American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

Phelan-Mc Dermid-Syndrome in a 7 Years-Old Boy: Pathogenic (Class 4) 2547_2548delGGinsTTC; P. (Arg849Lysfs*534) In Heterozygous Form

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To Cite This Article: *Stefan Bittmann*, Elena Moschüring Alieva, Elisabeth Luchter, Lara Bittmann and Gloria Villalon. Phelan-Mc Dermid-Syndrome in a 7 Years-Old Boy: Pathogenic (Class 4) 2547_2548delGGinsTTC; P. (Arg849Lysfs*534) In Heterozygous Form. Am J Biomed Sci & Res. 2023 19(3) AJBSR.MS.ID.002594,* DOI: 10.34297/AJBSR.2023.19.002594

Received: July 01, 2023; **Published:** July 10, 2023

Abstract

Phelan-McDermid syndrome (22q13.3 deletion syndrome, microdeletion 22q13.3 or abbreviated PMS) is a primarily genetic global developmental disorder usually associated with severe intellectual disability, lack of language development and neuromuscular symptoms. It is caused by a microdeletion on the long arm of chromosome 22. Phelan-McDermid syndrome was first described by Watt and coworkers in 1985 as partial monosomy 22q. Subsequently, further studies addressed the modes of inheritance and genetic alterations in different individuals. K. Phelan and H. McDermid were among the first researchers to characterize the syndrome in more detail phenotypically in a larger group of patients. More recent studies consider the loss of a copy of the gene ProSAP2/Shank3 (Shank3), which encodes a synaptic protein of neurons, as the cause of the phenotypic abnormalities. We present a case of Phelan-McDermid syndrome in a 7 years-old boy.

Keywords: Phelan-McDermid syndrome-SHANK3-child

Case Report Findings for A.D., Born 19.01.2016, 7 Years-Old Boy

Results of conventional chromosomal diagnosis and CGH array analysis: Chromosome analysis revealed a regular male chromosome set (46, XY) in the patient with no evidence of numerical or structural alteration. A band resolution of approximately 550 bands was obtained. A familial chromosomal change could thus be excluded with high probability in the patient. Whole exome sequencing showed the SHANK3 gene revealed the variant classified as likely pathogenic (class 4) 2547_2548delGGinsTTC; p. (Arg849Lysfs*534) in heterozygous form (present on one of the two rb carriers).

Discussion

Alterations in the SHANK3 gene follow the autosomal dominant corner pathway [1-24]. Athogenic alterations in the SHANK3 gene are associated with Phelan-McDermid syndrome [1-24]. Currently, about 1000 cases are diagnosed worldwide [1-24]. However, it is known from recent studies of large collectives of autistic patients that the proportion of patients with Phelan-McDermid syndrome alone in autism spectrum disorders is approximately 0.5% [3,6,10]. Thus, in all likelihood, the syndrome is significantly underdiagnosed [4,5,8]. Since not all PMS cases are associated with autism, epidemiological estimates are still very vague [3,6,10,13,14]. However, using the current prevalence figures for autism spectrum disorders as a basis, a conservative estimate of a frequency of at least 1:20,000 of all newborns with PMS or Shank3 mutations is obtained [3,6,10]. In Phelan-McDermid syndrome, severe muscle hypotonia is seen in neonates. In childhood, a pronounced speech developmental delay is found. In addition, other symptoms of varying severity may occur, such as autistic behaviors, seizures, reduced pain perception,

dysmorphic signs with abnormalities of the face such as protruding, malformed ears, large hands, underdeveloped toenails. A correlation of the SHANK3 variant with the clinical abnormalities or a part of the clinical abnormalities is likely [1-24]. The HNMT gene showed the variant classified as probably pathogenic (class 4) c.623T>C; p. (Leu208Pro) in heterozygous form. Alterations in the HNMT gene follow autosomal recessive inheritance. Pathogenic alterations in the HNMT gene are associated with autosomal recessive hereditary mental retardation type 51. The hereditary carriers (chromosomes) are present in duplicate in humans, with the exception of the sex chromosomes in males, since one chromosome is inherited from the mother and the other from the father. In autosomal dominant inheritance, a single altered hereditary predisposition (in one gene copy) is sufficient to cause the clinical onset of a disease. For children of affected individuals, the risk of inheriting the disease-causing genetic alteration is 50%. Autosomal recessive diseases only develop if a mutation in the same gene is present in both chromosomes of a pair. The parents of an affected person are so-called carriers and carry the mutation on only one chromosome of the corresponding chromosome pair. As a rule, they are symptom-free. For each child of these parents, there is a 25% risk of inheriting both mutations and developing the disease. The probability of not inheriting either parent's mutation is also 25%. The probability that the child will also be a carrier is 50%.

A connection of the HNMT variant with the clinical abnormalities could not be confirmed by molecular genetics, since a second pathogenic variant in the sense of a compound heterozygosity (both gene copies carry one variant each) could not be detected in the HNMT gene. In addition, the patient was found to have a probable pathogenic alteration in the EXOSC8 (c.815G>C; p. (Ser272Thr) and F12 gene (c.971_1018+24del). Alterations in these two genes also follow autosomal recessive inheritance, respectively. A symptom triad can be found in varying degrees in most affected individuals: Almost all patients present with a global developmental disorder, usually associated with severe intellectual disability, deficient language development, and marked muscle hypotonia. The psychiatric component is not uniform. However, current data indicate that approximately 80% of children can be diagnosed with early childhood autism or more broadly autism spectrum disorder, not infrequently accompanied by marked motor hyperactivity. Affected individuals with microdeletion 22q13.3 or mutations in the Shank3 gene are also known to develop further psychiatric disorders such as bipolar disorder or schizophrenia, particularly in later adolescence and adulthood. The speech disorder usually manifests itself very early in a lack of phonation or a very delayed onset of phonation. It is often reported that children are initially able to speak single words, in some cases even two-word sentences. This ability usually fades with age. The triad is completed by muscular hypotonia, which is often the first symptom to become apparent in the neonatal period. Other more common symptoms include an increased tolerance to pain and a tendency to infection. In addition, mild facial and limb malformations are regularly found. Internal malformations of the heart or kidneys and urinary tract are also common and appropriate investigations should be made. In more than 25%, patients suffer from epilepsy, which may be associated with brain malformations such as arachnoid cysts. Rarely, disorders of endocrine or internal organs such as autoimmune hepatitis have also been observed. The behavior of children with PMS is characterized by the severe intellectual disability and often by the autistic abnormalities such as lack of eye contact, lack of social reciprocity, and repetitive behaviors. Many children fail to develop a biphasic sleep-wake rhythm. An association with epilepsy, incontinence, psychiatric disorders and metachromatic disorders are described in literature [12,17,21]. In conclusion, Phelan-Mc Dermid syndrome is an extremely rare syndrome in childhood with about 1000 individuals worldwide.

Acknowledgement

None.

Conflict of Interest

None.

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