Parents and Researchers Interested in Smith-Magenis Syndrome

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Smith-Magenis Syndrome Research Symposium

Abstract Summaries

PRISMS is committed to providing information to the SMS community on the latest research findings and advancements. Please see below for summaries of research presented at PRISMS 9th SMS Research Symposium.

Assessment of Mitochondrial Deficiency in Smith-Magenis Syndrome
Michael D. Fountain, PhD, Baylor College of Medicine

Smith-Magenis Syndrome (SMS) is a developmental disorder caused by reduced amounts of RAI1. Based on previous research, we decided to study the functioning of mitochondria in individuals with SMS. Mitochondria are the structures in our cells that are responsible for creating the energy that our body needs to survive and function. Our results showed that mitochondria in skin cells of patients with SMS have abnormal functioning. Similar patterns of abnormal mitochondrial functioning have been noted in individuals with Down syndrome, fragile X syndrome, autism and Rett syndrome. Such findings may support comparable treatment approaches across these conditions.

Stem Cell Based Models for Human Neurons of Monogenic Neurological Disorders
Toshihiko Ezashi, DVM, PhD, University of Missouri

Developmental disorders caused by changes in a single gene (monogenic disorders) can help to improve our understanding of brain functioning. Stem cells are generalized cells that can become almost any type of cell, like neural cells or liver cells, etc. The specific genes that are active (aka expressed) in each cell determine what type of cell it will become. Induced pluripotent stem cells (iPSCs) are stem cells that are produced in the lab. We produced iPSCs from five patients with Smith-Magenis Syndrome (SMS), three patients with Pitt-Hopkins syndrome (PTHS), three patients with MBD5-associated neurodevelopmental disorder (MAND), and five patients who did not have any genetic disorder (called control cells). The iPSCs were then converted to neural progenitor cells (NPCs). NPCs are specialized cells that can become different types of neural cells. As an initial study, we compared NPCs produced from individuals with MAND to NPCs produced from control cells. We found a total of 299 genes that were expressed differently in the two types of cells.

Status of Gene Therapy for Neurological Diseases
Seng H. Cheng, PhD, Sanofi

Over the past 20 years, significant progress has been made in the field of gene therapy for several inherited and acquired disorders. Gene therapy is a technique in which a non-working gene is replaced with a working copy of the gene. The gene must be delivered to the cell through a vector (path). To date, the vector that has shown most promising results is the recombinant adeno-associated viral (AAV)-based vector. Currently, one gene therapy product is approved in Europe for a metabolic disorder called lipoprotein lipase deficiency, and based on clinical studies for other disorders including Leber congenital amaurosis-2, spinal muscular atrophy and hemophilia, approvals for gene therapy in these disorders may also be forthcoming. As new AAV vectors with greater efficiency become available, it may be expected that they will be applied to a broader range of disorders, like neurological disorders including Smith-Magenis Syndrome. However, while the ongoing clinical studies are encouraging, there are still many challenges with the use of this technology.

Viral Vector Design and Construction as a Proof of Concept for Gene Therapy in Smith-Magenis Syndrome
Siân Behrendt-McLeory, MS, Baylor College of Medicine

Smith-Magenis Syndrome (SMS) is a rare genetic disorder associated with typical facial features, intellectual disability, developmental delays, sleep disturbances, immunological issues, early-onset obesity, and behavioral and emotional problems. SMS is caused by a reduced amount of the RAI1 protein. Treatments for SMS currently only address specific symptoms like sleep difficulties or behavioral problems. However, there are no treatments that target the cause of SMS, which is a reduced amount of RAI1. We are currently working on a study to see if the RAI1 gene can be put into a cell effectively. We will also check to see if the other genes regulated by RAI1 are functioning appropriately and being produced at the right levels. At this stage, this project is simply to show whether or not RAI1 can be put back into a cell with a functional outcome. If this proves feasible, further studies will assess its use for gene therapy models.

Characterizing Distinct Features of Social Motivation in the Behavioral Phenotype of Smith-Magenis Syndrome
Antoinette Sabatino DiCriscio, PhD, Geisinger Autism & Developmental Medicine Institute

There have been several studies that note similarities in behavioral features between Smith-Magenis Syndrome (SMS) and autism spectrum disorder (ASD). However, while individuals with SMS do have impaired social skills, there seems to be a distinct difference in behaviors among those with SMS and ASD. Those with SMS show increased social motivation, attention seeking, and an excessive need for attention that can result in outbursts or aggression if not met. An objective measure of social functioning may help differentiate those with SMS from those with ASD. We used a simple eye tracking task along with behavioral measures in a small population of individuals with SMS to perform this. We found that these individuals, in general, maintained social motivation. This is the opposite of what is seen in individuals with ASD, which is decreased social motivation. In addition, we found that children with SMS preferred pictures of adults over pictures of children. We also used a scale called the Social Responsiveness Scale (SRS) to get a numerical measure of autism traits in the population. We found that while most individuals had scores that indicated severe ASD symptoms, scores on the social motivation subscale indicated increased social motivation.

Coping with a Sibling with Smith-Magenis Syndrome: Relations with Gratitude, Benefit Finding, and Internalizing and Externalizing Behaviors
Rebecca Foster, PhD, St. Louis Children's Hospital
Tina McGrevy, BS, Ed, The Ohio State University

Smith-Magenis Syndrome (SMS) is a rare genetic disorder associated with typical facial features, intellectual disability, developmental delays, sleep disturbances, and extreme behavioral and emotional difficulties. As a result, siblings of individuals with SMS may struggle with coping mechanisms. To better understand sibling challenges, we assessed adaptive and maladaptive coping styles of siblings of individuals with SMS, as well as their mood and behavioral concerns.

We found that the most common types of coping strategies noted were acceptance, positive reframing (being able to see the situation in a positive light), and self-distraction. Conversely, the least common types of coping strategies noted were denial, religion, and substance use. We also found that siblings who reported higher rates of benefit finding were also more likely to report "positive reframing" as a

coping strategy. In conclusion, further studies are needed to develop interventions aimed at developing life-long adaptive coping strategies to reduce risks of mental health concerns.

Family Studies of Social Responsiveness and Other Contributors to Clinical Variability in Smith-Magenis Syndrome
Brenda Finucane, MS, LGC, Geisinger Autism & Developmental Medicine Institute

Smith-Magenis Syndrome (SMS) is associated with typical behavioral and learning differences, although the severity of these features can vary widely among individuals. This variability is seen in other genetic syndromes as well, and makes it challenging to provide guidance on prognosis and interventions. We do know, however, that an individual's familial genetic background does play an important role in expression of features in genetic syndromes and common diseases. We recently showed that behavior and social functioning in individuals with 16p11.2 deletions are influenced by social responsiveness and IQ in parents. Few studies have examined relationships between parents' behavioral and mental functioning and neurodevelopmental outcomes in their children with genetic syndromes, and none specifically in those with SMS. We are currently studying 25 deletions and duplications, including SMS, to determine the influence of family genetic background on expression of features in these conditions. We have primary data on a family study of SMS using the social responsiveness scale (SRS). The SRS is a validated online tool that can assess social behavior. Further family studies on this and other aspects of SMS could ultimately lead to development of risk formulas similar to the ones used in cancer and cardiovascular counseling. The ultimate goal of this would be to customize interventions by identifying a child's main area of behavioral and mental weakness.

Gynecologic and Reproductive Health Issues in Patients with Smith-Magenis Syndrome
Melissa Meredith, MD, MPH, Medical Genetics Branch, National Human Genomic Research Institute, NIH

Smith-Magenis Syndrome (SMS) is a neurodevelopmental disorder most commonly caused by a deletion of 17p11.2, and less commonly by a mutation in RAI1. Most common features in those with SMS include typical facial features, developmental and speech and language delays, behavioral problems, and sleep difficulties. Information on gynecological issues, however, is limited. In an attempt to understand the reproductive health issues females with SMS face, we conducted evaluations on 19 females with SMS . The evaluations included gynecological history, physical exams, blood tests, and review of outside records at the NIH from 2003 to 2016.

We found that the average age at first menstrual cycle for the females evaluated was 12.5 years (range 6y-16y). Most (10 of 19) reported heavy bleeding, and some of the menstrual management issues included unwillingness to use pads, discomfort with blood on pads, and refusing to take daily OCPs. Ten patients reported increased emotional and behavioral issues right before the onset of menses, two patients had increased seizures, and three patients had problems with vaginal insertion. Hormone levels were normal in all 7 patients in whom they were measured. In conclusion, our results suggest a possible increased risk of heavy periods, premenstrual emotional/behavioral issues, and seizures in females with SMS. Menstrual management is also an issue in this population. Further studies on this topic are warranted.

Smith-Magenis Syndrome Patient Registry

Dianne Samad, MS, CGC, Baylor College of Medicine

Smith-Magenis Syndrome (SMS) is a neurodevelopmental disorder most commonly caused by a deletion of 17p11.2, and less commonly by a mutation in RAI1. Most common features in those with SMS include typical facial features, developmental delays, behavioral problems, and sleep difficulties. The diagnosis of SMS, however, is often challenging because of overlapping features with other neurodevelopmental disorders. To better understand the nature of SMS, we developed a patient registry that will allow us to collect data on SMS over several years. Information about the registry will be posted on the PRISMS website and Facebook page, through personal e-mails from PRISMS, and on other social media platforms. To be eligible for participation in the registry, the individual must have a genetically confirmed diagnosis of SMS. Those who are eligible will go through a formal consent process and be provided with a secure link to the website. The data will be stored on a secure REDCap server at the Baylor College of Medicine. REDCap is a secure electronic data collection tool used for research. In addition to allowing for more detailed understanding of SMS, this registry could lead to identification of features not previously known to be associated with SMS, as well as connecting interested individuals to each other and to future research and drug studies.