August 2021 Research Roundup

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

A push towards Whole Genome Sequencing and Whole Exome Sequencing in the clinic

In the U.S. and abroad, medical experts are working to incorporate more Whole Genome Sequencing and Whole Exome Sequencing in clinical visits for children with autism spectrum disorder, developmental delays, and intellectual disability. Clinical guidelines on this subject were released July 1 in the U.S. Clinical guidelines can be thought of as recommendations written by doctors to improve healthcare. Whole Genome Sequencing provides the most complete information of all genetic testing methods, by essentially "reading" (sequencing) the entire genome of a person, rather than searching for specific genes. Whole Exome Sequencing is also able to yield much more data than other standard approaches. The distinction between Whole Genome Sequencing and Whole Exome Sequencing, and the comparison to other standard genetic tests will be summarized in future posts.

Although sequencing has been available for some time, the decision to do sequencing is complex, based on financial considerations, preferences of the doctor and the family, and other factors. The new guidelines released July 1 by the American College of Medical Genetics and Genomics argued that the benefits, such as earlier diagnoses, outweigh potential harms. Costs of sequencing are becoming more affordable and performing sequencing before other tests can save time.

A similar initiative has been launched in France and its upcoming impacts on diagnosing autism and other developmental disorders is being summarized in *Spectrum* by PMSF's Scientific Advisory Committee Member, Dr. Thomas Bourgeron, who is a leader on this project. Based on the current response to this initiative, France could collect sequencing data on several thousand families of patients with neurodevelopmental disorders over the next few years.

What does this mean for PMS families?

Sequencing will become more commonly done in the clinic, for both PMS families and for other children with neurodevelopmental disorders. Long-term, this could lead to:

- a large amount of genetic data for scientific studies, including correlating genes (genotype) with symptoms (phenotype) to improve treatments and improve the ability to distinguish mechanisms of neurodevelopmental disorders
- More and faster diagnoses of PMS compared to standard genetic tests, increasing our support network and rationale for research
- More identification of very rare genetic variants in PMS, including *SHANK3* variants

U.S. guidelines link: https://www.nature.com/articles/s41436-021-01242-6

France Genomic Medicine Initiative summary link: https://www.spectrumnews.org/features/deep-dive/europes-race-ramp-genetic-tests-autism/

Progress in CRISPR gene editing clinical trials for human genetic disease

CRISPR gene editing holds tremendous promise for permanently altering the genome and treating genetic disease. Due to safety considerations, CRISPR gene editing trials have been done outside the human body - meaning the genome of cells are edited in the lab and then injected into the human. But in order to have an impact in genetic disease, the CRISPR complex needs to be injected into the body so it can reach tissues and alter the person's genome. Late last month, one of the first clinical trial results were published where a CRISPR gene editing drug was injected directly into the blood of people with a rare genetic disease called Transthyretin Amyloidosis. The trial demonstrated safety and efficacy, which is a monumental step forward for gene editing.

CRISPR-Cas9 is a tool that works like a pair of microscopic scissors, which can "snip" or "edit" the DNA at precise locations. If there is a gene that is problematic and causing disease, the scissors can be guided to that precise gene to snip the DNA away. The DNA can then repair itself or be given new DNA as part of the drug. In this study, CRISPR was used to fix a problematic gene.

It is important to note the distinction between gene editing and gene therapy. Gene therapy involves the delivery of a healthy gene, but does not edit the person's genome. This can be done using a virus that is not dangerous but can enter cells. Gene therapy is being increasingly used and injected into various tissues, such as the brain. For instance, earlier this month, a delivery system called AAV-9 was used to deliver a gene into the brains of patients with a rare neurological disorder called AADC deficiency which causes very low levels of dopamine and serotonin, chemicals which are necessary for stable mood and other bodily functions. The preliminary clinical trial showed that gene therapy helped locally in the brain to increase dopamine levels, improve some symptoms, and did not have serious adverse effects.

Combined, progress in gene editing and gene therapy are moving towards genetic alterations in the brain, which could ultimately be applied to PMS in the future.

Why does it matter for PMS?

Many people with PMS have missing or altered genes. To treat PMS with gene editing or gene therapy in the future, these drugs will likely be more effective if injected into participants. The first study demonstrates the principle that a CRISPR gene editing drug can be administered safely directly into patients, with few side effects, and can have a positive impact. The second study demonstrates mounting evidence that gene therapy drugs can be injected into the brain and have a local impact.

Importantly, neither of these studies were done on PMS patients, and much testing on safety, efficacy, and application to PMS remains to be done. Gene editing in particular is in early experimental stages and must undergo extensive testing over an extended period before these drugs can receive approval.

Article links:

CRISPR gene editing: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2107454?articleTools=true

Gene therapy: https://www.nature.com/articles/s41467-021-24524-8.pdf

Recently Published – A new study on the consequence of shuffling of genes in PMS

A new study was published this month, authored in part by PMSF Scientific and Medical Advisory Committee members including Dr. Curtis Rogers, Dr. Katy Phelan, and Dr. Luigi Boccuto. The study investigated what happens to genes when DNA is shuffled around due to genetic alterations in people with PMS.

Many individuals with PMS have translocations, or an unusual arrangement of chromosomes. These arrangements can cause pieces of chromosomes to be swapped with other chromosomes, lost, or added. Because chromosomes are made up of genes, these rearrangements can cause genes to be in a different place than they would normally.

Simply changing the location of a gene can impact how it is regulated, or how much of the gene there is, called "expression." This is because the genome can interact with itself physically and regulate genes. Even if a gene is not deleted, it's location can cause it to be "expressed" differently. And if one copy of a gene is deleted, the rearrangement of other genes can also cause the remaining copy to be expressed differently.

In this study, the researchers picked 12 genes which they predicted could be affected by changes in position and analyzed them in five PMS patients. The researchers confirmed that genes which had one copy deleted, such as *SHANK3*, were decreased in expression as expected, even with shuffling of other genes around them. This finding supports the concept that larger deletion sizes can sometimes result in more severe symptoms, due to the loss of function of many genes. In genes that were not deleted, there were some changes in expression that could be a result of new positioning, among other possibilities.

What does this mean for PMS research?

This study provides the basis to continue studying these genes, and other genes, for effects of shuffling. The methods used in this paper can be applied to larger groups of PMS patients, as it is important to note this is a small group of patients, and a small number of genes assessed. Studying the position of genes provides a more complete picture of the varied genetics of PMS patients.

Article link: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0253859

Recently published – measurement of visual processing in individuals with PMS

A recent study was completed at the Seaver Autism Center at Mount Sinai, led by Medical Advisory Committee member Dr. Alexander Kolevzon. This study is the first to assess visual processing in the PMS population using a method called Electroencephalography (EEG). EEG is a non-invasive technique that measures the activity of neurons in the brain. Electrodes are attached to the scalp which can measure activity in a certain part of the brain in response to a stimulus. In this study, a visual stimulus was given - a checkerboard changing in contrast.

A group of 31 individuals with PMS were compared to a group of people with autism spectrum disorder of unknown cause, and to typically developing persons, and siblings of individuals with PMS. The PMS group showed lower activity in neurons compared with all other groups. The autism group also had lower activity compared with the typically developing group and sibling group and shared some similarities with the PMS group.

What does this mean for PMS research?

Measuring visual processing in this way can be used in PMS clinical trials in the future. To see if a drug is working, tests like these can be used before and after drug treatment. This study confirms that individuals with PMS can be distinguished from other groups, which provides a starting point for treatments. EEG is also a practical alternative to other burdensome measures of brain activity for individuals with PMS with severe symptoms. EEG on various parts of the brain is a central focus of the new phase of the Natural History Study. Additionally, studies like these begin to unravel which symptoms are shared between autistic individuals and those with PMS. Last month's newsletter included a study with less overlap between these two groups - which showed that individuals with PMS experienced unique sensory processing compared with individuals with autism.

This article is still in the proof stage. Article link:

https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0890856721004743?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0890856721004743%3Fshowall%3Dtrue&referrer=https:%2F%2Fpubmed.ncbi.nlm.nih.gov%2F

Recently published – a characterization of 60 Spanish PMS patients

A recently published study which includes lead author Dr. Parellada-Redondo from the Spanish Association for Phelan-McDermid syndrome, describes clinical features of a large group of Spanish PMS patients for the first time. The study was especially focused on collecting information on behavior (i.e., irritability, social withdrawal) adaptive skills (i.e., daily living skills, communication, motor skills), and autism symptoms. There were many findings that align with previous characterizations of PMS, including absent, delayed, or impaired language, motor issues, and adaptive behavior challenges. Approximately 40% of cases were associated with a regression of skills during development. Importantly, the authors note that this group may represent the more severe cases of PMS that have been diagnosed earlier, and that clinical data will continue to evolve with more data.

What does this mean for PMS research?

This study was done on a large group of people and adds to the available characterization of clinical symptoms in people with PMS. The article also provides summaries of the usefulness of certain assessments and calls for a standardized approach to clinical assessments across countries.

Article link: https://jneurodevdisorders.biomedcentral.com/articles/10.1186/s11689-021-09370-5

Recently published – a better understanding of the impact of SHANK3 on social behavior

A new study from Harvard found that *SHANK3* is involved in the balance of recognizing the experience of others, versus oneself. Electrodes were implanted into the brains of mice which can detect the "firing" of individual neurons, a measure of their activity. The scientists found that in mice with genetically normal *SHANK*3, some neurons fired specifically when the mouse witnessed another mouse having either a positive experience, such as receiving food, or a negative experience, such as being in a narrow enclosure. A separate set of neurons lit up when the mouse had positive or negative experiences itself. Therefore, different cells in the brain appeared to recognize "other" versus self. In mice where *SHANK3* was altered, which is a model of PMS, the distinction between other and self was blurred. There were fewer neurons that specifically recognized the experience of other or self. There were particularly fewer neurons that responded to the experience of the other mouse, and less strongly. Giving genetically normal *SHANK3* back to these mice corrected this balance of recognizing the experience of others vs. self.

What does this mean for PMS research?

SHANK3 is altered in many people with PMS and is strongly associated with autism. Individuals with PMS and autism may have issues with social interaction, but it is not fully understood how or why this occurs. This paper represents one piece of that puzzle. Importantly, *SHANK3* can cause other changes to the brain not described here which could impact social behavior, and other genes besides *SHANK3* could also influence social behavior. But the more we learn about which genes cause which symptoms, the better we can define PMS, and PMS compared to other disorders.

Summary link: https://www.spectrumnews.org/news/autism-linked-mutation-may-blur-brains-boundary-between-self-others/

Article link: https://www.nature.com/articles/s41593-021-00888-4