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Review

SHANK3 Mutation and Phelan-Mcdermid Syndrome

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ABSTRACT

The 22q13.3 deletion syndrome, also known as Phelan-McDermid syndrome (PMS), has been identified in more than 2200 people worldwide. Globally, there is a delay in development, intellectual deficiencies, and most importantly, difficulty and delay in speech. In addition, there is low muscle tone, weaker eye contact, extreme sensitivity to touch, and aggressive behaviors that suggest communication and social influences like autism or autistic-like traits, which are also classified as neurological disorders. The majority of PMS cases are not inherited genetically. Most often, it happens by mistake when reproductive cells are developing or when a fetus is first developing. Prenatal testing for high-risk pregnancies can reassure in situations where there have been familial rearrangements. This review article provides general information about PMS. In addition, the relationship between PMS and autism spectrum disorder was examined. We also focus on the role of mutations in the SHANK3 gene in PMS.

Keywords: Deletion, neurological disorders, ovarium, Phelan-McDermid syndrome, SHANK3, sperm

The removal of the distal long arm (q) of chromosome 22 results in the contiguous gene deficiency known as 22q13.3 deletion syndrome, commonly known as Phelan-McDermid syndrome (PMS). It has been identified in more than 2200 patients globally. Autism or autistic-like traits that are present globally and are also classified as neurological disorders include developmental delay, intellectual deficiencies, particularly difficulty and delay in speech, poor muscle tone and weak eye contact, tactile sensitivity, and aggressive tendencies. Infants with PMS may begin to babble at a normal age, and young children may have a limited vocabulary by the time they are three or four years old. Although many kids at this age seem to lose their ability to talk, vigorous therapy and communication training can help them restore their verbal skills and expand their vocabulary. On the other hand, speaking will worsen over time.[1-4]

In contrast to other autosomal chromosome abnormalities frequently linked to growth deficiencies, most people with PMS develop within normal limits. Only 10% of the affected kids are underweight for their age, and some of them have growth that exceeds the 95th percentile. The severity of developmental delay varies. Motor developmental milestones like sitting, rolling, crawling, and walking frequently happen later than usual. Eighteen months is the typical age for sitting and rolling over. Although some people do not stand, walking often begins at the age of 27 months and is characterized by an erratic gait. It is usual to have mild to severe mental impairment.[1]

It can manifest in a variety of bodily parts. Long eyelashes, puffy eyelids, large eyebrows, large or unusual ears, very large hands, unusual toenails, full eyebrows, a narrow and disproportionate skull, full cheeks, a rounded and broadly arched nose, and a chin that is frequently pointed and may become prominent with age are common physical characteristics.[2,3]

One copy of SH3 and multiple ankyrin repeat domains 3 (SHANK3), which encodes a significant scaffolding protein present in the postsynaptic

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density of excitatory synapses, has been identified as the gene responsible for PMS. Reduced dendritic number and poor synaptic transmission and plasticity are caused by decreased expression of SHANK3.[2]

HISTORY OF PMS

In 1985, PMS was originally defined by describing its clinical characteristics. Speech impairments, severe intellectual incapacity, and dysmorphic characteristics have all been linked to pericentric inversion of chromosome 22.[5] Similar case reports, dysmorphic characteristics, and delays have been documented in the scientific literature. It has been determined that these symptoms are brought on by deletions in the long arm's terminal area of chromosome 22.[6] The genetic alteration of the acrosin (ACR), SHANK3, and RAB, members of the Ras oncogene family-like 2 (RABL2B) genes in the 100 kb (kilobase) region of the chromosome has been linked to PMS.[7] The ACR gene is a gene that, using the appropriate genetic sequence, causes the production of a protein molecule essential for fertilization in spermatozoa. This gene's deletion has just a small effect on the syndrome.[8] The members of the RAB, RAB2B gene produces a G protein that controls the movement of vesicles throughout the cell, however, the RAB2A gene on chromosome 2 neither replaces nor makes up for any RAB2B gene deletion.[9] The SHANK3 gene, which is expressed locally, produces protein molecules that protect the structural integrity of synaptic cells in the brain.[9-11] In a clinical investigation, Bonaglia et al.[12] found that the SHANK3 gene translocation between chromosomes 12 and 22 was well-characterized and correlated with PMS symptoms. This was validated by Wilson et al.[13] in research, they carried out in 2006 using their experiments on 56 cases.

Etiology

In the hippocampus, cerebellar granule cells, caudate-putamen, and thalamic nuclei, the post-translational SHANK3 messenger ribonucleic acid (mRNA) molecule is integrated and expressed at high levels. It is located in proximal and distal dendrites.[14-17] The SHANK3 protein has been linked to peripheral nervous system processing, including neuromuscular connections, using immunohistochemical methods.[18] To maintain appropriate synaptic development and operation, SHANK/Shank proteins interact with a wide range of diverse proteins, including cytoskeletal proteins, scaffolding proteins, and receptors.[19-22] In order to control receptor endocytosis, enable communication between signaling pathways, and promote synaptic plasticity-a crucial step in learning and memory SHANK/Shank protein molecules interact with signaling molecules and enzymes.[19,20]

Epidemiology

As chromosomal microarray has not yet fully merged into mainstream clinical practice, in accordance with the 2010 guidelines that set it as the standard of care for people with developmental disabilities, its prevalence is likely underestimated, although 1200 people worldwide have been diagnosed with PMS.[23] Recent research using chromosomal microarray analysis or sequencing for autism spectrum disorder (ASD) reveals that deletions 0.16% or mutations 0.31% in SHANK3 can account for at least 0.5% of autism. Additionally, genetic alteration of the SHANK3 gene has been linked to about 2% of ASD in people with moderate to profound intellectual disabilities.[24,25] Phelan-McDermid syndrome has an equal impact on both men and women.[26] Epidemiological research is being conducted to better understand and describe how paracrine genes affect the severity and phenotypic heterogeneity.[27]

Diagnosis

A wide range of clinical characteristics of PMS exists, and the severity of these characteristics differs among those who are affected. As of yet, the diagnosis has been determined genetically rather than based on the specific characteristics that make up the clinical aspects of PMS. The most frequent genetic tests to diagnose SHANK3 haploid deficiency include chromosomal microarray analysis and multiplex ligation-dependent amplification, which confirm relative gene copy number.[28] Chromosome microarray analysis cannot detect intragenic mutations in genes less than 30 kb; instead, deoxyribonucleic acid (DNA) sequencing methods are utilized to pinpoint specific base pairs in the genome.[29]

SHANK3 AND AUTISM SPECTRUM DISORDER

Research on this subject has increased as a result of the overlap in occurrence and the link of the SHANK3 gene with autism. There have been 100 genes discovered, and about 20% of autism has been related to certain chromosomal rearrangements.[30-32] In addition to the SHANK3 gene, the Fragile X syndrome-causing FMR1 gene mutation, the Rett syndrome-causing MeCP2 gene mutation, the tuberous sclerosis-causing TSC1/2 gene mutation, the Cowden syndrome-causing PTEN gene,

and the neurofibromatosis type 1–causing NF1 gene have also been identified in ASD.[30-33] Many genetic subgroups of autism share a considerable amount of the same physiological dysfunction, including deficiencies in synaptic function, synaptic plasticity, and excitatory glutamatergic transmission. A high connection has been found between various causes of autism, including genes like SHANK3 and TSC1, by creating a protein interaction network using protein molecules produced by known genes associated with autism.[31] Phosphatidylinositol-3 kinase/mammalian target of rapamycin/serine-threonine-specific protein kinase (PI3K/mTOR/AKT1) and mitogen-activated protein kinase downstream synaptic pathways, which are involved in a number of single-gene causes of autism, have also been found to be similar.[31-35] The consequences of these genetic alterations are extremely complicated and reliant on feedback mechanisms, crosstalk between signaling pathways, and the participation of other genes' genetic regulators. According to these findings, synaptic dysregulation caused by hypo- or hyperconnectivity as a result of altered genetic makeup and impacted protein molecules is assumed to be the cause of autism.[36-41]

In conclusion, PMS presents a wide range of clinical features and neurological characteristics. Due to these clinical features, it can affect many organs of the body. Loss of the SHANK3 gene parallels autistic behaviors. It causes PMS, which causes developmental delay, difficulty in speech, delayed speech development, and hypotonia. Since several SHANK3 mutations have been described in a specific phenotypic group of ASD patients, SHANK3 is strongly suspected to be involved in ASD. As medicine and technology have advanced, it has enabled more detailed research and understanding of the 22q13 haploid deficiency and SHANK3. It will be possible to ascertain whether the severity of clinical phenotypes and particular PMS manifestations are related to additional genetic differences as a result of improved knowledge about the variety and type of genetic defects thanks to genetic testing and a large database of genetic samples.

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