



Review

Consensus recommendations on Epilepsy in Phelan-McDermid syndrome

Irenaeus F.M. de Coo^{a,*}, Sarah Jesse^b, Thuy-Linh Le^c, Carlo Sala^d, The European Phelan-McDermid syndrome consortium^e, Thomas Bourgeron^f^a Department of Toxicogenomics, Unit Clinical Genomics, Maastricht University, MHeNs School for Mental Health and Neuroscience, Maastricht, the Netherlands^b Department of Neurology, University of Ulm, Ulm, Germany^c Human Genetics and Cognitive Functions, Institut Pasteur, Université de Paris, Paris, France^d CNR Neuroscience Institute, Milano, Italy^e University Medical Centre Groningen, the Netherlands^f Human Genetics and Cognitive Functions, Institut Pasteur, UMR3571 CNRS, IUF, Université Paris Cité, Paris, France

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ABSTRACT

Phelan-McDermid syndrome (PMS) is a 22q13.3 deletion syndrome that presents with a disturbed development, neurological and psychiatric characteristics, and sometimes other comorbidities like seizures. The epilepsy manifests itself in a variety of seizure semiologies. Further diagnostics using electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) are important in conjunction with the clinical picture of the seizures to decide whether anticonvulsant therapy is necessary. As part of the development of European consensus guidelines we focussed on the prevalence and semiology of epileptic seizures in PMS associated with a pathogenic variant in the *SHANK3* gene or the 22q13 deletion involving *SHANK3*, in order to then be able to make recommendations regarding diagnosis and therapy.

1. Introduction

This paper has been written as part of a European consensus guideline in Phelan-McDermid syndrome (PMS). The focus in this publication is on epilepsy in *SHANK3*-related PMS due to the presence of a pathogenic variant in *SHANK3* or a deletion of chromosome 22q13.3 including the *SHANK3* gene (Phelan et al., 2022). PMS presents with a developmental disorder with neurological and psychiatric symptoms sometimes accompanied by seizures (Schön et al., 2023). Epilepsy occurs relatively frequent in PMS. The prevalence of fever-related and non-fever-related seizures in patients with PMS is 20–30% (Kolevzon et al., 2014), but the life-time risk is more than 60% at adult age (Sarasua et al., 2014) and is reviewed in Holder and Quach (2016). Atypical absences are the most common type of seizures in PMS and are not always easy to detect. It is therefore important to be alerted on this high risk for the patient to present epileptic seizures, to train parents in semiology and to carry out an electroencephalogram (EEG), if there is any suspicion. It is desirable to start therapy early.

2. Methods

Based on the use of the AGREE II methodology and on bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives (Landlust et al., 2023), the following key questions have been formulated.

- What is the prevalence of epilepsy in PMS, and is there a specific type of epilepsy?
- What is the mechanism underlying epilepsy in PMS?
- What is the treatment for epilepsy in PMS?

We performed a general scientific literature search in the Pubmed database, using the following search terms: phelan-mcdermid syndrome AND (epilepsy OR seizure). For the EU Guidelines, there were 33 articles published between 01/01/2013 and 31/12/2020 that met the search criteria. Since then, 12 publications (including 5 reviews) have been published before September 2022. The literature was then selected and sorted based on the predetermined key questions.

For the questions regarding the prevalence, types, and mechanisms

* Corresponding author.

E-mail addresses: rene.decoo@maastrichtuniversity.nl (I.F.M. de Coo), sarah.jesse@uni-ulm.de (S. Jesse), thuy-linh.le@inserm.fr (T.-L. Le), carlo.sala@in.cnr.it (C. Sala), thomas.bourgeron@pasteur.fr (T. Bourgeron).<https://doi.org/10.1016/j.ejmg.2023.104746>

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of epilepsy in PMS, the following articles were included: Lund et al. (2013); Soorya et al. (2013); Figura et al. (2014); Sarasua et al. (2014); Lee et al. (2015); Holder and Quach (2016); Reiersen et al. (2017); Yoo et al. (2019) jun; Yoo et al. (2019) oct; Ali et al., 2021; Chen et al. (2020).

For the questions about treatments of epilepsy in PMS, the following articles were included: Lund et al., (2013); Soorya et al., (2013); Figura et al., (2014); Ishikawa et al. (2016); Holder and Quach (2016). In addition, references are made to the "Summary of recommendations for the management of infantile seizures" (Wilmschurst et al., 2015), the "Consensus guidelines into the management of epilepsy in adults with intellectual disability" (Kerr et al., 2009) and "Recommendations for the use of magnetic resonance imaging in the care of patients with epilepsy, ILAE consensus report" (Bernasconi et al., 2019). The level of scientific evidence was indicated in formulating the recommendations.

The authors addressed the questions by literature review and expert opinions to provide recommendations. Each question was reviewed by the complete consortium and all recommendations were discussed plenary at the almost monthly online meetings of the consortium. In June 2022, the final version of this PMS epilepsy guideline has been discussed and consented at a physical consensus meeting (Table 1).

3. Results

3.1. Review of the literature

3.1.1. Prevalence of epilepsy in PMS

The prevalence of epilepsy in PMS ranges from 17% to 70% (reviewed in Holder and Quach, 2016). The great differences in the studies available for PMS are due to different inclusion criteria and to the number of patients included. In the largest cohort of patients with PMS ($n = 201$), the prevalence of any type of seizures was 27%, with a significant increase with age: 11% under 5 years of age, 26% between 5 and 10 years old, 43% between 10 and 18 years old and 60% over the age of 18. (Sarasua et al., 2014). This study indicates that the life-time prevalence is high (>60%) and that age at onset for epilepsy can be different from one PMS patient to another.

In a study of 32 individuals with PMS (age from 1.6 to 45.4 years, mean = 8.8, SD = 9.2), parents report seizures in 41%, of whom 22% had febrile seizures, 13% had non-febrile seizures and 6% had both (Soorya et al., 2013). The non-febrile seizures include generalized and focal seizures and have proven EEG abnormalities. Notably, 13% of the individuals in this study have EEG abnormalities but no clinical seizures (Soorya et al., 2013). Thus, in PMS, epileptiform discharges in EEG can be seen in PMS-patients with or without clinical manifestations of epilepsy.

In another study of 24 individuals with PMS (age from 2 to 28 years), 11 individuals (46%) have at least one seizure, with variable age of onset (1-14 years, mean 5.2 years) (Holder and Quach, 2016). The most frequent type of seizure is atypical absences (90%). Other types of seizure are also observed, including tonic (54%), atonic (18%), tonic-clonic (9%), and myoclonic (9%) (Holder and Quach 2016). Six

Table 1
Recommendations on Epilepsy in Phelan McDermid syndrome, as agreed upon by the European Phelan-McDermid syndrome consortium.

In every individual with PMS, irrespective of age, caregivers should be alert for seizures and epilepsy.
In every individual with PMS in whom seizures are suspected but EEG studies are non-conclusive, overnight prolonged EEG studies should be considered.
Brain imaging, preferably by MRI, is advised in every individual with PMS who has epileptic seizures, and indicated when new neurological signs and symptoms, including seizures, occur
A paediatric neurologist or neurologist should be involved in the therapy for epilepsy. Anticonvulsant treatment of epilepsy in individuals with PMS should be provided according to national guidelines ^a .

^a See also ILAE guide Lines on <https://www.ilae.org/>.

(54%) have a combination of seizure types, and five (20%) have a status epilepticus. EEG findings include abnormally slow or absent occipital dominant rhythm (42%), focal spike and slow wave discharges (38%), and generalized spike and slow wave discharges (19%). Brain magnetic resonance imaging (MRI) shows anomalies of the corpus callosum (29%) and T2-weighted hyperintensities of the deep white matter (24%). However, there is to date no specific EEG abnormalities or structural abnormalities detected by brain MRI that can inform on the occurrence and/or types of epilepsy, or on pharmacoresistance (Holder and Quach 2016). A group of 14 patients with PMS and seizures have been investigated (Jesse et al., 2021) by means of high-resolution MRI with subsequent automatic morphometric MRI postprocessing analysis. Also, in this group no subtle cortical malformations explaining the epilepsy are detected.

In a cohort of 16 patients with PMS, including 7 with a diagnosis of epilepsy and 9 without clinical seizure, an overnight EEG leads to an increase in the detection of epileptiform activity to 75% (12 of 16 patients), compared to 18.75% (3 of 16 patients) detected by routine EEG (Khan et al., 2018). In cases where EEG analysis has failed to delineate the clinical condition, overnight prolonged video-EEG monitoring can be carried out to increase the probability of detection of epileptiform activity (Wilmschurst J et al., 2015). In accordance with previous observations by Holder and Quach, the EEG findings are highly variable (i.e. non-specific sharps, sharp and slow wave discharges, spike, polyspike and slow wave discharges), which is not specific to any type of seizures (i.e. focal, multifocal, and generalized) (Khan et al., 2018).

The relationship between epilepsy and regression has been investigated in a group of 50 patients with PMS (Reiersen et al., 2017). While a significantly higher risk of seizures is reported in patients with abnormal EEG (OR = 24.661, $p = 0.005$), neither seizures nor EEG abnormalities are associated with regression ($p > 0.223$) (Reiersen et al., 2017). As for epilepsy, to date, there are no clinical or biological markers known to help understand or predict the regression and/or psychiatric illness in patients with PMS (Kohlenberg et al., 2020).

3.1.2. Mechanism underlying epilepsy in PMS

The mechanism underlying epilepsy in PMS remains largely unknown and might be different from one patient to another. In cultures of neurons derived from iPSC from PMS patients the cell type composition is slightly different compared to their unaffected siblings, with an increase of excitatory neurons proportion as well as a reduction of inhibitory neurons proportion (Breen et al., 2020). *Shank3* knock out mice do not display epileptic seizures, however abnormal EEG (Yoo et al., 2019 jun) and increased excitation in some brain circuits have been described (Yoo et al., 2019 oct; Lee et al., 2015; Ahn et al., 2020; Chen et al., 2020). All these data suggest that loss or reduced levels of the SHANK3 protein might cause an increased excitation in the brain caused by a reduced function of the inhibitory neurons.

In a cohort of patients carrying deleterious *SHANK3* point mutations (16 between 3 and 15 yr and 1 at 42 yr), 5 out of 17 (29%) present with seizures, suggesting that, within the 22q13 region, *SHANK3* pathogenic variants or *SHANK3* haploinsufficiency might be risk factors for seizures (De Rubeis et al., 2018).

Different types of seizures are documented in patients carrying *SHANK3* pathogenic variants, including febrile, absence, focal, and generalized seizures, which can occur in combination. Like other PMS cases, EEG abnormalities are not observed in patients with *SHANK3* pathogenic mutations either with or without clinical seizures. Meanwhile, brain structural MRI showed white matter abnormalities in 3 (17.6%) patients, including 1 with leukodystrophy. In the same cohort, it should be noted that most patients with *SHANK3* point mutations did not present with seizures (De Rubeis et al., 2018), suggesting that in addition to *SHANK3*, other genetic and/or environmental factors may increase the risk of epilepsy in patients with PMS.

The size of the 22q13 deletion has been shown to be associated with a history of abnormal EEG, but not with the risk for epilepsy (Sarasua

et al., 2014; Reiersen et al., 2017; Tabet et al., 2017). Further analyses of patients with a 22q13 deletion and epilepsy led to the identification of additional copy-number variants (CNVs) that cover susceptibility genes for epilepsy, including *KCNT1*, *MYT1L*, *DEAF1* and *SLC25A22*, suggesting a polygenic/multifactorial model underlying the presence of epilepsy in patients with PMS (Tablet et al., 2017).

(Jain et al., 2022) investigated 57 individuals for the prevalence of seizures and the association with genetic and metabolic features. Among the participants, 46% have seizures with the most common type being absence and tonic-clonic seizures. They proposed the *TBC1D22A* gene as a susceptibility gene for epilepsy in addition to *SHANK3*. A metabolic profile, suggesting a disrupted utilization of main energy sources, could be more frequent in PMS patients with epilepsy.

Metachromatic leukodystrophy (MLD) is a rare hereditary disease caused by recessive mutations of the *ARSA* gene on chromosome 22q13. MLD is characterized by the accumulation of fats called sulfatides, causing the destruction of the protective fatty layer (myelin sheath) surrounding the nerves in both the central nervous system and the peripheral nervous system. Heterozygous carriers of a pathogenic variant in *ARSA* are healthy, however MLD symptoms have sporadically been reported in individuals with PMS (De Rubeis et al., 2018). The *ARSA* gene is involved in the 22q13 deletion in 77% of PMS patients (not a causative factor for MLD on its own) and has been proposed to be a risk factor for regression (Kolevzon et al., 2019, al. 2020, Mingbunjerdsuk et al., 2021). The heterozygous *ARSA* deletion, in addition to a second *ARSA* genetic variant on the non-deleted chromosome, (gene frequency of this pseudodeficiency allele at the *ARSA* locus is 13.7 – 17%), might also contribute to the risk of seizures.

Brain-MRI investigations can detect other epileptogenic brain malformations that might have contributed to the epilepsy and/or regression in PMS. These include – posterior fossa malformations, unilateral opercular polymicrogyria, bilateral and perisylvian polymicrogyria (Aldinger et al., 2013; Papetti et al., 2017; Kurtas et al., 2018).

In summary, within the 22q13 region, the loss of the *SHANK3* gene represents a risk factor for epilepsy. *SHANK3* haploinsufficiency might alter the excitation/inhibition balance or utilization of energy sources in specific brain circuits, but other genetic or environmental factors might be required to provoke seizures. The multifactorial model of epilepsy in PMS might explain why the risk and the type of epilepsy and the effective treatments for reducing seizures can be different from one individual to another.

3.2. Treatment of epilepsy in PMS

A wide range of antiepileptic drugs has been used to treat epilepsy in PMS, including lamotrigine, levetiracetam, topiramate, rufinamide, zonisamide, perampanel, felbamate, valproate, carbamazepine, oxcarbazepine, lacosamide, phenytoin, methsuximide, ethosuximide, chlorazepate, lorazepam, and phenobarbital (Figura et al., 2014; Ishikawa et al., 2016; Cortès-Saladelafont et al., 2016 et al., 2016, Holder and Quach, 2016). No antiepileptic drug has shown to be more efficient than others to treat epilepsy in PMS (Holder and Quach, 2016). Nevertheless, most cases respond well to one drug with a decreased frequency of seizures and improvement in behavior (Figura et al., 2014; Ishikawa et al., 2016; Cortès-Saladelafont et al., 2016; Holder and Quach, 2016). Patients suffering from multiple types of seizures are more likely to require a combination of two or more medications (Holder and Quach, 2016). A few individuals develop severe epileptic encephalopathy, such as Lennox-Gastaut syndrome, with pharmacoresistant epilepsy (Lund et al., 2013; Soorya et al., 2013; Ishikawa et al., 2016; Holder and Quach, 2016). Some patients are treated by temporal lobectomy (no further details provided), or implantation of a vagus nerve stimulator with a modest diminution in seizure frequency (Soorya et al., 2013; Holder and Quach, 2016). Based on these data, anticonvulsant therapy shall be given according to local guidelines.

4. Discussion

The pooled prevalence of seizures in PMS calculated from 14 unique studies is 32% (Holder and Quach, 2016), but the life-time prevalence at adult age can be up to 60%. It seems that there is no developmental period which is more at risk for the first seizure events. All types of seizures, both febrile and non-febrile, can occur in individuals with PMS. The most frequently occurring type are atypical absences. Other seizure types cover tonic, atonic, tonic-clonic and myoclonic semiology.

In PMS the prevalence of epilepsy and comorbidities like learning disabilities, mental health issues, and sleep disorders is relatively high (Ho et al., 2018). A change in sleep pattern might point to the presence of seizures (Landlust et al., 2023).

EEG abnormalities can be present in individuals with PMS with and without seizures. The EEG findings are not specific; the most seen pattern is a slow background pattern. Deletion of *SHANK3* increases the risk for all type of seizures, irrespective of the size of the deletion. Larger deletion sizes are associated with a history of abnormal EEG. EEG abnormalities and seizures are not associated with an increased risk for regression. The response to anticonvulsant treatment in individuals with PMS is not different from patients with epilepsy without PMS.

Brain imaging, preferably MRI, is indicated in every individual with PMS who shows neurological signs and symptoms, including seizures Wang et al. (2020). Given that epilepsy occurs with and without overt clinical manifestations in patients with PMS with a higher risk with increasing age, it is a concern. There are both, fever-related and non-febrile seizures, generalized and focal seizures. At clinical manifestation, the epilepsy shall be evaluated. In a minority of individuals with PMS, epilepsy develops into a pharmaco-resistant form. There is no evidence that individuals with PMS benefit from a specific pharmacotherapeutic treatment for seizures. Based on these data, anticonvulsant therapy should be given according to local guidelines.

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CRedit authorship contribution statement

Irenaeus F.M. de Coo: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Sarah Jesse:** Investigation, Data curation, Writing – review & editing. **Thuy-Linh Le:** Investigation, writing editing. **Carlo Sala:** Investigation, writing editing. **Thomas Bourgeron:** Conceptualization, Funding acquisition.

Data availability

Data will be made available on request.

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References

- Ahn, H., Seo, G.H., Keum, C., Heo, S.H., Kim, T., Choi, J., Yum, M.S., Lee, B.H., 2020. Diagnosis of metachromatic leukodystrophy in a patient with regression and Phelan-McDermid syndrome. *Brain Dev.* 42 (5), 414–417. <https://doi.org/10.1016/j.braindev.2020.02.003>.
- Aldinger, K.A., Kogan, J., Kimonis, V., Fernandez, B., Horn, D., Klopocki, E., Chung, B., Toutain, A., Weksberg, R., Millen, K.J., Barkovich, A.J., Dobyns, W.B., 2013. Cerebellar and posterior fossa malformations in patients with autism-associated chromosome 22q13 terminal deletion. *Am. J. Med. Genet. A.* 161A (1), 131–136. <https://doi.org/10.1002/ajmg.a.35700>.
- Ali, F., Shao, L.X., Gerhard, D.M., Sweasy, K., Pothula, S., Pittenger, C., Duman, R.S., Kwan, A.C., 2021. Inhibitory regulation of calcium transients in prefrontal dendritic spines is compromised by a nonsense Shank3 mutation. *Mol. Psychiatr.* 26 (6), 1945–1966. <https://doi.org/10.1038/s41380-020-0708-6>.
- Bernasconi, A., Cendes, F., Theodore, W.H., Gill, R.S., Koepp, M.J., Hogan, R.E., Jackson, G.D., Federico, P., Labate, A., Vaudano, A.E., Blümcke, I., Ryvlin, P., Bernasconi, N., 2019. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League against Epilepsy Neuroimaging Task Force. *Epilepsia* 60 (6), 1054–1068. <https://doi.org/10.1111/epi.15612>.
- Breen, M.S., Browne, A., Hoffman, G.E., Stathopoulos, S., Brennan, K., Buxbaum, J.D., Drapeau, E., 2020. Transcriptional signatures of participant-derived neural progenitor cells and neurons implicate altered Wnt signaling in Phelan-McDermid syndrome and autism. *Mol. Autism.* 11 (1), 53. <https://doi.org/10.1186/s13229-020-00355-0>.
- Chen, Q., Deister, C.A., Gao, X., Guo, B., Lynn-Jones, T., Chen, N., Wells, M.F., Liu, R., Goard, M.J., Dimidschstein, J., Feng, S., Shi, Y., Liao, W., Lu, Z., Fishell, G., Moore, C.I., Feng, G., 2020. Dysfunction of cortical GABAergic neurons leads to sensory hyper-reactivity in a Shank3 mouse model of ASD. *Nat. Neurosci.* 23 (4), 520–532. <https://doi.org/10.1038/s41593-020-0598-6>.
- Cortés-Saladefont, E., Molero-Luis, M., Hsjd Working Group, Artuch, R., García-Cazorla, A., 2016. Pyridoxal phosphate supplementation in neuropediatric disorders. *Semin. Pediatr. Neurol.* 23 (4), 351–358. <https://doi.org/10.1016/j.spen.2016.11.009>.
- De Rubeis, S., Siper, P.M., Durkin, A., Weissman, J., Muratet, F., Halpern, D., 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>.
- Figura, M.G., Coppola, A., Bottitta, M., Calabrese, G., Grillo, L., Luciano, D., et al., 2014. Seizures and EEG pattern in the 22q13.3 deletion syndrome: clinical report of six Italian cases. *Seizure* 23 (9), 774–779. <https://doi.org/10.1016/j.seizure.2014.06.008>.
- Ho, N.T., Kroner, B., Grinspan, Z., Fureman, B., Farrell, K., Zhang, J., Buelow, J., Hesdorffer, D.C., 2018. Rare epilepsy Network steering committee. Comorbidities of rare epilepsies: results from the rare epilepsy Network. *J. Pediatr.* 203, 249–258.e5. <https://doi.org/10.1016/j.jpeds.2018.07.055>.
- Holder, J.L., Quach, M.M., 2016. The spectrum of epilepsy and electroencephalographic abnormalities due to SHANK3 loss-of-function mutations. *Epilepsia* 57 (10), 1651–1659. <https://doi.org/10.1111/epi.13506>.
- Ishikawa, N., Kobayashi, Y., Fujii, Y., Yamamoto, T., Kobayashi, M., 2016. Late-onset epileptic spasms in a patient with 22q13.3 deletion syndrome. *Brain Dev.* 38 (1), 109–112. <https://doi.org/10.1016/j.braindev.2015.06.002>.
- Jain, L., Oberman, L.M., Beamer, L., Cascio, L., May, M., Srikanth, S., Skinner, C., Jones, K., Allen, B., Rogers, C., Phelan, K., Kaufmann, W.E., DuPont, B., Sarasua, S.M., Boccutto, L., 2022. Genetic and metabolic profiling of individuals with Phelan-McDermid syndrome presenting with seizures. *Clin. Genet.* 101 (1), 87–100. <https://doi.org/10.1111/cge.14074>.
- Jesse, Sarah, Huppertz, Hans-Jürgen, Ludolph, Albert Christian, Jan, Kassubek, 2021. Focal cortical dysplasia – relevant for seizures in Phelan McDermid syndrome? *Pediatr. Neurol.* 115, 7–9. <https://doi.org/10.1016/j.pediatrneurol.2020.11.005>.
- Kerr, M., Guidelines Working Group, Scheepers, M., Arvio, M., Beavis, J., Brandt, C., Brown, S., Huber, B., Iivanainen, M., Louise, A.C., Martin, P., Marson, A.G., Prasher, V., Singh, B.K., Veendrick, M., Wallace, R.A., 2009. Consensus guidelines into the management of epilepsy in adults with an intellectual disability. *J. Intellect. Disabil. Res.* 53 (8), 687–694. <https://doi.org/10.1111/j.1365-2788.2009.01182.x>.
- Khan, O.I., Zhou, X., Leon, J., Kessler, R., Gaughan, T., D'Souza, P., Gropman, A., Cohen, N., Rennert, O., Buckley, A., Inati, S., Thurm, A., 2018. Prospective longitudinal overnight video-EEG evaluation in Phelan-McDermid Syndrome. *Epilepsy Behav.* 80, 312–320. <https://doi.org/10.1016/j.yebeh.2017.11.034>.
- Kohlenberg, T.M., Trelles, M.P., McLarny, B., Betancur, C., Thurm, A., Kolevzon, A., 2020. Psychiatric illness and regression in individuals with Phelan-McDermid syndrome. *J. Neurodev. Disord.* 12 (1), 7. <https://doi.org/10.1186/s11689-020-9309-6>.
- 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.* 6 (1), 39. <https://doi.org/10.1186/1866-1955-6-39>.
- Kolevzon, A., Delaby, E., Berry-Kravis, E., Buxbaum, J.D., Betancur, C., 2019. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature. *Mol. Autism.* 10, 50. <https://doi.org/10.1186/s13229-019-0291-3>.
- Kurtas, N., Arrigoni, F., Errichello, E., Zucca, C., Maghini, C., D'Angelo, M.G., Beri, S., Giorda, R., Bertuzzo, S., Delledonne, M., Xumerle, L., Rossato, M., Zuffardi, O., Bonaglia, M.C., 2018. Chromothripsis and ring chromosome 22: a paradigm of genomic complexity in the Phelan-McDermid syndrome (22q13 deletion syndrome). *J. Med. Genet.* 55 (4), 269–277. <https://doi.org/10.1136/jmedgenet-2017-105125>.
- Landlust, Annemiek, Koza, Sylvia, Cooke, Jennifer, Cabin, Maya, Walinga, Margreet, Robert, Sandra, Vyshka, Klea, the European Phelan-McDermid syndrome consortium, Balkom, Inge van, Conny van Ravenswaaij-Arts, 2023. Parental Perspectives on Phelan-McDermid Syndrome; Results of a World-wide Survey. *EJMG (this issue)*.
- Lee, J., Chung, C., Ha, S., Lee, D., Kim, D.Y., Kim, H., Kim, E., 2015. Shank3-mutant mice lacking exon 9 show altered excitation/inhibition balance, enhanced rearing, and spatial memory deficit. *Front. Cell. Neurosci.* 9, 94. <https://doi.org/10.3389/fncel.2015.00094>.
- Lund, C., Brodtkorb, E., Røsbj, O., Rødningen, O.K., Selmer, K.K., 2013. Copy number variants in adult patients with Lennox-Gastaut syndrome features. *Epilepsy Res.* 105 (1–2), 110–117. <https://doi.org/10.1016/j.eplepsyres.2013.01.009>.
- Mingbunjerdsuk, D., Wong, M., Bozarth, X., Sun, A., 2021. Co-Occurrence of metachromatic leukodystrophy in phelan-McDermid syndrome. *J. Child Neurol.* 36 (2), 148–151. <https://doi.org/10.1177/0883073820960308>.
- Papetti, L., Ursitti, F., Pimpolari, L., Nicita, F., Novelli, A., Zicari, A.M., Duse, M., Tarani, L., Spalice, A., 2017. Unilateral opercular polymicrogyria in a girl with 22q13 deletion syndrome. *Int. J. Pediatrics & Child Care* 2, 1–7.
- Phelan, K., Boccutto, L., Powell, C.M., Boeckers, T.M., van Ravenswaaij-Arts, C., Rogers, R.C., Sala, C., Verpelli, C., Thurm, A., Bennett Jr., W.E., Winrow, C.J., Garrison, S.R., Toro, R., Bourgeron, T., 2022. Phelan-McDermid syndrome: a classification system after 30 years of experience. *Orphanet J. Rare Dis.* 17 (1), 27. <https://doi.org/10.1186/s13023-022-02180-5>.
- Reiersen, G., Bernstein, J., Froehlich-Santino, W., Urban, A., Purmann, C., Berquist, S., et al., 2017. Characterizing regression in Phelan McDermid Syndrome (22q13 deletion syndrome). *J. Psychiatr. Res.* 91, 139–144. <https://doi.org/10.1016/j.jpsychores.2017.03.010>.
- Sarasua, S.M., Boccutto, 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, Michael, Lapunzina, Pablo, Nevado, Julian, Matina, Teresa, Gunnarson, Cecilia, Hadzisev, Kinga, Verpelli, Chiara, Jesse, Sarah, Conny, M.A., Ravenswaaij, van, et al., 2023. Definition and Clinical Variability of SHANK3-Related Phelan-McDermid Syndrome. *EJMG (this issue)*.
- Soorya, L., Kolevzon, A., Zweifach, J., Lim, T., Dobry, Y., Schwartz, L., et al., 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>.
- Tabet, A.C., Rolland, T., Ducloy, M., Lévy, J., Buratti, J., Mathieu, A., Haye, D., Perrin, L., Dupont, C., Passemard, S., Capri, Y., Verloes, A., Drunat, S., Keren, B., Mignot, C., Marey, I., Jacquette, A., Whalen, S., Pipiras, E., Benzacken, B., Chantot-Bastaraud, S., Afenjar, A., Héron, D., Le Caignec, C., Beneteau, C., Pichon, O., Isidor, B., David, A., El Khattabi, L., Kemeny, S., Gous, L., Vago, P., Mosca-Boiron, A.L., Favier, L., Missirian, C., Philip, N., Sanlaville, D., Ederly, P., Satre, V., Coutton, C., Devillard, F., Dieterich, K., Vuillaume, M.L., Rooryck, C., Lacombe, D., Pinson, L., Gatinois, V., Puechberty, J., Chiesa, J., Lespinasse, J., Dubourg, C., Quelin, C., Fradin, M., Journel, H., Toutain, A., Martin, D., Benmansour, A., Leblond, C.S., Toro, R., Amsellem, F., Delorme, R., Bourgeron, T., 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>.
- Wang, I., Bernasconi, A., Bernhardt, B., Blumenfeld, H., Cendes, F., Chinvarun, Y., Jackson, G., Morgan, V., Rapp, S., Vaudano, A.E., Federico, P., 2020. MRI essentials in epileptology: a review from the ILAE Imaging Taskforce. *Epileptic Disord.* 22 (4), 421–437. <https://doi.org/10.1684/epd.2020.1174>.
- Wilmshurst, J.M., Gaillard, W.D., Vinayan, K.P., Tsuchida, T.N., Plouin, P., Van Bogaert, P., Carrizosa, J., Elia, M., Craiu, D., Jovic, N.J., Nordli, D., Hirtz, D., Wong, V., Glauser, T., Mizrahi, E.M., Cross, J.H., 2015. Summary of recommendations for the management of infantile seizures: task force report for the ILAE commission of pediatrics. *Epilepsia* 56 (8), 1185–1197. <https://doi.org/10.1111/epi.13057>.
- Yoo, Y.E., Yoo, T., Lee, S., Lee, J., Kim, D., Han, H.M., Bae, Y.C., Kim, E., 2019. Shank3 mice carrying the human Q321R mutation display enhanced self-grooming, abnormal electroencephalogram patterns, and suppressed neuronal excitability and seizure susceptibility. *Front. Mol. Neurosci.* 12, 155. <https://doi.org/10.3389/fnmol.2019.00155>.
- Yoo, T., Cho, H., Park, H., Lee, J., Kim, E., 2019. Shank3 exons 14-16 deletion in glutamatergic neurons leads to social and repetitive behavioral deficits associated with increased cortical layer 2/3 neuronal excitability. *Front. Cell. Neurosci.* 13, 458. <https://doi.org/10.3389/fncel.2019.00458>.