82	32.7
8.	Going to see professionals who are not knowledgeable about my child's genetic syndrome	1.93	36.6
9.	An educational placement that does not meet all of my child's needs	1.93	37.3
10.	The large amount of effort required to help my child reach developmental milestones (e.g. sitting up, self-feeding)	1.94	33.2
11.	Not being able to fully relax at home, as I need to attend to my child 24 h a day	1.96	36.5
12.	Having to be constantly vigilant about my child's state of health in case of a sudden change	2.03	39.7
13.	Arranging care (e.g. babysitting, respite) that is suitable for my child	2.08	43.6
14.	*Not knowing what is bothering my child due to limited communication possibilities*	*2.42*	*61.2*
15.	Worrying about the future for my child because of the lack of specialist services once they reach adulthood	2.56	68.1

3.9. Contextual factors

Regarding contextual factors there is a significant association between the continent where the respondent lives and worrying about adulthood care (p = 0.017), suitable educational placement (p = 0.012) and tension in the family (p = 0.004) with parents from South America scoring these items significantly higher than parents of other countries. No significant associations were found regarding level of care.

There were multiple remarks on factors contributing to parental stress in PMS in the remark section of the survey (open question). Remarks related to stress and worry were mostly child- and context-related. Example remarks on child-related factors contributing to parental stress are:

"Most stress is caused by behavioural problems and ID, which are far beyond the focus of most pediatricians"

"What does the future hold for us?"

"How to manage all of my child's needs without burning out?"

"I feel lost. She is becoming a teen and now everything seems to get harder".

Examples of remarks on context related factors contributing to parental stress:

"I really have no idea which doctors my son should visit"

"I find that the hardest and scariest part, who will take care of my adult child who will most likely always be a child".

"I find having to explain over and over and worry about her being safe and worrying about her future horribly stressful because I am trying my hardest to make sure she is getting all the things she needs".

"Battling insurance companies is also very stressful"

These and other remarks of parents often were related to experienced parental stress due to factors related their child's condition and contextual factors.

4. Discussion

This worldwide parental survey among families of individuals with PMS collected parental perspectives on care needs, genotypes, phenotypes, somatic issues, mental health issues and parental stress in this rare disorder and the results of this survey made critical contributions to the development and usefulness of the European consensus guideline for PMS. This survey presents a worldwide view as most continents were represented in the 587 surveys received from 35 countries. In this discussion we reflect on the answers given and how they contributed to the development of the guideline, paying special attention to care needs, aetiology and recurrence risk, the most frequent medical and behavioural issues and how these relate to genotype and age, and parental stress. Finally we discuss the strength and limitations of this study and give some recommendations for future studies.

4.1. Care needs

Parents from South America experienced less timely and adequate communication among healthcare professionals and were less informed about the genotype of their child as compared to parents on other continents. These differences could be due to a lack of infrastructure and expertise. Of note, most individuals from South America were Brazilian, so conclusions for the entire continent should be drawn with caution. The particularities of each country and continent are important to consider in an international guideline to achieve optimal implementation. Although this guideline will be a European guideline, it is the first international guideline on PMS, and may thus also be used on other continents. The somatic and psychiatric issues in PMS need structural healthcare evaluations in a multidisciplinary team as described in the paper on organisation on care in the PMS European guideline (van Eeghen et al., 2023, this issue). Our analysis showed that there were no significant differences between Northern & Western and Southern & Eastern Europe, so no additional recommendations on level of care for different parts of Europe were necessary.

4.2. Genotypes

Most individuals had a 22q13.3 deletion (78%), while 22% had a *SHANK*3 variant. 20/404 (5%) individuals with PMS had one parent who had an abnormal genetic testing result. Thus, most cases of PMS occur *de novo*. Nonetheless, if a parent is a carrier of a balanced translocation, a mosaic deletion, or a mosaic *SHANK3* variant there is an increased recurrence risk in future offspring (Koza et al., 2023, this issue). In this cohort, 50% of the unbalanced translocations were inherited from a carrier parent. Knowledge about the presence of a ring chromosome is also important. In our survey a ring was found in 43/397 (11%) individuals with a deletion 22q13.3 and NF2-tumours were reported in 2/43 (5%) individuals with a ring chromosome. A ring chromosome 22 can result in NF2-tumours due to somatic loss of the ring and subsequently a somatic mutation in the remaining NF2 gene (Koza et 2023 this issue). Noteworthy, in 13/397 (13%) individuals with a deletion 22q13.3 it was not known whether the deletion was caused by a ring or not.

Thus, recommendations on further genetic studies are important for counselling related to family planning and for the exclusion of a ring chromosome 22. Both are included in the guideline (Koza et al., 2023, this issue).

4.3. Phenotypes

Parents most frequently reported issues with speech and communication, learning disabilities/ID, and at least one behavioural issue (90%). Parents were asked about behavioural issues in two separate questions. One asked about general behaviour issues which 70% of respondents reported their child had. The other question was on specific behavioural issues, and 90% reported their child had at least one behavioural issue. However, parents may have different perspectives on what is considered a behavioural issue, possibly because they do not find certain behaviours problematic. This discrepancy should alert healthcare professionals that parents could need guidance during consultations about broad terms like "behavioural issues", to avoid missing out on valuable information. Recommendations on this can be found in the paper on mental health issues in PMS (van Balkom et al., 2023, this issue).

Most of our findings on reported issues agreed with the literature. Prevalences of high pain thresholds (77%) and sleeping issues (59%) were higher in this cohort than in literature; which reports; 65% and 38%, respectively (Table 1; Schön et al., 2023, this issue). As both issues can be challenging to recognise in consultation, the reported prevalence in literature may be an underestimation. It is therefore crucial for healthcare professionals to specifically ask about both issues and structured assessments are included in the guideline in the paper on sensory functioning (Walinga et al., this issue, 2023) and the paper on sleeping issues in PMS (San-Jose Caceras et al., this issue, 2023).

4.4. Influence of genotype on reported phenotypes

Prevalence of issues in speech and communication were similar in individuals with 22q13.3 deletions (97%) and *SHANK3* variants (94%), whereas a higher prevalence in deletions has been reported in literature (88% versus 70%, respectively). Similar prevalences of issues in regulating body temperature were reported in both groups (49%/49%), whereas literature describes a lower prevalence in *SHANK3* variants (8% *versus* 37% in deletions). Sleeping issues were also similarly prevalent in both groups (57%/64%). In contrast the literature describes a lower prevalence in 22q13.3 deletions (26%/52%).

Kidney issues and lymphoedema seem to be more common in individuals with deletions than in those with *SHANK3* variants, both in this cohort and in literature (De Rubeis et al., 2018). These prevalences lead to recommendations in the surveillance scheme and recommendations in screening (van Eeghen et al., 2023, this issue).

4.5. Influence of age on reported phenotypes

Associations were found between age and certain symptoms. The prevalence of mood issues, lymphoedema and severe mental health issues doubled or tripled after the age of 12 years, which shows that, although these issues can present at all ages they tend to arise around adolescence. Regression appeared to begin earlier in this cohort than previously described in literature (<4 vs. 6 years) (Reierson et al., 2017). Although regaining of skills has been reported (Phelan et al., 2018 & Burdeus-Olavarrieta et al., 2021), informing parents about the possibility of regression from an early age can contribute to its identification. Regression was discussed in the paper on mental health issues in PMS in this guideline (van Balkom et al., 2023, this issue). The prevalence of epilepsy slowly increased until the age of 18, then doubled in adulthood, suggesting that epilepsy can occur at any age but does tend to start after age 18. The consortium has developed a surveillance

scheme that is included in the guideline to assist healthcare professionals and parents with points of attention per developmental stage (van Eeghen et al., 2023 this issue).

4.6. Parental stress

Parental stress was relatively high among the parents of individuals with PMS. With a mean score of 1.8 on a 0–3 points Likert-scale, with a score of 2 being moderately stressful. This high mean score is in accordance with literature (Griffith et al., 2011; Adams et al., 2018; Droogmans et al., 2021) with mean scores ranging from 1.1 in parents of children with low levels of challenging behaviour and 1.3, 1.4, and 1.7 in other rare genetic syndromes. Fitzgerald and Gallagher (2021) showed greater distress amongst parents of children with rare genetic syndromes compared to other disabilities. They described four domains of factors (child-related, parent-related, family-related and contextual factors) associated with parental well-being in parents of children with rare genetic syndromes. Child-related factors were age of the child, intellectual and adaptive functioning, emotional and behavioural difficulties and physical health and genotype. Parent-related factors were parent demographics, parental mental health and coping. Family-related factors were family composition and family functioning. Contextual factors were support from family, friends and healthcare professionals and accessible and knowledgeable professional care. Syndrome-specific phenotypes seemed to contribute to parental stress.

Child-related factors and context-related factors influencing parental stress were included in the PMS survey. Regarding child-related factors, 61.2% of the parents scored the item "not knowing what is bothering my child due to limited communication possibilities" as "extremely stressful" and this item was significantly associated with a younger age (<12 years) in individuals with PMS ($p = 0.017$). Augmentative communication is an accessible intervention that can contribute to reciprocal communication and therefore reduce stress in children and parents and is described in the paper on communication, language and speech (Burdeus-Olavarrieta et al., 2023, this issue).

Behavioural issues were significantly associated with level of parental stress ($p < 0.00$) in this survey in accordance with literature. In Cornelia de Lange syndrome, another rare genetic disorder associated with ID, behavioural issues were the strongest predictor of parental stress (Wulffaert et al., 2009). Adams et al. (2018) combined longitudinal and cross-sectional data and concluded that chronic, long-term challenging behaviour in children with rare genetic syndromes is associated with an increase in maternal stress and parental stress was still elevated when repeating measurements after 6 or 7 years (Adams et al., 2018). Early interventions focusing on behaviour can contribute in preventing the mutually reinforcing cycle between challenging behaviour and parental stress (Hastings, 2002). Interventions focusing on beliefs of parents about their children and the behaviour of their children can contribute to reducing parental stress (Hartley et al., 2013). Further recommendations on behavioural observations and interventions in PMS are provided in the paper on mental health issues (van Balkom et al., 2023, this issue).

Bro et al. (2017) reported that sleep disturbance, a specific behavioural issue, in individuals with PMS is a statistically significant predictor of reported increased sleep disturbance and daytime sleepiness in their caregivers. Sleeping issues can have a short-term and long-term effect on both health and general well-being of parents. In this study sleeping issues were reported in 59% of the individuals with PMS. Interventions regarding sleep can not only be of help for the individual with PMS but also for the parents of an individual with PMS as sleeping issues are described as a strong predictor of lowered parental well-being. The paper on sleeping issues provides recommended interventions (San-José Cáceres et al., 2023; this issue). No significant associations were found regarding sex and level of ID.

Regarding contextual factors influencing parental stress, 68.1% of the parents scored the item "worrying about the future for my child because of the lack of specialist services once they reach adulthood" as "extremely stressful". Counselling should timely anticipate on the transition from childhood to adulthood and access to care to help reduce stress in parents. Recommendations are made in the paper on genetic counselling (Koza et al., 2023, this issue). There is a significant association between the continent of residence and worrying about adulthood care ($p = 0.017$), suitable educational placement ($p = 0.012$) and tension in the family ($p = 0.004$). Parents from South America scored significantly higher on these items compared to parents of other continents. No significant associations were found regarding level of care. The guideline paper on organisation of care in PMS provides recommendations for healthcare professionals on contextual-factors and a surveillance scheme with lifelong age-specific care needs (van Eeghen et al., 2023, this issue). Healthcare professionals should actively pay attention to the level of parental stress in different stages of development and discuss potential specific stress factors, taking into account the phenotype of the syndrome and contextual factors like access to care in adulthood care (Koza et al., 2023, this issue). Parental stress has negative impacts on different levels: on micro-level for the parent, on meso-level for the child in need of co-regulation of stress, and on macro-level on participation in society (Griffith et al., 2011; Adams et al., 2018; Droogmans et al., 2021; Fitzgerald and Gallagher, 2021). Therefore, it is of utmost importance, to make appropriate interventions available for families with an individual with PMS.

4.7. Strengths & limitations

One of the main strengths of this study was its large sample size. With 587 completed surveys, it is believed to be the largest international cohort ever described in PMS literature. It represents parents from 35 countries and all continents, except Antarctica, which increases the validity of the results. This study focused on the perspectives of parents. Since parents have first-hand experience with the issues and the organisation of care of their children, they are a reliable and indispensable source of information in developing a guideline. This survey used the analysis of specific factors contributing to parental stress previously suggested by Griffith et al. (2011) combined with a qualitative design. The items of the GSSS and the remarks from parents provide a more detailed insight into specific contributing factors. There were also limitations. Participating parents were identified through patient organizations, and their experiences might not reflect those of parents who do not join such organizations. The survey was further administered online, therefore only parents with internet access were able to complete it. The survey also did not include questions about the parents, such as their socioeconomic status, cultural or ethnic background, age or education, even though these factors could influence their knowledge and perspectives. The median age of the individuals with PMS was 12 years, therefore less information was obtained about ageing individuals, although the age range was 60 years (0–60 years). It is worth mentioning that the prevalence of clinical issues is cumulative, as the survey asked which complaints were present upon completing the survey or had been present in the past, instead of asking only about current issues. Findings on the genotype should be interpreted with caution as it was not possible to confirm them with genetic testing results. Native speaking consortium members influenced selection of languages and translations, as well as determined accessibility to patient organizations by their affiliation. These factors may have had an impact on survey dissemination and response rates in countries not represented in the consortium. Additionally, the international character of the survey made it challenging to include open questions, such as follow-up questions on specific signs and symptoms.

4.8. Future research

One of the recent initiatives of the PMS Foundation was the PMS DataHub (https://pmsf.org/datahub/), an online data collection

platform meant for families of individuals with PMS. A similar initiative is also at an early stage in Europe and aims to create a European PMS database. This initiative will be part of the International Library of Intellectual disability and Anomalies of Development (ILIAD), coordinated by the European Reference Network for Rare Malformation Syndromes, Intellectual and other Neurodevelopmental disorders (ERNITHACA, https://ern-ithaca.eu/). With both initiatives, cross-referencing will be possible for further validation of data on PMS. Longitudinal data on parental stress could help delineate different influencing factors such as age or family interventions. In future research, parents can contribute to topics for future research through a knowledge agenda to delineate topics for future research based on patient and public involvement.

5. Conclusion

We present a worldwide cross-sectional study of parental perspectives on the level of care, genotype, phenotype and mental health issues in individuals with PMS and on the level of stress in their parents. In total, 587 surveys were analysed, from 35 countries representing most continents. Parents reported a wide variety of developmental, neurological, and other clinical issues in individuals with PMS, with the most common being issues with speech and communication, learning disabilities/ID, and behavioural issues. Most issues were present across all age groups and genotypes. However, the prevalences of epilepsy, lymphoedema, and psychiatric issues increased with age, highlighting the need for special counselling in adolescents and adults. Furthermore, individuals with a 22q13.3 deletion had a higher rate of kidney issues and lymphoedema compared to individuals with *SHANK3* variants. Parental stress was high, with different contributing factors that related to specific issues in PMS. Interventions should focus on child- and context-related factors contributing to parental stress. Differences between continents in the organisation of care were reported, and these are relevant in counselling and implementation of the guideline. As the largest and the most internationally diverse cohort to date, these findings are valuable for parents, healthcare professionals and validation of the European PMS guideline. Future research should focus on exploring the genotype in PMS, and subsequently to studying genotype-phenotype associations as well as interventions to improve family well-being. In research on PMS issues important to and for families should be prioritised. This study on parental perspectives and experiences contributes to the comprehensive and complete description of PMS and to a well-balanced guideline, that is not solely based on literature.

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Ethics

The study was registered in the study registry of the UMCG (study number: 202100595). The Medical Ethics Review Board of the UMCG (METc UMCG) assessed the protocol and waived the need for a full protocol review because the project is not clinical research with human subjects as meant in the Medical Research Involving Human Subjects Act (niet WMO-plichtig, METc, 2021/475). The survey was anonymous, and it only contained questions regarding sex, year of birth, and country, which were all optional. Before starting the survey, participants were informed about the use of their data in developing the PMS guideline and in a potential publication. After being informed, participants had to give consent, which was mandatory to continue and submit the survey.

CRediT authorship contribution statement

Annemiek M. Landlust: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Sylvia A. Koza:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Maya Carbin:** Writing – review & editing. **Margreet Walinga:** Conceptualization, Methodology, Writing – review & editing. **Sandra Robert:** Writing – review & editing. **Jennifer Cooke:** Conceptualization, Writing – review & editing. **Klea Vyshka:** Conceptualization, Methodology, the European Phelan-McDermid syndrome consortium, Conceptualization, Methodology, Writing – review & editing. **Ingrid D. C. van Balkom:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Conny van Ravenswaaij-Arts:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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