Important Message from Our Medical Advisory Committee

June 19, 2020

The Phelan-McDermid Syndrome (PMS) 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 PMS, and which are associated with significant developmental regression in early childhood. Developmental regression is known to occur in children and adolescents with PMS. 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 PMS 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 PMS also at risk for these otherwise rare disorders? PMS 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 PMS, the gene may already be absent on one chromosome because of the deletion related to PMS. 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 PMS be aware that if someone has PMS 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. As of this writing (2020), we are aware of only three people with PMS who have developed MLD. There is currently at least one clinical trial in a gene therapy to treat MLD.

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 PMS with MLC1.

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 PMS Neuropsychiatric Consultation Group: https://pmsf.org/neuropsychiatric-consultation-group/