Understanding Your Loved One's Positive Genetic Test Result for *SHANK3* Haploinsufficiency

Information for individuals with a pathogenic or likely pathogenic variant

Phelan-McDermid Syndrome Foundation

Disclaimer: This positive reference guide is not part of your loved one's genetic test report and does not represent medical advice. This guide is general and may not reflect all applicable guidelines or recommendations. It is important to discuss genetic test results with your healthcare provider who can help you understand what the results mean for your loved one and your family.

What does a positive *SHANK3* genetic test result mean?

A positive (or diagnostic) *SHANK3* genetic test result means that a genetic change involving the *SHANK3* gene, located on chromosome 22, was found.[1,2]

This genetic change, known as *SHANK3* haploinsufficiency, occurs when one copy of the *SHANK3* gene is deleted or contains a pathogenic variant and the remaining copy cannot produce enough *SHANK3* protein to support healthy brain function.[3]

A positive *SHANK3* genetic test result on its own cannot predict how an individual may be affected. Your healthcare provider will be able to explain your loved one's specific genetic test result[1,2]

What is *SHANK3* haploinsufficiency?

SHANK3 haploinsufficiency is a leading monogenic cause of autism spectrum disorder (ASD) that is diagnosed as Phelan-McDermid syndrome[4,5,6]

- Individuals with Phelan-McDermid syndrome present with lifelong and severe neurobehavioral, communicative, motor, cognitive and social impairments characterized by delayed or absent developmental milestones[3,6,7,8]
- Additional features of Phelan-McDermid syndrome include neonatal hypotonia (low muscle tone), seizures, impaired sleep, and gastrointestinal problems[3,6]
- Current research indicates that *SHANK3* pathogenic variants may be present in approximately 0.5%-0.69% of individuals with ASD.[4,5] The prevalence of *SHANK3* variants increases to 2.12% in patients with ASD who also have moderate to profound intellectual disability.[5]

Most individuals with Phelan-McDermid syndrome have de novo genetic changes, which means the genetic change was not inherited from their parents but was the result of a spontaneous change.[9]

How is Phelan-McDermid syndrome managed? Are there recommendations for treatment?

Currently, there are no FDA-approved treatments for Phelan-McDermid syndrome. In 2023, updated consensus guidelines on managing individuals with Phelan-McDermid syndrome highlighted multidisciplinary care across genetics, neurology, neurodevelopment, gastroenterology, primary care, physiatry, and other specialties.[9] These guidelines provide recommendations for monitoring

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disease, symptom management that may include medication, behavioral intervention, speech and language therapy, physical therapy, and educational support.[9]

Consensus guidelines are designed to review the latest scientific knowledge and provide guidance for clinicians, researchers, and the general community. Consensus guidelines are written by taskforce members, including clinical experts and representatives from the patient community.

Are there clinical trials for individuals with Phelan-McDermid syndrome?

Clinical trials are research studies involving human volunteers that evaluate the safety and effectiveness of medical products.[10] In addition to clinical trials, there are natural history studies which are observational studies that monitor the progression of a disease over time. These studies collect data that help physicians and researchers better understand the symptoms of a disease and how they change over time. Understanding the course of a disease without a targeted treatment can help in the design and development of therapies to treat rare diseases, like Phelan-McDermid syndrome.

Talk with your healthcare provider to learn more about these opportunities to determine if they are right for your loved one.

Because individuals with Phelan-McDermid syndrome can present with a range of clinical symptoms,[3,6] it is important to talk with your healthcare provider to determine which recommendations might be applicable to your loved one.

Click HERE to reference the current consensus guidelines on the management of Phelan-McDermid syndrome.[9]

What resources exist for individuals with Phelan-McDermid syndrome?

Receiving a positive *SHANK3* genetic test result can be overwhelming. Patient advocacy organizations dedicated to supporting and connecting families of individuals with Phelan-McDermid syndrome exist. These organizations are committed to bringing hope, help and answers to families through ongoing community engagement and partnerships with researchers, healthcare providers and industry professionals to accelerate treatment options for Phelan-McDermid syndrome.

You can learn more about these advocacy organizations by visiting Phelan-McDermid Syndrome Foundation (www.pmsf.org) and CureSHANK (www.cureshank.org).

What happens next?

Talk with your healthcare provider about your loved one's genetic test result. It may be helpful to gather your loved one's medical records or previous test results to provide to your healthcare team. Your healthcare team can help you understand what this result may mean for your loved one, including whether additional follow-up or referrals may be appropriate.

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