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Consensus recommendations on altered sensory functioning in Phelan-McDermid syndrome

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ABSTRACT

Altered sensory functioning is often observed in individuals with *SHANK3* related Phelan-McDermid syndrome (PMS). Compared to typically developing individuals and individuals with an autism spectrum disorder, it has been suggested that there are distinctive features of sensory functioning in PMS. More hyporeactivity symptoms and less hyperreactivity and sensory seeking behaviour are seen, particularly in the auditory domain. Hypersensitivity to touch, possible overheating or turning red easily and reduced pain response are often seen.

In this paper the current literature on sensory functioning in PMS is reviewed and recommendations for caregivers, based on consensus within the European PMS consortium, are given.

1. Introduction

Phelan McDermid Syndrome (PMS) is a neurodevelopmental disorder with neurological and psychiatric symptoms and variable other characteristics, most commonly due to a 22q13.3 deletion or pathogenic variant involving *SHANK3* (Schön et al., 2023, this issue). The phenotype is very variable, common characteristics are a global developmental delay with a marked speech impairment. Autism spectrum disorder and to a lesser extent hyperactivity are relatively common (Schön et al., 2023, this issue). In PMS atypical responses to sensory stimuli are often reported (Kolevzon et al., 2014; Mieses et al., 2016; Phelan et al., 2022; De Rubeis et al., 2018; Soorya et al., 2018; Tavassoli et al., 2021; Tomchek and Dunn, 2007).

This paper describes the specific characteristics of sensory functioning in individuals with SHANK3 related Phelan-McDermid syndrome. It aims to offer recommendations to parents/caregivers and clinicians about how to recognize, assess, support and address altered sensory functioning in PMS.

Sensory processing differences have been described in syndromic and non-syndromic autism spectrum disorders (ASD) and can be seen in people with an intellectual disability (Battaglia, 2011; Boyd et al., 2010; Tavassoli et al., 2017).

Atypical sensory responses are a DSM-5 (American Psychiatric Association, 2013) criterium of ASD and described as hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment. Hyperreactivity describes a strong reaction to a sensory stimulus (e.g. covering ears in response to normal sounds, avoiding wearing clothes of a certain texture). Hyporeactivity is characterized by delayed or absent responses to sensory stimuli (e.g. not reacting to alarming sounds). Sensory seeking behaviour can be seen as fascination with certain sensory stimuli (e.a. repeatedly touching certain textures or intentionally squinting).

The seven sensory systems include the proprioceptive system (posture and movement), vestibular system (balance), visual system (vision), auditory system (hearing), olfactory system (smell), gustative system (taste) and tactile system (touch, pain, physical sensations).

Processing the sensory stimuli, also called sensory integration, is described as a neurological process that organizes sensory sensations, resulting in an effective use of the body in its environment (Ayres, 1972). A sensory processing disorder, formerly referred to as a "sensory

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integration dysfunction", influences all domains of sensory modalities. In a general European PMS consensus meeting in June 2022, the more positive sounding term "altered sensory functioning" was preferred above the terms 'dysfunction' and 'disorder'.

2. Methods

Starting in 2020, a Dutch guideline on 22q13-deletion syndrome (Nederlandse Richtlijn 22q13 deletiesyndroom (PMS), 2018) was adapted to the European situation, initiated by the European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies). The established international consortium of experts and patient representatives discussed and determined the subjects of this special issue on PMS. One of the discussed subjects was the altered sensory functioning in PMS. The most important questions that needed to be addressed were defined by a working group on sensory functioning and a literature search was performed. Search terms were added during the process (also using AND/OR) and included: sensory dysfunction, sensory processing disorder, sensory profile, senses, Phelan McDermid, 22q13, *SHANK3*, autism, heat, temperature, pain, balance, hearing, auditory, vision. The presented text on Altered Sensory Functioning was critically reviewed and discussed by the members of the consortium and the recommendations were approved during the final consensus meeting.

The following fundamental questions were formulated, substantiated by the parental survey (Landlust et al., 2023, this issue).

- Does altered sensory functioning occur in patients with PMS? How often and of what kind?
- What is the mechanism behind the altered sensory functioning seen in PMS?
- What should healthcare professionals and parents/carers pay attention to regarding altered sensory functioning in patients with PMS?

For the basic question about the *occurrence of altered sensory functioning*, the following articles were included: Battaglia (2011); Kolevzon et al. (2014); Mieses et al. (2016); Phelan et al. (2001); Phelan et al. (2005); Philippe et al. (2008); De Rubeis et al. (2018); Sarasua et al. (2014); Soorya et al. (2013); Tavassoli et al. (2017, 2021); Xu et al. (2020).

For the basic question about the *mechanism of altered sensory functioning* the following articles were included: Han et al. (2016); Li et al. (2017); Noda et al. (2020); Orefice et al. (2016); Philippe et al. (2008).

For the basic question about *points of attention regarding altered sensory functioning* the following articles were included: Denayer et al. (2009); Mieses et al. (2016); Philippe et al. (2008); Siper et al. (2017, 2021); Soorya et al. (2018) and Denayer et al. (2009) Dunn (2007). The conclusions from literature are summarized in Table 1.

3. Review of the literature; results

In general, in people with PMS alterations in sensory functioning, such as vision and hearing impairments, reduced pain perception, heat regulation disorder and changed sensitivity are commonly reported (Kolevzon et al., 2014). Altered sensory functioning affects behaviour and can lead to increased anxiety and uncertainty. Sensory stimuli can produce unexpected and aberrant behaviour. While sensory reactivity symptoms are widely reported in people with ASD, few studies have examined sensory symptoms in PMS. Altered sensory processing in PMS may be associated with ASD, but the haploinsufficiency of *SHANK3* may also have a direct effect on sensory processing.

Using the Short Sensory Profile test (Kientz and Dunn, 1997; Dunn 2014), Mieses et al. (2016) and Tavassoli et al. (2017) found that children with PMS have less pronounced altered sensory functioning than children with ASD and low intellectual functioning, but they have an equally reduced response to pain.

Tavassoli et al. (2021) also found a specific sensory reactive phenotype in children with PMS, who demonstrated greater hyporeactivity symptoms and fewer hyperreactivity and sensory seeking symptoms across visual, tactile, and auditory sensory domains, compared to children with ASD and typically developing children. Differences were particularly prominent in the auditory domain. No differences were found between the different sizes of 22q13.3 deletions or the *SHANK3* variants.

Below the characteristics of the seven sensory systems are described.

3.1. Proprioceptive system (posture and movement)

Stimulus seeking proprioceptive behaviour is reported in PMS, like repetitive use of objects, specific body postures or complex motor mannerisms, repetitive hand and finger movements (Soorya et al., 2013). Xu et al. (2020) mentioned repetitive behaviour in 65% if people with a 22q13.3 deletion and in 86% of people with a *SHANK3* variant. Gait abnormalities (ataxic, wide based) were mentioned in 82–93% (De Rubeis et al., 2018). Differentiating stimulus seeking behaviour from underlying discomfort or pain can be difficult, this is further addressed below in Discussion and considerations.

3.2. Vestibular system (balance)

In PMS individuals with a ring chromosome 22, attention should be given to vestibular schwannoma, related to neurofibromatosis type 2, which can also cause dizziness and balance problems (Denayer et al., 2009; Koza et al., 2023, this issue).

3.3. Visual system (vision)

In order to assess the visual sensory processing, it is important to rule out vision problems due to other medical causes. Vision may be impaired due to strabismus and myopia (Sarasua et al., 2014; Soorya et al., 2013). Phelan and McDermid H (2011), registered that in a few cases (6%) cortical visual impairment was detected. Vision disturbances occur in 22% of individuals with a 22q13.3 deletion (Brignell et al., 2021; Richards et al., 2017; Tabet et al., 2017) and in 29% of people with a *SHANK3* variant (De Rubeis et al., 2018). Tavassoli et al. (2021) demonstrated that children with PMS show more hyporeactivity symptoms (e.g. delayed or absent responses to the sight) than children with ASD or typically developing children. Noda et al. (2020) found impaired somatosensory evoked potentials (SEP) in individuals with ASD (not PMS), suggesting that visual attention affects the later stages of somatosensory processing.

3.4. Auditory system (hearing)

It is important to be aware of hearing problems before assessing the sensory processing. Hearing is normal in most individuals with PMS, but hearing loss could arise due to conduction problems as a result of frequent middle ear infections (Soorya et al., 2013). When PMS is caused by a ring chromosome 22, hearing loss can occur as one of the first

Table 1
Conclusions on sensory functioning in Phelan-McDermid syndrome from the literature.

In people with PMS, altered sensory functioning is often reported. In order to assess the sensory processing, it is important to rule out general problems with hearing and vision.
Children with PMS demonstrate a distinct sensory profile in comparison to children with ASD and typically developing children. They show more hypo-reactivity symptoms, fewer hyper-reactivity and sensory seeking symptoms across visual and particularly auditory sensory domains. Hypersensitivity to touch is seen at all ages.
Reduced pain response in people with PMS is mentioned with an average of 70%.
Individuals with PMS overheat or turn red easily and report decreased perspiration.

symptoms of an acoustic neuroma (Koza et al., 2023, this issue; Phelan et al., 2005).

An important finding regarding the sensory processing is that there is often a delayed response to verbal and auditory cues. Ten individuals with PMS underwent auditory evoked potentials, most of them showed longer N250 latency (related to language) compared to the norm for age (Ponson et al., 2018), but given the small sample size, statistical analyses could not be made. Tavassoli et al. (2021) found that children with PMS showed more hyporeactivity symptoms and less hyperreactivity than children with ASD and typically developing children, particularly seen in the auditory domain. Additionally, people with PMS may have difficulties to distinguish words from background noises (Phelan and McDermid H, 2011). The delayed or absent response to auditory cues is relevant for care-givers, because there can also be an under-responsiveness to warning sounds. In a small study (n = 8), Philippe et al. (2008) found that children with PMS had an overreaction to sudden sounds.

3.5. Olfactory system (smell) and gustative (taste) system

Research from Mieses et al. (2016) showed that children with PMS had fewer sensory reactivity symptoms on taste/smell sensitivity, as compared to children with ASS. Behaviour characterized by

inappropriate chewing of clothing, toys, or other non-food items, licking objects or smelling things or people was observed in 70% of children with PMS. These behavioural characteristics decrease as children grow older (Phelan et al., 2001).

4. Temperature sense, tactile and pain perception

Abnormal reactions to changes in temperature, touch and pain have been reported in individuals with PMS (Phelan et al., 2001; Tavassoli et al., 2021). In people with PMS, heat regulation disorder was reported in 68% by Sarasua et al. (2014), described as overheating or turning red easily and having decreased perspiration (60%). The underlying cause is unclear but individuals with PMS may not always be able to react adequately to temperature changes by changing clothes for example.

In a study with 201 participants of all ages with PMS, Sarasua et al. (2014) mentioned in 46% a hypersensitivity to touch. Philippe et al. (2008) also mentioned an overreaction to touch in children. Orefice et al. (2016) investigated the effect of peripheral mechanosensory nerve dysfunction on tactile response and behaviour in multiple mouse models for ASD, including a *SHANK3* model. The mice showed altered tactile discrimination and were hypersensitive to soft tactile stimuli. In this way, they showed that a disturbance in the peripheral sense of touch contributes to behavioural problems such as increased anxiety and decreased social interaction in mice (Orefice et al., 2016).

In a review of Kolevzon et al. (2014) based on 13 publications describing approximately 584 cases with PMS, reduced pain response is mentioned in parental reports with an average of 42%. Other papers mention a much higher prevalence; reduced pain response was found in 62% (70/114) of individuals with a 22q13.3 deletion (Jeffries et al., 2005; Phelan et al., 2001; Samogy-Costa et al., 2019; Xu et al., 2020) and in 79% (23/29) of individuals with a *SHANK3* variant (De Rubeis et al., 2018; Xu et al., 2020). Sarasua et al. (2014) reported a small increase with age: 69% at the age of 5 years, 79% at 5–10 years, 84% at 10–18 years and 89% at 18–65 years. Pain experience can be expressed verbally or vocally, by facial expression, or by other behaviours (Rattaz et al., 2013). In PMS, heterozygous deletion of *SHANK3*, which is involved in the formation and stabilization of postsynaptic glutamate receptors, is suggested to contribute to the altered pain response (Roussignol et al., 2005). Han et al. (2016) showed that *SHANK3* is expressed in sensory nerves and the spinal cord and that *SHANK3* haploinsufficient mice showed reduced pain sensitivity. In addition, the authors showed that *SHANK3* influences peripheral pain regulation via presynaptic pain transmission. Based on the current literature, however, we cannot verify that *SHANK3* is responsible for the altered sensory information processing in PMS, so other factors may also play a role.

5. Discussion and considerations

5.1. Assessing and supporting altered sensory functioning

In PMS, altered sensory functioning can be seen. Individuals have a reduced pain-response and show a distinct sensory profile with more hypo-reactivity symptoms particularly in the auditory domain, a general hypersensitivity to touch and a tendency to overheat easily. These are relevant findings for parents and caregivers as well as clinical physicians and other healthcare workers.

Awareness of safety concerns resulting from sensory hypo-reactivity is there for very important. Individuals with PMS can have somatic complications due to a high pain threshold or overheating, but also have an under-responsiveness to warning sounds such as sirens or for example a car passing by. Environmental adjustments such as a good acoustic space, avoidance of sudden noises, abrupt changes in heat or cold, or sudden touch, could be considered.

It is conceivable that altered sensory functioning can influence language development (Burdeus M. et al., 2023, this issue) and cause or worsen behavioural problems (van Balkom et al., 2023, this issue). Because of the possible altered pain response and reduced expressive communication, injuries or inflammation may be diagnosed late or may remain unnoticed. This hinders effective recognition and treatment by clinicians and parents or caregivers. Extra attention should therefore be paid to the possibility of ear infections, gastroesophageal reflux, dental problems, constipation and other medical conditions.

It is also useful to know the persons individual behaviour and recognize changes in behavioural and emotional patterns.

To track down possible sensory impairments, first thorough medical and (psycho-)neurological examination should be done (Kolevzon et al., 2014). The frequency of screening vision and hearing was discussed in our consortium and there was consensus to screen at least once and furthermore according to the national guidelines (Matuleviciene et al., 2023, this issue).

Self-report of pain is preferable, but in case of suspicion of pain, reliable and valid tools for signalling pain in people with intellectual disabilities who have less verbal expression are available (Herr et al., 2019). Suggested pain scales for children are **Non-communicating Children's Pain Checklist – Revised** (NCCPC-R, Breau et al., 2002), **r-FLACC** (Malviya et al., 2006) or the **Paediatric Pain Profile** (Hunt et al., 2004). For adults the **Chronic Pain Scale for Nonverbal Adults with Intellectual Disabilities** (Lotan et al., 2009) can be used.

For the assessment of the sensory profile of a person with PMS, several tools are available. The Short Sensory Profile (SSP) is one of the most commonly used measures of sensory features in children with autism spectrum disorder. The SSP is a shortened form of Dunn's Sensory Profile 2 caregiver questionnaire (Dunn, 2014) developed as a screening tool to identify children aged 0 to 14; 11 years with sensory processing difficulties. The SSP has demonstrated discriminate validity of over 95% in identifying children with and without sensory modulation differences (Tomchek and Dunn, 2007).

The recently developed SAND (Sensory Assessment for Neurodevelopmental Disorders), a clinician-administered observation and corresponding caregiver interview that captures sensory symptoms based on the DSM-5 criteria for autism spectrum disorder, can also be used (sensitivity 95.5% and specificity 91.7%; Siper et al., 2017 and2021). After assessing the sensory profile, appropriate support can be given.

Based on these considerations, recommendations were formulated and unanimously adopted during a European consensus meeting (Table 2). As agreed in this final consensus meeting; the most important recommendation is, that in the event of a change in behaviour, always take into account that the change can be caused by pain or other

Table 2
Recommendations on sensory functioning in Phelan-McDermid syndrome, as agreed upon by the European Phelan-McDermid syndrome consortium.

Caregivers and health care providers should be aware that individuals with PMS often have a reduced responsiveness to sensory stimuli such as pain, sudden sounds and heat. After every (suspected) trauma or physical incident the individual should be carefully examined.
Every individual with PMS needs to be screened for hearing and visual disturbances at the time of diagnosis and subsequently put under surveillance according to national guidelines.
Sensory integration functioning should be checked in every person with PMS using a validated screening instrument[a]. If altered sensory function is present a sensory integration therapist should be consulted.
In case of behavioural changes in individuals with PMS, evaluation of possible causes should include a search for pain and altered sensory function. The use of a validated non-verbal pain scale is recommended.

[a] e.g. the Short Sensory Profile or Sensory Assessment for Neurodevelopmental Disorders.

underlying sensory problems.

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Margreet Walinga: Conceptualization, Writing – original draft, Writing – review & editing. **Sarah Jesse:** Writing – review & editing. **Norma Alhambra:** Writing – review & editing. **Griet Van Buggenhout:** Review & Editing, Funding acquisition.

Data availability

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References

Battaglia, A., 2011. Sensory impairment in mental retardation: a potential role for NGF. Arch. Ital. Biol. 149 (2), 193–203. https://doi.org/10.4449/aib.v149i2.1362.

van Balkom, I.C.D., Burdeus-Olavarrieta, M., Cooke, J., de Cuba, A.C., Turner, A., 2023. The European Phelan-McDermid syndrome consortium, Vogels A, Maruani A. Consensus recommendations on Mental health issues in Phelan-McDermid syndrome. EJMG (this issue).

Boyd, B., Baranek, G., Sideris, J., Poe, M., Watson, L., Patten, E., et al., 2010. Sensory features and repetitive behaviors in children with autism and developmental delays. Autism Res. 78–87. https://doi.org/10.1002/aur.124.

Breau, L.M., McGrath, P.J., Camfield, C.S., Finley, G.A., 2002. Psychometric properties of the noncommunicating children's pain checklist-revised. Pain 99 (1–2), 349–357. https://doi.org/10.1016/s0304-3959(02)00179-3.

Brignell, A., Gu, C., Holm, A., et al., 2021. Speech and language phenotype in Phelan-McDermid (22q13.3) syndrome. Eur. J. Hum. Genet. 29, 564–574. https://doi.org/10.1038/s41431-020-00761-1.

Burdeus, M., Scholten, S., Nevado Blanco, J., Parker, S., 2023. The European Phelan-McDermid syndrome consortium, Swillen A. Consensus recommendations on Communication, speech and language in Phelan-McDermid syndrome. EJMG (this issue).

Denayer, E., Brems, H., de Cock, P., Evans, G.D., Van Calenbergh, F., Bowers, N., Sciot, R., Debiec-Rychter, M., Vermeesch, J.V., Fryns, J.P., Legius, E., 2009. Pathogenesis of vestibular schwannoma in ring chromosome 22. Med. Genet. 10, 97. https://doi.org/10.1186/1471-2350-10-97.

Dunn, W., 2014. Sensory Profile 2 Users Manual. Bloomington (Pearson).

Han, Q., Kim, Y.H., Wang, X., Liu, D., Zhang, Z.-J., Bey, A.L., et al., 2016. *SHANK3* deficiency impairs heat hyperalgesia and TRPV1 signaling in primary sensory neurons. Neuron 92 (6), 1279–1293. https://doi.org/10.1016/j.neuron.2016.11.007.

Herr, K., Coyne, P.J., Ely, E., Gélinas, C., Manworren, R.C.B., 2019. Pain assessment in the patient unable to self-report: clinical practice recommendations in support of the ASPMN 2019 position statement. Pain Manag. Nurs. 20 (5), 404–417. https://doi.org/10.1016/j.pmn.2019.07.005.

Hunt, A., Goldman, A., Seers, K., Crichton, N., Mastroyannopoulou, K., Moffat, V., Brady, M., 2004. Clinical validation of the paediatric pain profile. Dev. Med. Child Neurol. 46 (1), 9–18. https://doi.org/10.1017/s0012162204000039.

Jeffries, A.R., Curran, S., Elmslie, F., Sharma, A., Wenger, S., Hummel, M., et al., 2005. Molecular and phenotypic characterization of ring chromosome 22. In: Am J Med Genet A. Wiley Subscription Services, Inc., A Wiley Company, vol. 137, pp. 139–147. https://doi.org/10.1002/ajmg.a.30780, 2.

Kientz, M.A., Dunn, W., 1997. A comparison of the performance of children with and without autism on the sensory profile. In: American Journal of Occupational Therapy. American Occupational Therapy Association, vol. 51, pp. 530–537. https://doi.org/10.5014/ajot.51.7.530, 7.

Kolevzon, A., Angarita, B., Bush, L., Wang, A.T., Frank, Y., Yang, A., et al., 2014. Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring. J Neurodev Disord. BioMed Central Ltd 6 (1), 39. https://doi.org/10.1186/1866-1955-6-39.

Koza, S., Tabet, A.C., Bonaglia, C., Andres, S., Stiefsohn, D., Anderlid, B.M., Aten, E., 2023. The European Phelan-McDermid syndrome consortium, Evans G, van Ravenswaaij-Arts C, Kant S. Consensus recommendations on counselling in Phelan-McDermid syndrome. EJMG (this issue).

Landlust, A., Koza, S., Cooke, J., Cabin, M., Walinga, M., Robert, S., Vyshka, K., 2023. The European Phelan-McDermid Syndrome Consortium, Van Balkom I, Van Ravenswaaij-Arts C. Parental Perspectives on Phelan-McDermid Syndrome; Results of a World-wide Survey. EJMG (this issue).

Li, C., Schaefer, M., Gray, C., Yang, Y., Furmanski, O., Liu, S., et al., 2017. Sensitivity to isoflurane anesthesia increases in autism spectrum disorder *SHANK3*+/Δc mutant mouse model. Neurotoxicol. Teratol. 60, 69–74. https://doi.org/10.1016/j.ntt.2016.11.002.

Lotan, M., Ljunggren, E.A., Johnsen, T.B., Defrin, R., Pick, C.G., Strand, L.I., 2009. A modified version of the non-communicating children pain checklist-revised, adapted to adults with intellectual and developmental disabilities: sensitivity to pain and internal consistency. J. Pain 10 (4), 398–407. https://doi.org/10.1016/j.jpain.2008.09.006. Epub 2009 Feb 8. PMID: 19201658.

Malviya, S., Voepel-Lewis, T., Burke, C., Merkel, S., Tait, A.R., 2006. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Pediatric Anesthesia 16, 258–265. https://doi.org/10.1111/j.1460-9592.2005.01773.x.

Matuleviciene, A., Siauryte, K., de Kuiper, E., 2023. The European Phelan-McDermid syndrome consortium, Grabrucker AM. Consensus recommendations on Chewing, swallowing and gastrointestinal problems in Phelan-McDermid syndrome. EJMG (this issue).

Mieses, A.M., Tavassoli, T., Li, E., Soorya, L., Lurie, S., Wang, A.T., et al., 2016. Brief report: sensory reactivity in children with phelan-McDermid syndrome. In: 46J Autism Dev Disord, pp. 2508–2513. https://doi.org/10.1007/s10803-016-2754-0. second ed. Springer US, 7.

Noda, H., Tokunaga, A., Imamura, A., Tanaka, G., Iwanaga, R., 2020. Visual attention affects late somatosensory processing in autism spectrum disorder. Int. J. Neurosci. 1–8. https://doi.org/10.1080/00207454.2020.1849186.

Orefice, L.L., Zimmerman, A.L., Chirila, A.M., Sleboda, S.J., Head, J.P., Ginty, D.D., 2016. Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs. Cell 166 (2), 299–313. https://doi.org/10.1016/j.cell.2016.05.033.

Phelan, M.C., Rogers, R.C., Saul, R.A., Stapleton, G.A., Sweet, K., McDermid, H., et al., 2001. 22q13 deletion syndrome. Am. J. Med. Genet. 101 (2), 91–99. https://doi.org/10.1002/1096-8628(20010615)101:2<91::aid-ajmg1340>3.0.co;2-c.

Phelan, K., McDermid H, E., 2011. The 22q13.3 deletion syndrome (phelan-McDermid syndrome). Mol.Syndromol. 2, 186–201. https://doi.org/10.1159/000334260.

Phelan, K., Boccuto, L., Powell, C.M., et al., 2022. Phelan-McDermid syndrome: a classification system after 30 years of experience. Orphanet J. Rare Dis. 17, 27. https://doi.org/10.1186/s13023-022-02180-5.

Philippe, A., Boddaert, N., Vaivre-Douret, L., Robel, L., Danon-Boileau, L., Malan, V., et al., 2008. Neurobehavioral profile and brain imaging study of the 22q13.3 deletion syndrome in childhood. Pediatrics 122 (2), e376–e382. https://doi.org/10.1542/peds.2007-2584.

Ponson, L., Gomot, M., Blanc, R., et al., 2018. 22q13 deletion syndrome: communication disorder or autism? Evidence from a specific clinical and neurophysiological phenotype. Transl. Psychiatry 8, 146. https://doi.org/10.1038/s41398-018-0212-9.

Rattaz, C., Dubois, A., Michelon, C., Viellard, M., Poinso, F., Baghdadli, A., 2013. How do children with autism spectrum disorders express pain? A comparison with developmentally delayed and typically developing children. Pain 154 (10), 2007–2013. https://doi.org/10.1016/j.pain.2013.06.011.

Richards, C., Powis, L., Moss, J., et al., 2017. Prospective study of autism phenomenology and the behavioural phenotype of Phelan–McDermid syndrome: comparison to fragile X syndrome, Down syndrome and idiopathic autism spectrum disorder. J. Neurodev. Disord. 9, 37. https://doi.org/10.1186/s11689-017-9217-6.

Roussignol, G., Ango, F., Romorini, S., Tu, J.C., Sala, C., Worley, P.F., et al., 2005. *SHANK3*expression is sufficient to induce functional dendritic spine synapses in aspiny neurons. J. Neurosci. 25 (14), 3560–3570. https://doi.org/10.1523/JNEUROSCI.4354-04.2005.

De Rubeis, S., Siper, P.M., Durkin, A., et al., 2018. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by *SHANK3* point mutations. Mol. Autism. 9, 31. https://doi.org/10.1186/s13229-018-0205-9.

Samogy-Costa, C.I., Varella-Branco, E., Monfardini, F., et al., 2019. A Brazilian cohort of individuals with Phelan-McDermid syndrome: genotype-phenotype correlation and identification of an atypical case. J. Neurodev. Disord. 11, 13. https://doi.org/10.1186/s11689-019-9273-1.

Sarasua, S., Boccuto, L., Sharp, J.L., Dwivedi, A., Chen, C.-F., Rollins, J.D., et al., 2014. Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome. Hum. Genet. 133 (7), 847–859. https://doi.org/10.1007/s00439-014-1423-7.

Schön, M., Lapunzina, P., Nevado, J., Matina, T., Gunnarson, C., Hadzsiev, K., Verpelli, C., Jesse, S., van Ravenswaaij, C.M.A., 2023. The European Phelan-McDermid syndrome consortium, Hennekam R. Definition and clinical variability of SHANK3-related Phelan-McDermid syndrome. EJMG (this issue).

Siper, P.M., Kolevzon, A., Wang, A.T., Buxbaum, J.D., Tavassoli, T., 2017. A clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with ASD. Autism Res. 10 (6), 1133–1140. https://doi.org/10.1002/aur.1750.

Soorya, L., Kolevzon, A., Zweifach, J., Lim, T., Dobry, Y., Schwartz, L., Frank, Y., Wang, A.T., Cai, G., Parkhomenko, E., Halpern, D., Grodberg, D., Angarita, B., Willner, J.P., Yang, A., Canitano, R., Chaplin, W., Betancur, C., Buxbaum, J.D., 2013. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and *SHANK3* deficiency. Mol. Autism. 4 (1), 18. https://doi.org/10.1186/2040-2392-4-18.

Soorya, L., Leon, J., Pilar Trelles, M., Thurm, A., 2018. Framework for assessing individuals with rare genetic disorders associated with profound intellectual and multiple disabilities (PIMD): the Example of Phelan McDermid Syndrome. Clin. Neuropsychol. 32 (7), 1226–1255. https://doi.org/10.1080/13854046.2017.1413211.

Tabet, A.C., Rolland, T., Ducloy, M., et al., 2017. A framework to identify contributing genes in patients with Phelan-McDermid syndrome. npj Genom. Med. 2, 32. https://doi.org/10.1038/s41525-017-0035-2.

Tavassoli, T., Miller, L.J., Schoen, S.A., Jo Brout, J., Sullivan, J., Baron-Cohen, S., 2017. Sensory reactivity, empathizing and systemizing in autism spectrum conditions and sensory processing disorder. Dev Cogn Neurosci. https://doi.org/10.1016/j.dcn.2017.05.005.

Tavassoli, T., Layton, C., Levy, T., Rowe, M., George-Jones, J., Zweifach, J., Lurie, S., Buxbaum, J.D., Kolevzon, A., Siper, P.M., 2021. Sensory reactivity phenotype in phelan–McDermid syndrome is distinct from idiopathic ASD. Genes 12, 977. https://doi.org/10.3390/genes12070977.

Tomchek, S.D., Dunn, W., 2007. Sensory processing in children with and without autism: a comparative study using the short sensory profile. Am. J. Occup. Ther. 61 (2), 190–200. https://doi.org/10.5014/ajot.61.2.190.

Xu, N., Lv, H., Yang, T., et al., 2020. A 29 Mainland Chinese cohort of patients with Phelan–McDermid syndrome: genotype–phenotype correlations and the role of *SHANK3* haploinsufficiency in the important phenotypes. Orphanet J. Rare Dis. 15, 335. https://doi.org/10.1186/s13023-020-01592-5.

Other sources

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Author, Arlington, VA.

Ayres, A.J., 1972. Sensory Integration and Learning Disorders. Western Psychological Services, Los Angeles, ISBN 978-0-87424-303-1.

Phelan, K., Rogers, R.C., Boccuto, L., 2005. Phelan-McDermid syndrome. In: Adam, M.P., Ardinger, H.H., Pagon, R.A., et al. (Eds.), GeneReviews® [Internet]. Seattle (WA). University of Washington, Seattle, pp. 1993–2021 [Updated 2018 Jun 7].

Nederlandse Richtlijn 22q13 deletiesyndroom (PMS) ©, 2018. https://richtlijnendatabase.nl/richtlijn/22q13_deletiesyndroom_pms/startpagina_-_22q13ds_pms.html.