Important Message from the PMSF Medical Advisory Committee

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Potential Rare Conditions in Phelan-McDermid Syndrome; MLD & MLC

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Dear families in the Phelan-McDermid syndrome community,

The PMSF Medical Advisory Committee would like to inform the patient community and the providers who care for them about two very rare disorders that may occur with Phelan-McDermid syndrome, and which are associated with significant developmental regression in early childhood. Developmental regression is known to occur in children and adolescents with Phelan-McDermid syndrome. While some triggers for regression have been described, such as infection, seizures, and puberty, most regressions occur without a known underlying cause. Regression in early childhood should be evaluated further in children with Phelan-McDermid syndrome who are six years old or younger and experience significant loss of language or motor skills. This evaluation is usually organized by a neurologist and may include additional laboratory and genetic testing and possibly brain imaging.

Why are some people with Phelan-McDermid syndrome also at risk for these otherwise rare disorders? Phelan-McDermid syndrome is caused by deletions or mutations at the end of the 22nd chromosome that encompass the *SHANK3* gene. However, there are other genes in this region that are associated with other well-described disorders that affect nerve and motor function. Two disorders in particular are **metachromatic leukodystrophy** (MLD) caused by variants in the arylsulfatase A (*ARSA*) gene, and **megalencephalic leukoencephalopathy with subcortical cysts (MLC)** caused by variants in the *MLC1* gene. Even small deletions (<1 Mb) in the end of chromosome 22 may affect both *ARSA* and *MLC1*. Sequence variants that are contained within the *SHANK3* gene alone will not cause these problems.

Both MLD and MLC are “recessive”, which means that the gene only causes problems when a person has two malfunctioning copies of the gene, one on each of their 22nd chromosomes. Having two disease-causing copies is very rare and affects only 1 in 40,000-160,000 people. However, 1 out of 100-200 people may be carriers of the disease-causing variant, that is, they have only one disease-causing copy, and would typically not have any symptoms. In Phelan-McDermid syndrome, the gene may already be absent on one chromosome because of the deletion related to Phelan-McDermid syndrome. If the copy on the person’s other chromosome is then a disease-causing variant, problems can develop. It is important that caregivers of people with Phelan-McDermid syndrome be aware that if someone has Phelan-McDermid syndrome due to a deletion that includes *ARSA* on just one copy of their 22nd chromosome, and they also carry a disease-causing *ARSA* variant on their other chromosome 22, they may develop MLD. The same mechanism may occur with MLC1 also.

MLD is a neurodegenerative disease with onset in the first four years of life. Regression may be rapid and the affected individuals usually have loss of speech, low muscle tone, reduced reflexes, and gait disturbances. The typical brain magnetic resonance imaging (MRI) finding includes white matter changes in a leopard skin pattern. MLC1 is a neurodegenerative disease with onset in infancy and a slow progressive course of illness. Clinical features include gait disturbances, spasticity and motor delays, and seizures. Brain MRI reveals diffuse swelling of cerebral white matter with other diffuse white matter changes and large cysts in the frontal and temporal lobes. We are aware of one case of Phelan-McDermid syndrome with MLC1.

UPDATE (2026): We are aware of six people with Phelan-McDermid syndrome who have developed MLD. Additionally, there have been two major advances in MLD: 1) The first gene therapy has been FDA-approved to treat MLD and 2) MLD has been included on the updated Recommended Uniform Screening Panel (RUSP), prompting several states to include it in newborn screening panels. These two developments will not directly change most care plans for loved ones with Phelan-McDermid syndrome, but they are critically important to understand for those families whose child has a deletion that includes the *ARSA* gene.

If you wish to learn more about these risks or about what testing will help to detect these genetic variants, please contact a genetics specialist. For a consultation, please have your physician contact the Phelan-McDermid Syndrome Neuropsychiatric Consultation Group (PMS-NCG): https://pmsf.org/neuropsychiatric-consultation-group/