

# WHAT IS PHELAN-MCDERMID SYNDROME (PMS)?

## A BRIEF OVERVIEW.

PMS is a rare genetic condition most commonly caused by a deletion (loss) of genetic material on chromosome 22. The specific region of chromosome 22 that is affected is called “22q13”, leading some to call it “22q13 deletion syndrome”. PMS may also be caused by a sequence (spelling) change (also called a disease-causing, or “pathogenic”, variant) in the *SHANK3* gene.

*Manifestations:* PMS may cause several different health conditions, including intellectual disability, absent or delayed speech, autism spectrum disorder or autistic behaviors, low muscle tone, feeding difficulties, gastroesophageal reflux, constipation and decreased perception of pain. Other health concerns may include kidney abnormalities, seizures, brain abnormalities, and heart defects. PMS is a highly variable condition, meaning those affected with PMS will likely show different symptoms of the condition. The manifestations may be present in varying levels of severity. It is not possible to predict which manifestations a person diagnosed with PMS will have.

There are some facial and body features that are seen more commonly in those with PMS. Many of these features have no impact on someone’s overall health, but are things a doctor may look for when considering a diagnosis of PMS. For a complete list of these features, please visit [https://www.pmsf.org/about\\_pms/medical-issues/](https://www.pmsf.org/about_pms/medical-issues/).

Based on a survey of PMS families, the primary concerns caregivers reported about having a child with PMS include behavioral difficulties, sleep issues and communication limitations. Other concerns include regression of skills and seizures. Despite these challenges, those with PMS are often described as pleasant individuals with sweet dispositions.

## HOW IS PMS DIAGNOSED?

### UNDERSTANDING THE GENETIC TESTING.

To better understand the testing, a brief review of genetics may be helpful. Within each cell of the body, there are **chromosomes**, where genetic information (DNA) is stored. There are 46 total chromosomes in

each cell that can be further divided into 23 distinct pairs. One copy of each pair is inherited from the mother, and the other copy is passed on from the father. On each chromosome are stretches of DNA that are called **genes**. Genes are important in helping the body develop, grow and function. Genes are responsible for each person’s unique features, such as hair color and eye color. Some genes are very important in the development and function of the brain, starting very early in pregnancy. If these important genes do not work properly, the brain may not work as expected.

The diagnosis of PMS requires genetic testing. Most people are diagnosed using a genetic test called **chromosomal microarray analysis** (also called CMA, SNP array or array-CGH). This test can detect extra or missing pieces of genetic information by scanning the length of each chromosome. For a diagnosis of PMS, the microarray testing will show a deletion (loss) of genetic information on chromosome 22q13 that includes part, or all, of the *SHANK3* gene.

In addition to chromosomal microarray analysis, two other tests can help to further define the underlying genetic abnormality. A **karyotype** provides a picture of the structure of the chromosomes. Chromosomes are typically shaped like long rods. About 10% of the time, individuals with PMS will have a ring (circular) structure of chromosome 22. When the ring forms, a small amount of genetic information is deleted from the area of 22q13. Individuals diagnosed with PMS due to a ring chromosome 22 should be followed more closely by their doctors for other potential health concerns. Another genetic test called **fluorescence in situ hybridization**, or FISH, may also be used when looking at chromosome structure. FISH can identify a deletion of genetic information or an unbalanced swapping of genetic information between chromosomes (called a “translocation”) that can result in a diagnosis of PMS.

**Sequencing** is another type of genetic test that is used in diagnosis of PMS. Sequencing involves reading the *SHANK3* gene from start to finish, looking for any spelling changes (variants) that may cause the gene not to work properly. The *SHANK3* gene is important in the function of the brain. If a disease-causing variant is found within the *SHANK3* gene, a diagnosis of PMS can be made.

In most cases of PMS, a sporadic (or isolated) genetic change has occurred in either the sperm or the egg that joined to create the individual. In other



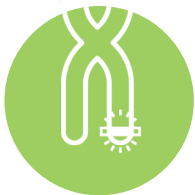
### MICROARRAY

can detect deletion on chromosome 22q13 that includes part, or all, of the *SHANK3* gene



### KARYOTYPE

can depict ring structure of chromosome 22 that occurs in ~10% of individuals with PMS



### FLUORESCENCE IN SITU HYBRIDIZATION

can identify a deletion or swapping of genetic information



### SEQUENCING

can read the *SHANK3* gene and look for any spelling changes that may cause dysfunction

words, PMS does not usually happen because of a parent's DNA. However, sometimes PMS happens because a parent has a "balanced translocation", or equal swapping of genetic information between chromosomes. A balanced translocation causes no health issues for the carrier parent but may result in the parent passing on an "unbalanced translocation", which can lead to a chromosomal deletion and PMS in their child. Therefore, parents of children with such deletions should be tested using FISH to see if they have a balanced translocation. Parents of children diagnosed with PMS due to a *SHANK3* variant should be offered sequencing testing to confirm the variant was "de novo", meaning that the gene variant is found in the child but is not present in either parent.

It is important to remember that there are several different genetic tests that can lead to a diagnosis of PMS. The number of tests ordered or the sequence in which they are ordered may vary based on a child's presenting features, the healthcare provider's professional opinion or health insurance coverage.

For more information regarding genetic testing, please visit [www.pmsf.org](http://www.pmsf.org).

## IS THERE A CURE?

### AN OVERVIEW OF AVAILABLE TREATMENTS.

While researchers are working hard to better understand the cause of PMS and potential treatments, there is not yet a cure available. Instead, individuals with PMS are treated for specific manifestations they may have. Treatment and management of health issues may come from a team of medical specialists. This team may include specialists from neurology, developmental pediatrics, psychiatry, genetics, gastroenterology, nephrology, endocrinology, or cardiology. Affected individuals may also receive supportive therapies, such as physical therapy to assist with gross motor skill development, occupational therapy to assist with fine motor skill development (including feeding difficulties) and speech therapy. Children with PMS often receive some (or all) of these services through their school programs.

## WHAT IS THE PHELAN-MCDERMID SYNDROME FOUNDATION (PMSF) AND HOW CAN IT HELP?

We encourage anyone with a deletion of the 22q13 region or a *SHANK3* variant to join PMSF (<https://www.pmsf.org/membership/>). PMSF provides:

**Support and Services:** Every family is supported through the Regional Parent-to-Parent Program, access to social media support groups, regional gatherings, access to genetic counselors, fundraising support, and the biennial international conference.

**Resources:** A variety of resources for families, including website access, PMSF newsletters, webinars and easy-to-print literature that families may share with their individual medical providers and therapists.

**Research:** Access to the Phelan-McDermid Syndrome International Registry (PMSIR) and Phelan-McDermid Syndrome Data Network (PMS\_DN), where families can share information about their loved ones with PMS and contribute to future PMS-focused research studies. To enroll in the registry, please visit <https://www.pmsf.org/registry/>.