September 2021 Research Roundup

A monthly summary of research and news relevant to Phelan-McDermid syndrome

Consideration of the impact of PMS genetics on the metabolism of drugs

A review was recently published by several authors from the PMSF Scientific and Medical Advisory committees, including Dr. Luigi Boccuto, Dr. Katy Phelan, and Dr. Curtis Rogers. The objective of a review paper is to summarize current knowledge in a field and highlight trends.

This paper focused on the idea that variations in genes can impact how drugs are metabolized. Because many patients with PMS have deletions or alterations to their DNA, genes may be missing or changed which are important for breaking down drugs so they can be usable by the body.

In particular, the authors highlighted one gene which codes for CYP2D6, an important component to metabolizing antidepressants and antipsychotic drugs. This gene is in the 22q13.2 region and may be affected in individuals with large deletions. This gene is an important target for future research consideration since a subset of individuals with PMS experience psychiatric symptoms. *CYP2D6* is well-studied and may already be considered in your loved one's treatment plan - but is highlighted here as an example of a gene that can impact drug metabolism. If a drug is not properly absorbed, it may cause more side effects than usual, and may not be as beneficial.

It is important to note that many other factors besides genetics can influence responses to treatment. But this paper highlights the benefits of conducting more studies to assess the impact of genetics on drug metabolism.

What does it mean for PMS research?
Because there is no cure for PMS, and because individuals experience a range of symptoms, PMS treatment approaches can vary between individuals. But this review highlights a way to personalize treatments further, based on genes that are missing, or impacted, that can influence drug responses. These findings represent the views of leaders in the field and their hopes for the future. To be fully adopted, more studies would need to be conducted linking PMS genetics to treatment responses, and these findings would need to be integrated into widely accepted clinical guidelines.

Article link:
https://www.mdpi.com/2073-4425/12/8/1192/htm

A better understanding of the importance of SHANK3 in strengthening connections between neurons

PMSF Scientific Advisory Committee members Dr. Carlo Sala and Dr. Chiara Verpelli, among others, recently published an investigatory study in mice focused on the role of SHANK3 in a neurological phenomenon called **synaptic plasticity**. Alterations to the *SHANK3* gene are strongly associated with Phelan-McDermid syndrome and autism.

A synapse is the space between neurons where they interact. Within this space, one neuron can release chemicals that excite or inhibit the other neuron. If a collection of interconnected neurons become

activated, they work together to form a circuit and carry out a shared function. **Synaptic plasticity** is the strengthening or weakening of specific neuronal connections over time. If certain neurons interact more, their connection strengthens, solidifying memories or thought processes. A lot of synaptic plasticity happens in early development, which is why a child's learning and memory are considered more "plastic."

Research has shown that SHANK3 plays an important role in anchoring all the machinery necessary for a neuron to receive chemicals from another neuron. SHANK3 does this by connecting to other structural components in the cell. In this study, the researchers looked more closely at exactly what happens to all this machinery when SHANK3 is functional, and when it is not.

They found that normally, when a neuron excites another neuron and synapse strengthening begins, a structure involving SHANK3 disassembles. This allows the neuron to go into a "locked" state where the neuron does not receive more signals and the connection to the other neuron is strengthened. When *Shank3** was altered in this study, however, this disassembly is not maintained, and the neuron has trouble strengthening the connection with the other neuron. Mice with the altered *Shank3* experienced anxiety-like and repetitive behaviors, similar to autistic behaviors.

Importantly, the researchers were able to improve synaptic plasticity by bypassing SHANK3 and building a bridge in the machinery of the synapse.

What does it mean for PMS research?

This study is known as a mechanistic study – an in-depth investigation into how something works. This study provides more insight into the role of SHANK3, what occurs when SHANK3 is altered, and a possible way the synapse machinery can be improved if SHANK3 is not operating properly. Although these studies may not translate to immediate clinical applications, they can serve as a foundation of knowledge for drug targets and treatments in the future. These studies are important for building up knowledge of what goes awry in PMS and they complement clinical research.

Article link: https://www.nature.com/articles/s41380-021-01230-x

*Note: SHANK3 may appear in these summaries in several different notations (capitalized, italicized, etc.) which specify referral to the gene versus the protein, and referral to humans versus other model systems.

A possible new *SHANK3* variant in PMS

(and the complicated picture of classifying genetic variants as disease-causing)

A group of researchers in Finland, with corresponding author Dr. Maria Arvio, recently published a case study – an in-depth look at two siblings with symptoms consistent with Phelan-McDermid syndrome. This brother and sister both had intellectual disability when they were younger, and in their teenage years and beyond, experienced psychiatric symptoms. Although one sibling declined more quickly than the other, both struggled with seizures, psychosis, and a lack of skill progression in adulthood.

A genetic microarray, which looks for deletions or additions to DNA, did not reveal any genetic alterations which could explain the symptoms. But Whole Exome Sequencing identified a variant in the *SHANK3* gene, a gene strongly linked with Phelan-McDermid syndrome and autism. **Whole Exome Sequencing** essentially "reads" the parts of the genome that code for proteins, which are action-oriented molecules that play many roles in the body. A new *SHANK3* variant was found in the siblings and was also found to be present in some cells of the father.

Many variants in *SHANK*3 have been identified, and whether they are classified as disease-causing for PMS can be a complicated picture. Sometimes a copy of the *SHANK3* gene can be missing because of a deletion, or letters of the *SHANK3* gene can be misspelled, or cut short, so the gene/protein are no longer functional. Some of these variants are considered disease-causing. In other cases, the variant, such as a misspelling a letter in the makeup of the gene, doesn't make a big impact on the SHANK3 protein and is not considered disease-causing.

Many types of data are required for a variant to be considered disease-causing. These include identification of the same variant in the population with disease but not in healthy individuals, in-depth analysis of the impact of the variant on the makeup and function of gene/protein, inheritance data, and other data. Over time, consensus is formally reached about whether a variant is likely disease-causing or not. In 2015, the American College of Medical Genetics (ACMG) released guidelines on this classification process. In this case, this new variant is not yet considered disease-causing by ACMG standards, but studies like this can begin to build evidence for the future.

What does it mean for PMS research?

Because case studies typically focus on individuals, or on a rare occurrence, they often require more information to make general conclusions about a disease. But case studies can often be an important step to identifying a trend. This study highlights several important trends in PMS research:

- Whole exome sequencing is being done more often and can identify small changes in genes, such as *SHANK3*, which over long periods of time, can help identify more cases of PMS. This study identified a particularly rare variant in *SHANK3*.
- Case reports on siblings and twins can continue to help unravel the impact of genes, versus environment, on the development of disease symptoms.
- This study adds to a growing body of research on psychiatric illness in the PMS population – providing data on when symptoms arise, the genetics involved, and logging interventions which have been tried.

Article link:
https://onlinelibrary.wiley.com/doi/full/10.1002/mgg3.1780