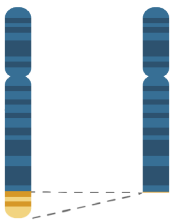
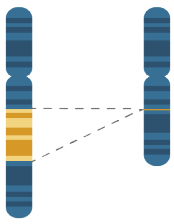
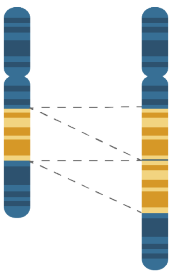
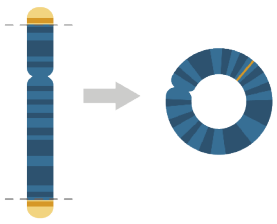
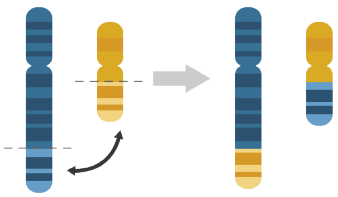
Follow-up Genetic Testing in Phelan-McDermid Syndrome

NOTE:
*If your child has been diagnosed with a **22q13 deletion**, please refer to the **green** section below.*

*If your child has been found to carry a **SHANK3 variant**, please refer to the **blue section**.*

22q13 DELETIONS

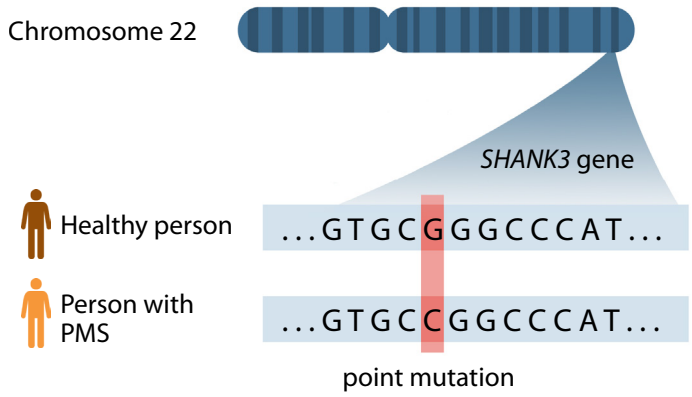
What do you need to know about your child's deletion?	How can you find out?	Why is it important?
1 What is the **size** of the deletion?	Chromosomal microarray analysis will include deletion size	Deletion size and position provide a way to determine which genes are deleted. Most deletions in PMS involve the **SHANK3** gene & are sometimes referred to as **PMS-SHANK3 related**. In some interstitial deletions, the SHANK3 gene remains intact; these cases are called **PMS-SHANK3 unrelated.**
2 Is it a **terminal deletion** or an **interstitial deletion**?	The microarray will identify the position of the deletion	
3 Is the deletion associated with a **ring chromosome**? (11% of PMS cases)	Karyotype testing needs to be performed	Patients with **ring 22** have an increased risk of developing **neurofibromatosis type 2**, a condition that causes tumors in the nervous system and hearing loss, and must be monitored.
4 Is the deletion associated with a **translocation**? (8% of PMS cases) (More likely in individuals in whom the microarray showed a terminal 22q13 deletion and a terminal duplication of another chromosome.)	The presence of an unbalanced translocation can be confirmed by metaphase FISH testing; if large chromosome segments (>5MG) are involved, karyotyping can be used	'Unbalanced' translocations (associated with deletions or duplications) may be inherited from unaffected parents with a 'balanced' translocation. Carriers of balanced translocations are at increased risk of having other affected children.
5 Is the deletion **de novo** (absent from parents) or **inherited**?	FISH testing in parents needs to be performed (and in other family members if parents are positive). Small deletions are not visible with FISH, and should be tested with microarray or MLPA.	Parents (and other family members) may have chromosomal rearrangements that increase their risk of having a child with a deletion.

Terminal deletion	Interstitial deletion	Duplication	Ring chromosome	Translocation
				

SHANK3 VARIANTS

What do you need to know about your child's *SHANK3* variant?	How can you find out?	Why is it important?
What is the **type** of variant?	Sequencing *SHANK3* (through targeted sequencing, gene panel, whole exome or genome sequencing)	Nonsense, frameshift, and splice variants are more likely to be pathogenic (deleterious) than missense variants.
Is the variant **de novo** (absent from parents) or **inherited**?	Both parents must have *SHANK3* sequenced	Almost all pathogenic variants occur **de novo.** If the variant is inherited from an unaffected parent, it is most likely not the cause of the child's developmental delays.
Has the variant been reported in other PMS patients?	The geneticist should look for the variant in the scientific literature and databases	Some *SHANK3* variants are known to cause PMS. These are called pathogenic variants or mutations.
Has the variant been reported in unaffected people?		Some *SHANK3* variants occur frequently in unaffected people and do not cause PMS. These are called benign variants. Pathogenic variants are all very rare and are not found in healthy persons.
Has the variant been found in neither PMS patients nor unaffected people?		Some *SHANK3* variants are not well understood and are considered 'variants of unknown significance.'

A *SHANK3* 'variant' or 'point mutation' is a change in the sequence of the gene, affecting one or a few nucleotides (letters). They can be pathogenic, benign or of unknown significance.



Phelan-McDermid Syndrome Foundation

pmsf.org

info@pmsf.org | Version 2, November 2022