



Editorial

Editorial: Towards a European consensus guideline for Phelan-McDermid syndrome



1. Introduction

In 2001, Katy Phelan and Heather McDermid described the clinical and cytogenetic characteristics of 37 people with a 22q13.3 deletion (Phelan et al., 2001). The 22q13.3 deletion syndrome was since then referred to as Phelan-McDermid syndrome (PMS) (OMIM#606232). Later on, the deletion of a single gene, i.e. *SHANK3* (OMIM#606230), was found to be responsible for the majority of the clinical features. Individuals with a pathogenic variant in *SHANK3* appeared to have a similar phenotype, that is also referred to as Phelan-McDermid syndrome (Schön et al., 2023, this issue; Vitrac et al., 2023, this issue). Since not all individuals referred to in the original publication of Phelan and McDermid may have had a deletion 22q13.3 including *SHANK3* there has been some debate on how the phenotype should be called when *SHANK3* is not involved. Consequently, a distinction in different types of Phelan-McDermid syndrome has been proposed: PMS *SHANK3*-related and PMS *SHANK3*-unrelated (Phelan et al., 2022).

1.1. Aim of the guideline

In 2020, the Guidelines working group of the European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) (see Other Sources) initiated the translation of the Dutch guideline for 22q13 deletion syndrome (see Other Sources) and established an international consortium of professional and lived experience experts representing 14 European countries (Suppl 1), in order to update and adapt the guideline to the European situation.

The aim of the guideline is to provide recommendations for resolving the bottlenecks experienced in practice and to achieve more uniform and better-coordinated care for individuals with Phelan-McDermid syndrome. Patient representatives were involved in the selection of topics and participated in writing the guideline. The recommendations are based on a careful weighing of the latest scientific insights and expert opinion. The guideline supports clinical decision-making and primarily targets those healthcare professionals involved in the care of children and adults with PMS, while also providing transparency to patients, parents and caregivers. A short practical version of the guideline (Suppl 2), a clinical surveillance scheme and emergency card (van Eeghen et al., 2023, this issue), and a lay version in different European languages have been made as well.

1.2. What does the guideline cover?

This guideline addresses issues for individuals diagnosed with Phelan-McDermid syndrome (PMS), due to a deletion 22q13.3 or a

pathogenic variant in the *SHANK3* gene. For the deletions, we specifically focus on deletions including *SHANK3*. This can be terminal or interstitial deletions and also includes deletions caused by unbalanced translocations or a ring chromosome 22 (Koza et al., 2023, this issue). For clarity and because the majority of the data is available for genetic abnormalities affecting the *SHANK3* gene, we focus on individuals with a *SHANK3* haploinsufficiency (functional copy number loss), i.e. PMS *SHANK3*-related. Nonetheless parts of this guideline may be applied to deletions 22q13 *not* including *SHANK3*, i.e. PMS *SHANK3*-unrelated.

2. Methods

A survey exploring the most important topics and needs experienced by parents was developed and made available online in different languages (English, French, Spanish, Portuguese, Dutch, German, Italian, Hungarian, Lithuanian, Swedish). Links to the survey were distributed among parents with the help of patient organisations. The survey was completed anonymously by the parents of almost 600 patients worldwide and the results can be found in Landlust et al., (2023) (this issue).

The guideline is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010), which is an internationally accepted instrument and considered the most useful instrument to use in guideline development for rare disorders (Pavan et al., 2017). After identification of the most important questions that needed to be addressed by the guideline, an extensive literature search was performed as described in the respective papers.

Each chapter of the guideline was critically reviewed by the consortium members, including the patient representatives. The final text was discussed in detail with all consortium members during a consensus meeting in June 2022 in Groningen, Netherlands, and the recommendations were rephrased until consensus was met. A voting process allowed each member to vote regarding the reliability of each recommendation.

2.1. Overview of topics of the European consensus guideline

For background information and the consensus recommendations we refer to the respective papers in this special issue. A summary for practical use can be found in Suppl. 2. The following topics have been addressed:

- Definition and clinical variability of *SHANK3*-related PMS (Schön et al., 2023, this issue)
- Counselling in PMS (Koza et al., 2023, this issue)

- Communication, language and speech in PMS (Burdeus-Olavarrieta et al., 2023, this issue)
- Chewing, swallowing and gastrointestinal problems in PMS (Matuleviciene et al., 2023; this issue)
- Altered sensory functioning in PMS (Walinga et al., 2023, this issue)
- Epilepsy in PMS (de Coo et al., 2023, this issue)
- Sleeping problems in PMS (San José Cáceres et al., 2023, this issue)
- Lymphedema in PMS (Damstra et al., 2023, this issue)
- Mental health issues in PMS (van Balkom et al., 2023, this issue)
- Organization of care in PMS (van Eeghen et al., 2023, this issue)

For background information, a chapter has been added on the genetic background in PMS: dissecting the 22q13 region to explore the genetic and phenotypic diversity of patients with Phelan-McDermid syndrome (Vitrac et al., 2023; this issue).

2.2. Implementation

This guideline will be available at ITHACA's website (see Other Sources) together with lay versions in different languages. A short electronic brochure will be developed to inform patient organisations and relevant professional organisations about the existence of the guideline. Presentations at international parent support group meetings in Madrid (Spain), Paris (France) and Ulm (Germany) are scheduled for 2023 and we expect more to follow, since we are convinced that parents and their families are the best advocates for a guideline on a rare disorder. We aim to update the guideline regularly when new scientific data becomes available. Consequently, the latest version of the guideline will be accessible on ITHACA's website.

2.3. Sustainability

Not all clinical problems that occur in but are not specific for Phelan-McDermid syndrome are covered by the papers in this special issue and therefore no recommendations are given. However, whenever enough evidence was available they are mentioned in the surveillance scheme. E.g. the suggestion to perform a renal ultrasound, since renal abnormalities occur in 15% of individuals with a deletion 22q13.3 (Schön et al., 2023 this issue).

New problems may occur and be published in case reports, that may warrant the attention of the clinician, even if there is no sound evidence yet. The PMS Guideline Consortium has agreed that 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 (see Other Sources). An official revision of the guideline will take place upon request of and under the responsibility of the Guideline working group of ERN-ITHACA. Only after formal revision new information may result in new consensus recommendations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmg.2023.104736>.

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