SSBP Syndrome Sheets

Phelan-McDermid Syndrome – (22q13.3 Deletion Syndrome)

Alternative names

Previously known as 22q13.3 Deletion Syndrome, the condition is now commonly called Phelan-McDermid syndrome (PMS). Some individuals have a pathogenic variant of the gene *SHANK3*, but no detectable deletion in 22q13.3. It should be noted that individuals with ring chromosome 22 commonly have a deletion of the distal part of chromosome 22.

History of the syndrome

Ring chromosome 22 was described as a possible deletion syndrome in 1968 (Weleber, Hecht, & Giblett, 1968), and a description of 'pure' partial monosomy syndrome was published by Watt et al. (1985). In 1992, Phelan et al. published an article with a detailed description of a case with 22q13 deletion (M. C. Phelan et al., 1992). Two subsequent reports highlighting the role of *SHANK3* in explaining the phenotype of the syndrome were published by Bonaglia et al.(2001) and Luciani et al. (2003). The main characteristics of the PMS phenotype are described below but diagnosis can only be confirmed by genetic analysis. Previously, it was thought that involvement of *SHANK3* was necessary for diagnosing the syndrome, but a recent article has proposed a nomenclature that specifies PMS as being either PMS-*SHANK3* related or PMS-*SHANK3* unrelated (K. Phelan et al., 2022).

Incidence/prevalence

Figures on prevalence are limited; current estimates are around 1/30 000 live births but the syndrome is probably underdiagnosed. Studies in populations with intellectual disability (ID) have reported prevalence figures of PMS ranging from 0.25-3.33 %, with the highest estimates associated with more severe-profound ID (Schön et al., 2023).

Physical features and natural history

The phenotype and natural history of the syndrome are variable. More than 75% of individuals have neonatal hypotonia which may persist into childhood, and motor abnormalities are common (Frank, 2021; K. Phelan, Rogers, & Boccuto, 2018; Schön et al., 2023). There may be minor morphological features such as large and fleshy hands, long eyelashes or large and prominent ears. Multiple comorbidities can occur throughout the lifetime. Gastrointestinal problems such as gastroesophageal reflux, cyclic vomiting, constipation or diarrhoea, as well as chewing and swallowing problems and frequent airway infections are common in children (K. Phelan et al., 2018). Epilepsy, involving different types of seizure, can start at any age (Frank, 2021). One study reports that the life time prevalence of epilepsy may be as high as 60% (de Coo, Jesse, Le, Sala, & Bourgeron, 2023).

Cognitive development, behavioural aspects and psychiatric disorders

PMS is characterised by global developmental delay with moderate to profound ID. Marked speech impairment is present in the majority of cases, and alternative and augmentative communication is recommended (Vogels, Droogmans, Vergaelen, Van Buggenhout, & Swillen, 2021). Autism or autism like behaviour is common and is reported in up to 70-80% of individuals with PMS (van Balkom et al., 2023; Vogels et al., 2021). Bipolar disorder and (periodic) catatonic symptoms seem to be particularly prevalent (Verhoeven, Egger, & de Leeuw, 2020). Autism can be identified by the use of the same instruments in

PMS as in idiopathic autism, and similarly ID and level of ID can be identified in PMS by the same assessment methods as in individuals without PMS. (Vogels et al., 2021). Many individuals have disturbed sleep. Reduced response to pain is common, and this poses a risk for somatic issues, such as constipation, ear infections, gastroesophageal reflux or dental problems to be diagnosed late or remain unnoticed (Walinga, Jesse, Alhambra, & Van Buggenhout, 2023). Disturbed heat regulation with a tendency to overheat and decreased perspiration are also frequently reported (Frank, 2021).

Regression

Neurodevelopmental regression, with of loss previously acquired skills, is a key feature of PMS (Dille, Lagae, Swillen, & Buggenhout, 2023; Frank, 2021; Reierson et al., 2017). Regression may involve loss of language/communication, motor or adaptive skills. Both sudden and gradual onset of regression at different ages have been reported. There is no apparent cause in most cases, but symptoms may appear after acute events such as infections, prolonged seizures, or environmental changes. Acute onset of psychiatric symptoms such as catatonia, hallucinations and bipolar disorders can occur in adults. Dille et al. (2023) identified a distinct pattern of developmental regression with four stages across the lifespan: (I) Acute onset of language regression in children, (II) followed by a plateau, (III) severe acute-onset psychiatric symptom in adults/adolescents and (IV) late neuromotor deterioration. The last stage is often preceded by an acute trigger or event such as severe sickness, hormonal shifts, and psychosocial stress. Diagnostic identification and appropriate treatment of psychiatric and somatic disorders are essential when regression occurs.

Genotype Phenotype correlations

SHANK3 is considered the major gene for PMS, and this gene is closely linked to autism symptoms. In general, a smaller deletion is associated with higher cognitive and adaptive levels. Previously, it had been thought that the clinical features were apparent in all individuals with a non-mosaic 22q13.3 deletion, but it has been reported that small deletions of *SHANK3* may have variable penetrance suggesting that some individuals may have compensating mechanisms (Tabet et al., 2017). It should be noted that some individuals seem to have additional copy number variations (CNVs) such as 16p11.2 and 15q11q13 contributing to the phenotype (Tabet et al., 2017). Neurofibromatosis type 2 (NF2) pathogenic variants lie adjacent to the region deleted in PMS, and individuals with ring chromosome 22 have a specific risk of developing (NF2). These individuals should be followed as if they had an affected parent (K. Phelan et al., 2018).

Available guidelines

European Journal of Medical Genetics have published European consensus guidelines for PMS, which were supported by The European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) (van Ravenswaaij-Arts et al 2023).

Kristin A Bakke and Sissel Berge Helverschou : June 2023

Key References:

Bonaglia, M. C., Giorda, R., Borgatti, R., Felisari, G., Gagliardi, C., Selicorni, A., & Zuffardi, O. (2001). Disruption of the ProSAP2 gene in a t(12;22)(q24.1;q13.3) is associated with the 22q13.3 deletion syndrome. *Am J Hum Genet, 69*(2), 261-268. doi:10.1086/321293

de Coo, I. F. M., Jesse, S., Le, T.-L., Sala, C., & Bourgeron, T. (2023). Consensus recommendations on Epilepsy in Phelan-McDermid syndrome. *European Journal of Medical Genetics, 66*(6), 104746. doi:https://doi.org/10.1016/j.ejmg.2023.104746

Dille, Y., Lagae, L., Swillen, A., & Buggenhout, G. V. (2023). Neurodevelopmental profile and stages of regression in Phelan–McDermid syndrome. *Developmental Medicine & Child Neurology, 65*(7), 917-925. doi:https://doi.org/10.1111/dmcn.15482

Frank, Y. (2021). The Neurological Manifestations of Phelan-McDermid Syndrome. *Pediatr Neurol, 122*, 59-64. doi:https://doi.org/10.1016/j.pediatrneurol.2021.06.002
Luciani, J. J., de Mas, P., Depetris, D., Mignon-Ravix, C., Bottani, A., Prieur, M., . . . Mattei, M. G. (2003). Telomeric 22q13 deletions resulting from rings, simple deletions, and translocations: cytogenetic, molecular, and clinical analyses of 32 new observations. *J Med Genet, 40*(9), 690-696. doi:10.1136/jmg.40.9.690
Phelan, K., Boccuto, L., Powell, C. M., Boeckers, T. M., van Ravenswaaij-Arts, C., Rogers, R. C., . . . Bourgeron, T. (2022). Phelan-McDermid syndrome: a classification system after 30 years of experience. *Orphanet J Rare Dis, 17*(1), 27. doi:10.1186/s13023-022-02180-5
Phelan, K., Rogers, R. C., & Boccuto, L. (2018). Phelan-McDermid Syndrome. In M. P. Adam, G. M. Mirzaa, R. A. Pagon, & et al. (Eds.), *GeneReviews®*.
Phelan, M. C., Thomas, G. R., Saul, R. A., Rogers, R. C., Taylor, H. A., Wenger, D. A., & McDermid, H. E. (1992). Cytogenetic, biochemical, and molecular analyses of a 22q13 deletion. *Am J Med Genet, 43*(5), 872-876. doi:10.1002/ajmg.1320430524
Reierson, G., Bernstein, J., Froehlich-Santino, W., Urban, A., Purmann, C., Berquist, S., . . . Hallmayer, J. (2017). Characterizing regression in Phelan McDermid Syndrome (22q13 deletion syndrome). *J Psychiatr Res, 91*, 139-144. doi:10.1016/j.jpsychires.2017.03.010
Schön, M., Lapunzina, P., Nevado, J., Mattina, T., Gunnarsson, C., Hadzsiev, K., . . . Hennekam, R. C. (2023). Definition and clinical variability of SHANK3-related Phelan-McDermid syndrome. *European Journal of Medical Genetics, 66*(7), 104754. doi:https://doi.org/10.1016/j.ejmg.2023.104754
Tabet, A. C., Rolland, T., Ducloy, M., Lévy, J., Buratti, J., Mathieu, A., . . . Bourgeron, T. (2017). A framework to identify contributing genes in patients with Phelan-McDermid syndrome. *NPJ Genom Med, 2*, 32. doi:10.1038/s41525-017-0035-2
van Balkom, I. D. C., Burdeus-Olavarrieta, M., Cooke, J., de Cuba, A. G., Turner, A., Vogels, A., & Maruani, A. (2023). Consensus recommendations on mental health issues in Phelan-McDermid syndrome. *European Journal of Medical Genetics, 66*(6), 104770. doi:https://doi.org/10.1016/j.ejmg.2023.104770
van Ravenswaaij-Arts, C. M. A., van Balkom, I. D. C., Jesse, S., & Bonaglia, M. C. (2023). Editorial: Towards a European consensus guideline for Phelan-McDermid syndrome. *Eur J Med Genet, 66*(5), 104736. doi:10.1016/j.ejmg.2023.104736
Verhoeven, W. M. A., Egger, J. I. M., & de Leeuw, N. (2020). A longitudinal perspective on the pharmacotherapy of 24 adult patients with Phelan McDermid syndrome. *Eur J Med Genet, 63*(3), 103751. doi:10.1016/j.ejmg.2019.103751
Vogels, A., Droogmans, G., Vergaelen, E., Van Buggenhout, G., & Swillen, A. (2021). Recent developments in Phelan-McDermid syndrome research: an update on cognitive development, communication and psychiatric disorders. *Curr Opin Psychiatry, 34*(2), 118-122. doi:10.1097/yco.0000000000000672
Walinga, M., Jesse, S., Alhambra, N., & Van Buggenhout, G. (2023). Consensus recommendations on altered sensory functioning in Phelan-McDermid syndrome. *European Journal of Medical Genetics, 66*(5), 104726. doi:https://doi.org/10.1016/j.ejmg.2023.104726
Watt, J. L., Olson, I. A., Johnston, A. W., Ross, H. S., Couzin, D. A., & Stephen, G. S. (1985). A familial pericentric inversion of chromosome 22 with a recombinant subject illustrating a 'pure' partial monosomy syndrome. *J Med Genet, 22*(4), 283-287. doi:10.1136/jmg.22.4.283
Weleber, R. G., Hecht, F., & Giblett, E. R. (1968). Ring-G chromosome, a new G-deletion syndrome? *Am J Dis Child, 115*(4), 489-493. doi:10.1001/archpedi.1968.02100010491015

Kristin A Bakke and Sissel Berge Helverschou: June 2023

Copyright © 2023 K.A.Bakke & S.B.Helverschou

The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation