October 2021 Research Roundup

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

Linking PMS genetics with symptoms – a large study on 170 individuals

Leaders of the PMS Natural History Study including senior author Dr. Alex Kolevzon recently published a large study on 170 individuals with PMS.

The study focused on the connection of genotype (a person's specific genetic code including any alterations) and phenotype (symptoms, or outward manifestations of disease). While there have been many genotype-phenotype studies in PMS, this is the largest to date. Over time, these studies complement each other and can help reach consensus about which genes are most strongly connected to specific symptoms and may inform which treatment strategies may be beneficial in the future.

The study covered infants to adults and people with terminal deletions in chromosome 22, ring chromosome 22, and sequence variants in *SHANK3* (mutations).

The researchers characterized two major groups of PMS genetics which were linked with symptoms:

Class 1: Individuals with either a small deletion impacting *SHANK3* and a few neighboring genes, or variations in the *SHANK3* gene

- The researchers found this group was more likely to reach appropriate developmental milestones, but regress later
- This group was more likely to have mental illness such as bipolar disorder, depression, and schizophrenia/schizoaffective disorder

Class 2: Individuals with larger deletions in chromosome 22 which include *SHANK3*

- The researchers found this group more likely to have more complex medical problems, including eye issues, reduced muscle tone, kidney issues, spine abnormalities, and affected gait
- This group had more severe intellectual disability / developmental delays
- This group was less likely to reach developmental milestones (speaking, walking independently)

There were no major differences between groups in: autistic traits, physical features, heart issues, hearing issues, recurrent infections, thyroid issues, sleep, anxiety, poor feeding, lymphedema, epilepsy, GI issues, and genital abnormalities.

What does it mean for PMS research?

This study focused on many individuals and used rigorous statistics to look for true impacts of genotype on symptoms, rather than other factors. The data brings power and confidence to understanding PMS genotypes and which symptoms may arise from them. The data supports a theme that has previously been noted in PMS - that larger deletion sizes generally lead to more complex medical issues (especially speech and muscle tone). It also supports the observation that smaller alterations affecting *SHANK3* are more common in those with severe psychiatric symptoms. These are important trends to note for the management of PMS symptoms.

It is still an open question why certain genotypes relate to certain outcomes, but noting these trends is an important step in helping the medical community and families manage PMS cases based on genetics.

Article link: https://pubmed.ncbi.nlm.nih.gov/34559195/ *This link is online ahead of print and may not contain the full text yet.

A characterization of sleep issues in PMS compared with a related rare disorder

Previous research has shown that a high percentage of people with PMS and autism spectrum disorder have sleep issues. These sleep issues can lead to increased severity of symptoms and can impact the sleep of loved ones.

A research study led by Dr. Jimmy Holder, longstanding researcher in PMS, was recently published that expands on this concept by comparing people with PMS to both typically developing siblings and to people with another rare disorder, caused by alterations in the *SYNGAP1* gene, which is linked to intellectual disability. Both *SYNGAP1* and genes affected in PMS, such as *SHANK3,* play important roles at the synapse – the space between neurons where they communicate. Disorders affecting the synapse are called “synaptopathies” and often share similar characteristics.

Comparing symptoms such as sleep between disorders can begin to unravel which dysfunctions at the synapse can lead to which symptoms.

The authors used a standardized survey called the Children’s Sleep Habits Questionnaire (CSHQ) to assign a score to a variety of sleep difficulties. In most categories, people with PMS and *SYNGAP1*-related intellectual disability had worse sleep issues than typically developing siblings.

People with PMS especially had worse “parasomnias” (nightmares, sleepwalking, etc), more night awakening, more bedtime resistance, and daytime sleepiness, than typically developing

siblings. In most cases, people with *SYNGAP1*-related intellectual disability had more severe symptoms, although similar to PMS.

The researchers also split people into age categories – those under 10 years old, and those over 10 years old. Those over 10 years old with PMS and *SYNGAP1*-ID generally had worse symptoms. This is a topic for future study and could be due to impacts of puberty, time, and other possible compounding factors.

What does it mean for PMS research?
This study adds confidence to previous observations of sleep-related issues in PMS, by using a detailed numerical scale with additional comparison groups. More documentation can mean more attention paid to this symptom in the future. And because clear deficits in sleep were found in PMS compared with typically developing people, this study provides evidence that sleep could theoretically serve as an outcome measure for testing clinical trial drugs in the future. This study also demonstrates similar sleep outcomes between PMS and another synaptopathy, *SYNGAP1*-ID, which adds to our knowledge of similarities and differences in these disorders. It is important to note that this study was done on a sample of 30-40 people per group, which may not be large enough to identify all significant differences. This study also saw less severe symptoms than an earlier study, which could be due to a difference in comparison groups. In the future, continuing to study large groups over time can contribute to fully characterizing sleep issues in PMS.

Article link: https://www.mdpi.com/2076-3425/11/9/1229/htm

Progress in developing model systems from patient cells

A review article was recently published summarizing progress in using human cells to study autism and PMS in the lab. These models are called **iPSC-derived neurons** and **organoids.** The lead author is Dr. Alex Shcheglovitov from the University of Utah, who has been using these tools for years to study autism and PMS.

iPSC is short for "induced pluripotent stem cell." These are cells, such as skin or blood cells, which have been collected and reprogrammed to a more immature form, where the cell has not yet taken on any specific functions. These cells can then be exposed to growth factors and other signals in the lab to program it to become a certain specialized cell type – such as a neuron.

Why would this be useful? Research in neuroscience, and in general, can be done on many levels. Scientists can look at a whole tissue for widespread abnormalities, using imaging for instance. But to fully understand *why* something is occurring, such as a brain connectivity issue, studying individual cells in detail can be useful. iPSCs give scientists a way to study neurons with

the same genetic abnormalities that patients have, by sampling cells from people that are possible to collect and then programming them to become neurons.

This publication reviewed how these cells are being used to create better models. One way is to transplant these iPSC-derived neurons into the brains of animal models, to study how the cells function in the complex brain environment. Scientists can then find these cells and study how they physically connect, how activated they become, and what kind of capabilities the cells have.

Scientists can compare cells with certain genetic abnormalities connected with autism or PMS, such as in *SHANK3* alterations, with cells that do not, to gain more information on how these alterations affect the neuron. Research suggests that *SHANK3* is crucial as brain cells migrate, mature, and form connections.

The iPSC-derived neurons can also be used to create organoids, which are considered smaller 3D models of a tissue, which are simpler and made of fewer cells. These organoids can be studied on their own or can be transplanted into animal brain tissue. Studies have found that these organoids integrate well when transplanted, connecting with cells already there and forming their own vascular system.

The limitation to these techniques is cells can behave differently when isolated, programmed, and transplanted, then when they are existing normally in human brain tissue.

What does it mean for PMS research?

Using human skin and blood cells to develop models of autism and PMS is not brand new, but this publication represents a trend that these models are progressing and yielding relevant information. Specifics of individual studies in this area will continue to be summarized as they are published. By using cells from patients, many different types of genetic alterations can be studied, and more quickly than making an animal model. Studying how a genetic change impacts a cell, or group of cells, can inform our knowledge of what causes symptoms, and how we can better target neurons to improve outcomes in the future.

Article link: https://www.nature.com/articles/s41380-021-01288-7.pdf