

Adelphi

ADELPHI VALUES



Understanding Phelan-McDermid Syndrome: Patient and Caregiver Experience from the Perspective of Published Literature

Report prepared for CureSHANK

v2_0

9 March 2022

Background

- > Phelan-McDermid Syndrome (PMS) is a rare mutation (sequence variants or deletion) of the SHANK3 gene; while it is estimated that 1% of people with autism have PMS,¹ its exact prevalence is unknown^{1,2}
- > There are various signs, symptoms, and impacts of PMS, including:
 - Intellectual disability with cognitive and language impairments
 - Sensory issues
 - Hypotonia
 - Gastrointestinal dysfunction
 - Seizures
 - Other medical and psychiatric conditions
- > The goal of CureSHANK is to accelerate the development of treatments for PMS and other SHANK-related disorders
- > CureSHANK wishes to document the signs, symptoms and quality of life impacts associated with PMS from the perspective of the published literature on PMS, with the goal of presenting a conceptual model to pharmaceutical companies to support the inclusion of clinical outcome assessments (COA) in future clinical trials of pharmacological treatments for PMS
- > The focus of this report is the methodology and results of the literature review and the resulting conceptual model

1. Phelan-McDermid Syndrome Foundation. "What Is Phelan-McDermid Syndrome?" <https://pmsf.org/about-pms/> Accessed December 7, 2021.
2. Phelan K, Rogers RC, Boccuto L. Phelan-McDermid Syndrome. 2005 May 11 [Updated 2018 Jun 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Accessed May 19, 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1198/>

Project goals and objectives

- > Goal:
 - To better understand and document the signs, symptoms and quality of life impacts associated with PMS from the perspectives of the published literature

- > Objectives:
 - Conduct a targeted, structured search of published literature to identify recent publications on PMS symptoms and quality-of-life burdens
 - Review the selected publications and extract relevant information
 - Review additional publications (either published or in press) provided by CureSHANK from previously-conducted activities to gather information on the patient and caregiver experience of PMS
 - Develop PMS disease conceptual model

Literature search

Literature search methodology

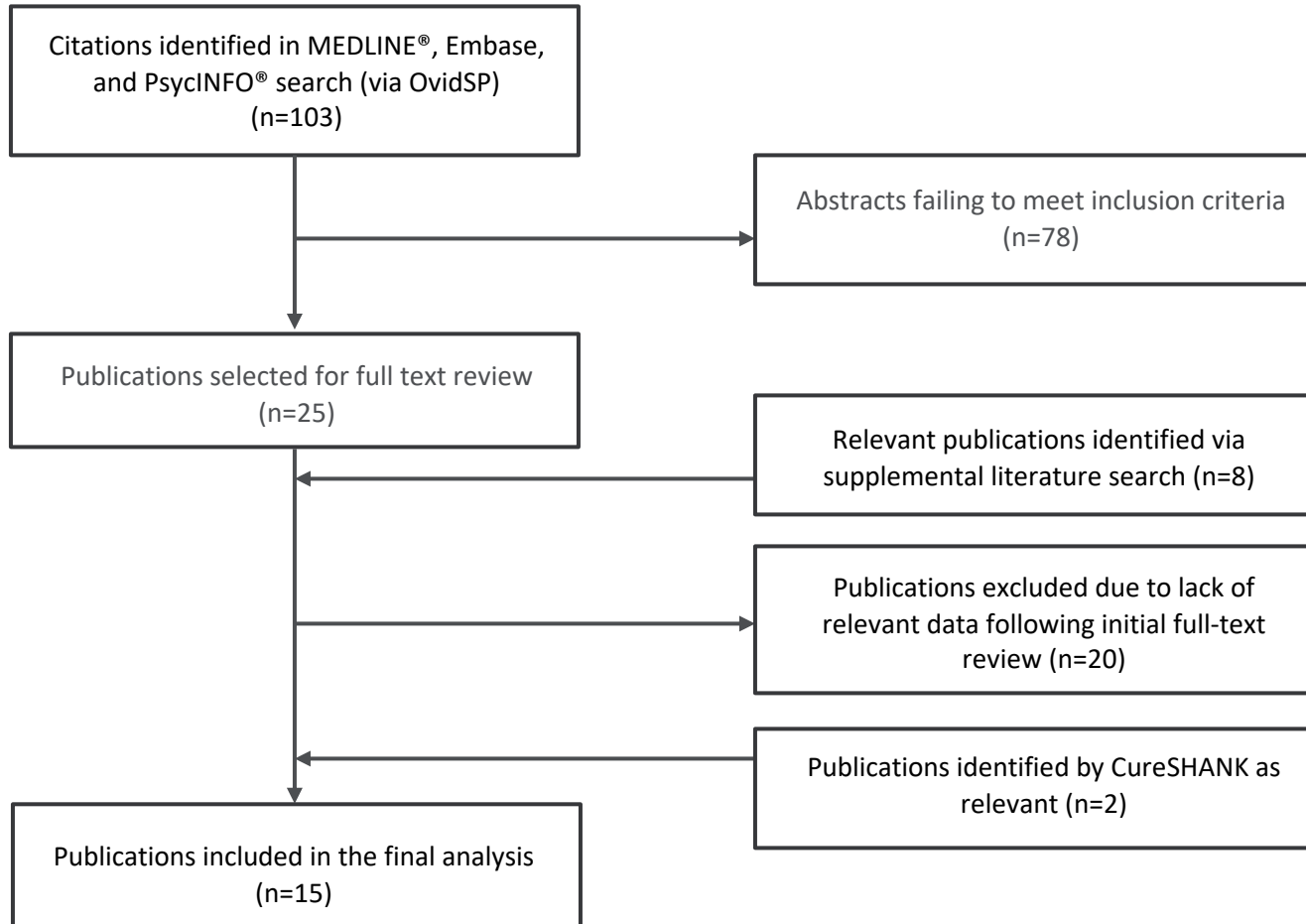
- > In keeping with scientific best practices for these types of reviews³, a targeted systematic literature search was conducted on 3 June 2021 using the OVID SP platform to search the Embase, MEDLINE®, and PsycINFO® databases to identify peer-reviewed abstracts focusing primarily on the experience of patients with PMS or their caregivers. Please see backup slides for full search strategy and inclusion criteria.
- > Abstracts were screened, and publications selected for full review if they primarily focused on research on PMS that assesses signs, symptoms, and quality of life in patients or caregivers.
- > Additionally, a supplemental search was conducted on 28 June 2021 in Google Scholar and PubMed to identify additional publications not included in the targeted search.
- > CureSHANK provided two additional publications that were included in the review, both of which were published (or in press) in peer-reviewed journals.

3. Kysh, L. "What's in a name?: The difference between a systematic review and a literature review and why it matters. Medical Library Group of Southern California & Arizona (MLGSCA) and the Northern California and Nevada Medical Library Group (NCNMLG) Joint Meeting." (2013).

Literature search results

- > The targeted systematic literature search identified 103 abstracts of potentially relevant publications.
- > The identified abstracts were screened, and 25 publications were selected for review.
- > In addition, eight publications were identified for review by the supplemental search
- > Upon review, 20 of the 33 publications were found not to contain relevant information and so were excluded from analysis
- > CureSHANK also provided two relevant publications which were reviewed and included in the analysis
- > A total of 15 publications have been included in the analysis reported here
- > Please see the following slide for a summary diagram of the literature search results

Literature search summary diagram



Data extraction

Data extraction methodology

- > In keeping with scientific best practices for these types of reviews⁴, publications were reviewed for concepts (i.e., signs, symptoms, or impacts) and who is able to report on them (e.g., patient, clinician, or caregiver)
- > For each publication, the following information was extracted and summarized in a set of data extraction tables (please see backup slides for tables):
 - Description of study being reported and study population
 - Condition(s) being studied in the publication (e.g., PMS)
 - Observable signs of PMS (i.e., those things which could be seen and reported by a clinician or caregiver)
 - Symptoms of PMS, if any (i.e., those things which patients could report about themselves)
 - Impacts to patients
 - Impacts to caregivers
 - Other key findings of the publication (such as genetic markers and hypothesized relationship to signs and impacts)

4. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*, 62(10), e1-e34.

Data extraction results

- > The reviewed publications identified 96 signs and symptoms associated with PMS.
 - The most frequently reported were autism/autistic traits and mild to profound intellectual disability (each reported in nine out of fifteen publications).
- > 13 observer-reportable patient impacts were identified, including difficulties at school, social avoidance, difficulty concentrating, food refusal, and impacts related to sleep disruption.
- > 31 caregiver impacts were reported.
- > The most frequently reported signs and symptoms and key caregiver impacts are presented in the following slides; please see backup slides for full data extraction tables.

Most frequently reported* signs/symptoms

Concept	Frequency of report (N=15) n/15	Concept	Frequency of report (N=15) n/15
Autism and/or autistic traits	9/15	Developmental regression	5/15
Intellectual disability, mild to profound	9/15	Gastrointestinal dysfunction	5/15
Constipation	7/15	Pica	5/15
Hyperactivity	7/15	Renal anomalies	5/15
Hypotonia	7/15	Urinary incontinence	5/15
Seizures	7/15	Gastroesophageal reflux	4/15
Sleep disturbance	7/15	Repetitive behavior	4/15
Decreased social function and communication	5/15		
Delayed to absent speech	5/15		

*Reported in four or more publications; please see backup slides for full data extraction tables

Key reported caregiver impacts

Type of impact	Frequency of report (N=15) n/15	Specific impacts reported
Emotional impacts	2 /15	<ul style="list-style-type: none">• Concern• Stress• Worry
Family impacts	1/15	<ul style="list-style-type: none">• Impacts on family functioning• Diminished marital satisfaction
Sleep impacts	1/15	<ul style="list-style-type: none">• Lack of sleep• Awakened by child during night• Feeling tired during the day• Too tired to do things they want to do
Social impacts	1/15	<ul style="list-style-type: none">• Feeling ostracized from community

Development of conceptual model

Concept selection

- > A list of all identified concepts from the literature review was compiled and grouped by Adelphi Values researchers under headings (e.g., clinician-reportable signs and symptoms, caregiver-reportable impacts)
- > A meeting with CureSHANK and Adelphi Values was held on 30 September 2021 to review the list and select concepts for inclusion in a conceptual model; concepts were included in the model based on:
 - Frequency of report in reviewed publications
 - Consideration by CureSHANK that they represented key signs, symptoms, and impacts of PMS

Conceptual model development (1)

- > Proposed by Wilson and Cleary (1995),⁵ a conceptual model is a heuristic classification scheme that links a specified disease state or condition to its proximal and increasingly distal health outcomes. The conceptual model acts as a framework for understanding a disease and/or its treatment and specifies concepts to foster the development of the questionnaires, outcomes, and endpoints.
- > The selected concepts were organized into a conceptual model that noted the population of interest, a brief overview of disease mechanism, the observable signs of PMS, comorbidities, impacts to patients, and impacts to caregiver

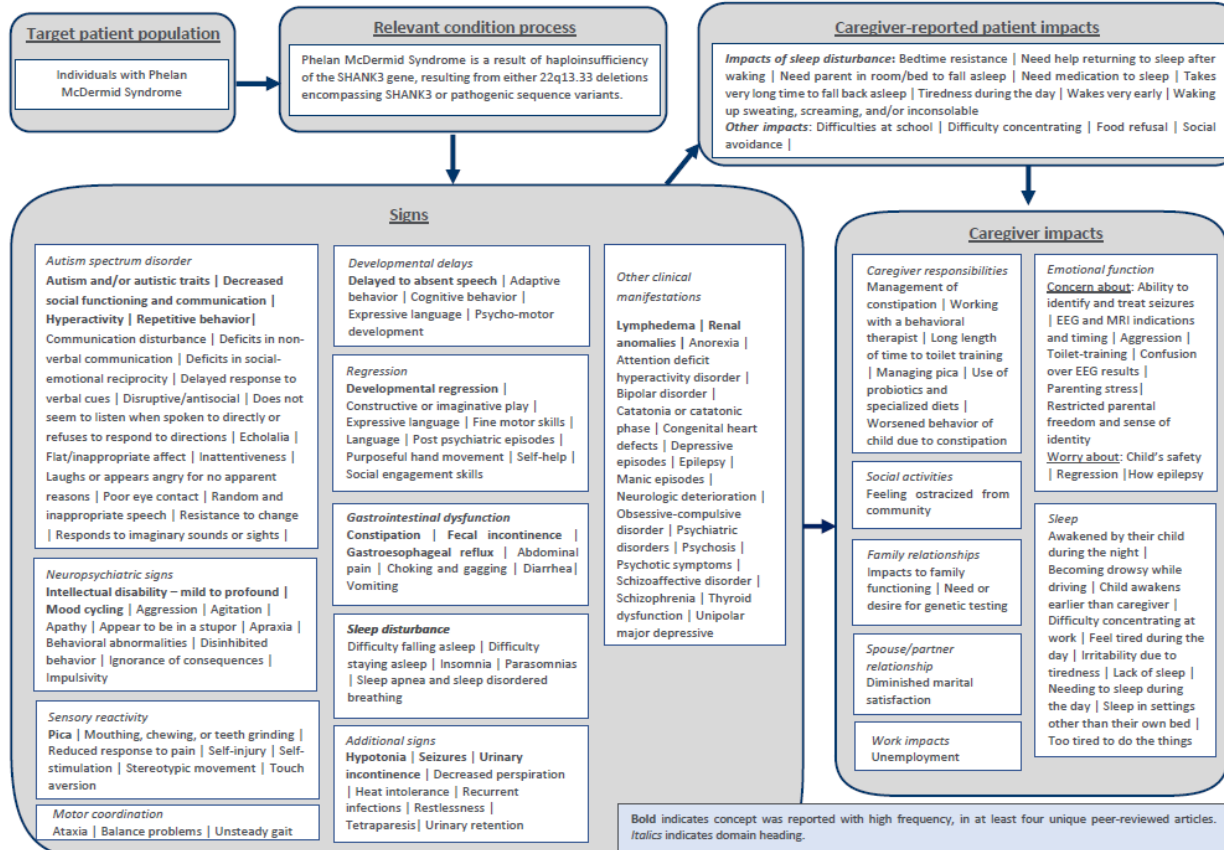
5. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995;273(1):59-65.

Conceptual model development (2)

- > The concepts in the model were grouped by Adelphi Values researchers into domains (e.g., neuropsychiatric signs, sensory reactivity, autism or autistic behavior, motor skills).
 - Bold font was used to denote concepts that were reported with higher frequency (in at least four unique publications).
 - Italicized font was used to denote domain.
- > The conceptual model was reviewed by a clinical expert identified by CureSHANK; based on that review, some changes were made to the model to ensure that the domains and concepts were organized in ways that were clinically sound and thematically coherent.
- > The conceptual model was further refined based upon feedback from CureSHANK; the final conceptual model is presented in the next slide.

Disease conceptual model

Figure 1. Phelan-McDermid Syndrome conceptual model



Bold indicates concept was reported with high frequency, in at least four unique peer-reviewed articles. Italics indicates domain heading.

Discussion and Conclusion

Discussion

- > The reviewed publications highlighted the variety of ways in which PMS manifests itself, which can range from developmental delay or regression and intellectual or cognitive disability to gastrointestinal dysfunction and sleep disturbance
- > They also shed light on the ways in which caregivers for individuals with PMS experience impacts to their quality of life, particularly emotional impacts, impacts on sleep, impacts on family life, and social impacts

Limitations (1)

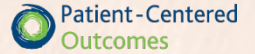
- > While the reviewed publications shed some light on the caregiver experience in PMS, only four of the 15 publications reviewed (26.7%) reported on quality of life impacts to caregivers. Further research, such as a literature search specifically targeted to the caregiver experience, or interviews or focus groups involving caregivers for individuals with PMS could help provide greater insight into the caregiver experience
- > While six of the 15 publications reviewed (40.0%) reported on patient populations that included adults with PMS, three of them reported a mean or median age under 12 years, while two did not report on the median or mean age of the study sample; only one publication reported a mean age of 20 years in their study sample. Thus, the concepts identified in the literature review may be skewed towards those relevant to a pediatric population with PMS. Additional research may help provide greater insight into the adult PMS experience.

Limitations (2)

- > The majority (8/13) of the impacts to individuals with PMS reported in the literature were related to sleep disruption. This may reflect a limitation in the published literature, which appears to focus primarily on sleep studies. Further research could expand understanding of other impacts that might be more important or concerning to these individuals and their caregivers.



ADELPHI VALUES



Boston, USA
T: +1 617 720 0001

Manchester, UK
T: +44 (0)1625 576815

Roger Lamoureux
Senior Research Manager

Roger.Lamoureux@adelphivalues.com

Leighann Litcher-Kelly
Director

Leighann.Litcher-Kelly@adelphivalues.com

Backup Slides

Search strategy (1)

Step	Search Term	Search type	Hits
1	Phelan-McDermid Syndrome* OR Phelan-McDermid* OR SHANK gene OR SHANK3 OR 22q13 deletion syndrome	Key Words	452
2	Impact* OR quality of life OR QOL OR health related quality of life OR HRQOL OR well being OR well-being OR burden OR humanistic* OR relationship* OR emotional impact* OR social impact* OR health status OR physical impact* OR daily activities OR activities of daily living OR ADL OR burden* OR interfere* OR function* OR sign* OR symptom*	All fields	29,933,940
3	(1) AND (2)	-	339
4	Limit to Step 3 to English language	-	336
5	Limit Step 4 to human	-	182
6	Limit Step 5 to published in the last 5 years ("2015-Current")	-	142
7	Remove duplicates	-	103

Search performed June 3rd 2021 in Ovid SP, using Embase, MEDLINE, and PsycINFO. Databases searched included Embase 1996 to 2021 Week 21, Ovid MEDLINE(R) ALL 1946 to June 03, 2021, and PsycINFO 2002 to May Week 5 2021.

*indicates truncation used for search term

Search strategy (2)

- > Publications were included in analysis if they:
 - Primarily focused on research on PMS that assess symptoms and quality of life in patients and caregivers

- > Publications were excluded from analysis if they:
 - Did not focus on PMS
 - Did not include patients and/or caregivers of patients with PMS
 - Focused on the genetics or molecular biology of PMS without signs and/or symptoms, or quality of life related to PMS;
 - Primarily focused on non-human research;
 - Presented a case study of one or a few individuals;
 - Were not available in English; or
 - Were published prior to 2015.

Data Extraction Tables

See complete tables [HERE](#).