prisms Research Symposium

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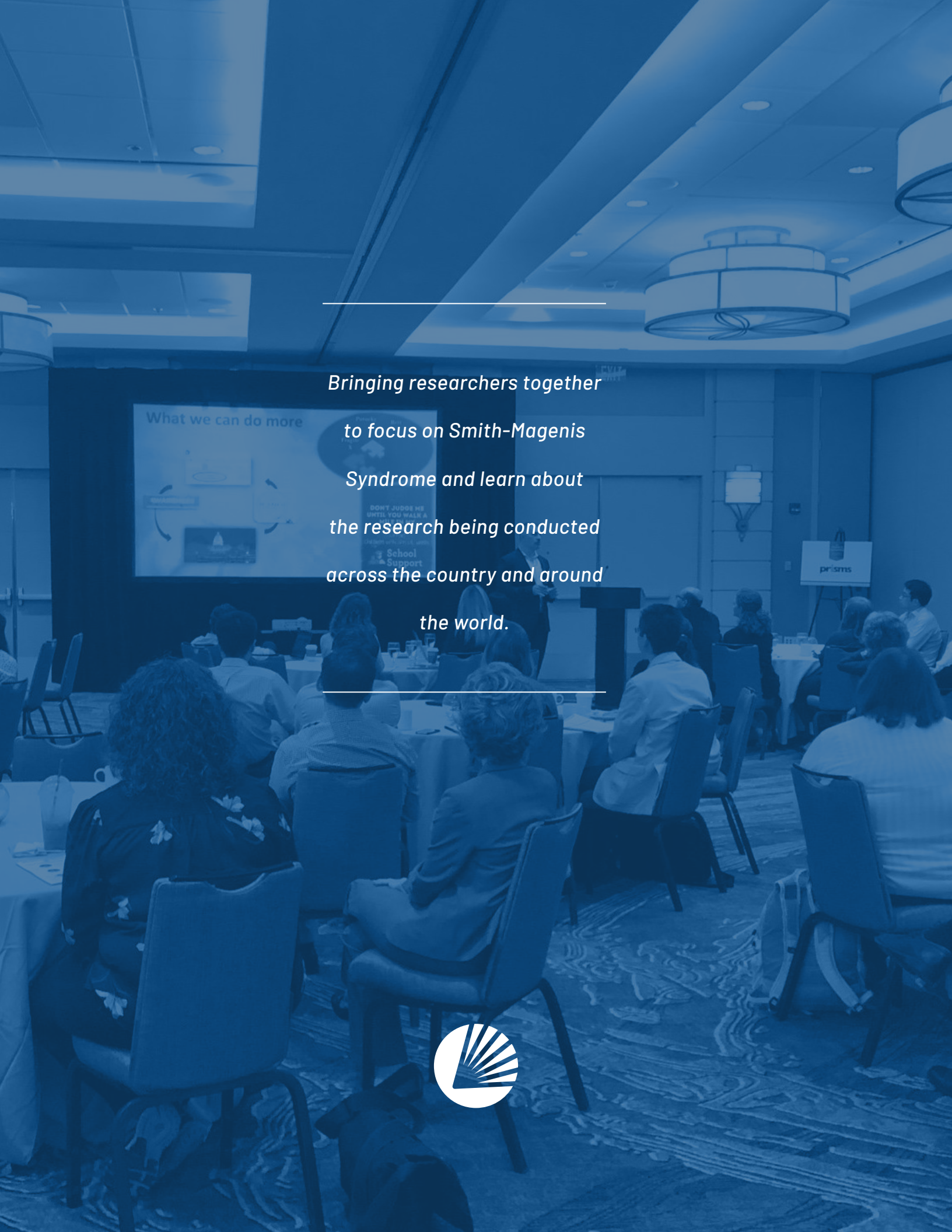

Bringing researchers together to focus on Smith-Magenis Syndrome and learn about the research being conducted across the country and around the world.

prisms Research Symposium

SCIENTIFIC & LAY ABSTRACTS

ABSTRACT

Emerging Roles of RAI1 in Neuronal Transcription and Synaptic Plasticity

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Smith-Magenis syndrome (SMS) is an autosomal-dominant neurodevelopmental genetic disorder caused by RAI1 haploinsufficiency that leads to childhood-onset hyperlipidemia, truncal obesity, sleep disorder, developmental delays, and behavioral problems. Mouse models of Rai1 haploinsufficiency reliably replicate relevant features, including impaired satiety, hyperphagia, altered fat deposition, and elevated leptin levels without insulin resistance. These models show similar feeding behavior trends, with high carbohydrate and high-fat diets leading to increased obesity during adolescence and early adulthood in mice. To further investigate the behavioral and metabolic phenotypes associated with RAI1 haploinsufficiency, we fed ad libitum a 45% high-fat diet from 5 weeks of age to male Rai1+/- mice and their wild-type littermates. Weights were recorded weekly from 3 weeks of age. Mice were housed in the Comprehensive Laboratory Animal Monitoring System (CLAMS) for 24-hour monitoring of metabolic parameters (ambulatory activity, wheel running, food and water consumption, O2 consumption, CO2 production) from 7-10 weeks of age. Mice were kept in a 12-hour light-dark cycle, and data were recorded over 24 h periods. Metabolic output was calculated using O2 consumption and CO2 production in the Oxymax calculation of "heat" for caloric output.

Raw CLAMS data grouped by genotype were assessed using GraphPad Prism 10.1.0. Between genotype differences in metabolic variables were analyzed by 2-way RANCOVA grouped by genotype, by time, and by the interaction of genotype and time. 1-way ANOVA was used to analyze changes across weeks 7-10 within each genotype for each variable. Rai1+/- mice exhibited a significant difference in weight and rate of weight gain compared to the wild-type mice after 6 weeks of age. Furthermore, the weight difference between Rai1+/- and wild-type mice continued to widen throughout the study period ($P \leq 0.0029$). Rai1+/- mice consistently consumed ~40% more food than wild-type mice during the study period ($P < 0.0369$). Rai1+/- mice displayed decreased total 24-hour horizontal movement from weeks 7 to 10 ($P \leq 0.0242$); however, vertical activity was not different between genotypes. Furthermore, wild-type mice exhibited significantly greater daily wheel running activity throughout the study ($P \leq 0.0181$), while Rai1+/- mice demonstrated a significant decrease in total 24-hour activity from weeks 7 to 10 ($P < 0.0041$). Additionally, Rai1+/- mice ran on the wheel for shorter periods of time compared to their wild-type littermates. Significant differences in metabolic output were not observed between genotypes.

Our findings reveal consistent patterns of greater weight gain, food consumption, and reduced activity in Rai1+/- mice compared to wild-type littermates, particularly evident after 6 weeks of age. The observed differences in activity levels combined with food consumption between Rai1+/- and wild-type mice support a combination of behavioral differences contributing to the development of obesity, reflective of those observed in humans with Smith-Magenis Syndrome (SMS). Metabolic pathways important for energy expenditure and stamina are likely altered due to Rai1 haploinsufficiency and require further study. These data further support a primary role for RAI1 in the observed behavioral differences underlying the hyperphagia, increased adiposity, and circadian function observed in Smith-Magenis syndrome.

Lay Abstract: Our group has been investigating the cellular function of RAI1, the gene responsible for Smith-Magenis Syndrome (SMS). Our work has revealed that RAI1 plays a key role in controlling the expression of other genes in neurons. RAI1 appears to also act as a brake on specific gene expression programs from being engaged when conditions are not appropriate, so loss of RAI1 leads to premature activation of these genes. We have also been examining RAI1's role in human neuron development and find that in human neurons, RAI1 also acts to control gene expression and its loss results in altered timing of neuronal differentiation and neural circuit formation.

ABSTRACT

The Role of TCF20 Complex in Neurodevelopment and Autism Spectrum Disorders

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Loss of function mutations in MECP2 cause Rett syndrome (RTT) while duplications spanning the gene cause MECP2 duplication syndrome (MDS). While the phenotypes of both disorders overlap with those of other autism spectrum disorders (ASDs), the precise molecular mechanism driving pathogenesis remains unclear. MeCP2 binds methylated DNA and recruits chromatin modifying proteins but the relationship between these proteins and gene expression changes is not clear. Therefore, identifying and characterizing MeCP2 interactors is crucial to fully understand the pathogenesis of MECP2-associated disorders and beyond. To this end, we performed proximity-dependent biotin identification (BioID) in cultured rat primary neurons using a biotin ligase fused to MeCP2.

Our unbiased approach identified a novel MeCP2-interacting complex which includes TCF20, RAI1, PHF14, and HMG20A. Among them, mutations in TCF20 and RAI1 are known to cause TCF20-associated neurodevelopment disorder (TAND) and Smith–Magenis syndrome (SMS), respectively. We found MeCP2 interacts with the TCF20 complex via PHF14 and that several RTT-causing MECP2 mutations reduce the binding between MeCP2 and the TCF20 complex. Next, we found that Tcf20 modulates MECP2-mediated synaptogenesis in cultured primary neurons by co-regulating the key neuronal gene Bdnf. Further, reducing Tcf20 partially rescued the behavioral deficits caused by MECP2 overexpression in mice, underscoring a functional relationship between MeCP2 and TCF20 in MDS pathogenesis. We next assessed global gene expression changes in mouse models and found a significant proportion of differentially expressed genes in Tcf20+/– mice were also altered in Mecp2–/y mice; a majority of these genes changed in the same direction and with similar magnitude.

Through CUT&RUN experiments, we found a significant reduction of TCF20/PHF14 binding to the downstream genes shared between Tcf20+/– and Mecp2–/y brains upon loss of MeCP2, suggesting that MeCP2 recruits TCF20 complex to chromatin to co-regulate gene expression. Notably, we identified PHF14 missense mutation in patients that display developmental delay and other neurological features, and found that these mutations disrupt MeCP2-PHF14-TCF20 interaction. Our data demonstrate the critical role of a novel TCF20 complex for brain function and revealed a converging molecular mechanism whereby mutations of genes encoding several subunits in the same complex potentially contribute to symptoms shared between multiple disorders, including RTT, MDS, TAND and SMS.

Lay Abstract: Chromatin regulators orchestrate neuronal gene expression that gives rise to complex human behaviors. These processes often go awry in disease, therefore chromatin regulators are among the most frequently mutated genes in individuals with neurodevelopmental conditions, such as Autism Spectrum Disorder (ASD). ASD-associated chromatin regulators are often part of the same protein complex and converge on shared downstream pathways. Such is the case for a novel chromatin complex centered around TCF20 that we discovered in the brain. Each subunit of this protein complex is associated with a group of syndromic ASDs: TCF20 with TCF20-associated neurodevelopmental disorder (TAND), RAI1 with Smith-Magenis syndrome (SMS), and MECP2 with Rett syndrome (RTT), suggesting a converged mechanism for this group of disorders. Using biochemical, morphological, behavioral, and transcriptional studies, we examined the importance of this protein interaction for brain function. We found that the TCF20 complex plays a direct role in neuronal gene regulation and modifies synaptic and behavioral deficits in the mouse models. Moreover, we identified new mutations in PHF14, a subunit of the complex that has never been associated with neurological diseases, in individuals with developmental delay and other neurological features. Our data uncovered a previously unknown molecular aspect of the TCF20 complex and revealed a converging molecular mechanism, whereby mutations of genes encoding several subunits in the same complex contribute to shared neurological symptoms.

ABSTRACT

Exploring Hyperphagia and Weight Gain: Metabolic and Behavioral Analyses in an RAI1+/- Mouse Model of Smith-Magenis Syndrome

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Smith-Magenis syndrome (SMS) is an autosomal-dominant neurodevelopmental genetic disorder caused by RAI1 haploinsufficiency that leads to childhood-onset hyperlipidemia, truncal obesity, sleep disorder, developmental delays, and behavioral problems. Mouse models of Rai1 haploinsufficiency reliably replicate relevant features, including impaired satiety, hyperphagia, altered fat deposition, and elevated leptin levels without insulin resistance. These models show similar feeding behavior trends, with high carbohydrate and high-fat diets leading to increased obesity during adolescence and early adulthood in mice. To further investigate the behavioral and metabolic phenotypes associated with RAI1 haploinsufficiency, we fed ad libitum a 45% high-fat diet from 5 weeks of age to male Rai1+/- mice and their wild-type littermates. Weights were recorded weekly from 3 weeks of age. Mice were housed in the Comprehensive Laboratory Animal Monitoring System (CLAMS) for 24-hour monitoring of metabolic parameters (ambulatory activity, wheel running, food and water consumption, O2 consumption, CO2 production) from 7-10 weeks of age. Mice were kept in a 12-hour light-dark cycle, and data were recorded over 24 h periods. Metabolic output was calculated using O2 consumption and CO2 production in the Oxymax calculation of "heat" for caloric output.

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Our findings reveal consistent patterns of greater weight gain, food consumption, and reduced activity in Rai1+/- mice compared to wild-type littermates, particularly evident after 6 weeks of age. The observed differences in activity levels combined with food consumption between Rai1+/- and wild-type mice support a combination of behavioral differences contributing to the development of obesity, reflective of those observed in humans with Smith-Magenis Syndrome (SMS). Metabolic pathways important for energy expenditure and stamina are likely altered due to Rai1 haploinsufficiency and require further study. These data further support a primary role for RAI1 in the observed behavioral differences underlying the hyperphagia, increased adiposity, and circadian function observed in Smith-Magenis syndrome.

Smith-Magenis syndrome (SMS) is a genetic disorder that affects development and behavior, causing issues like obesity, sleep disorder, developmental delays, and behavioral problems. This condition is linked to having only one working copy of the RAI1 gene. To better understand SMS, we studied mouse models with a similar genetic makeup that alter only one copy of the Rai1 gene. These mice exhibit increased eating, altered fat buildup, and a variety of other features consistent with SMS, such as craniofacial differences. We studied a model that we previously showed to develop obesity during adolescence and early adulthood. To further explore activity and metabolic output, we fed male mice, both with and without the Rai1 gene mutation, a high-fat diet starting at 5 weeks of age. At 7 weeks of age, the mice were placed in a housing system individually to measure metabolic parameters such as activity, food and water consumption, oxygen production, and energy expenditure until 10 weeks of age. The mice were kept on a 12-hour light-dark cycle, and their weights were recorded weekly. Results showed that mice with the Rai1 mutation gained more weight faster than their wildtype littermates, starting from 5 weeks old. These mice also ate more food and were generally less active over the entire day and across several weeks than wildtype mice. Interestingly, while their wildtype littermates showed increasingly greater activity on a running wheel after 7 weeks, the Rai1 mutant mice showed a significant decrease in total activity during this same period, Mice with 1 functional copy of Rai1eat more food, weigh more, gain weight at a greater rate, and are less active than their wildtype littermates. The obesity observed in the SMS mice is multi-factorial, due to a combination of overeating and reduced activity, with increasing rate of weight gain when mice are not group-housed, suggesting additional behavioral components to the development of obesity. These findings help us understand how RAI1 might contribute to the behaviors and medical concerns commonly observed in people with SMS.

ABSTRACT

RAI1 Haploinsufficiency Associated With Increased Liver Triglycerides in Mouse Model of SMS

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Smith-Magenis syndrome (SMS, OMIM #182290) is a complex neurodevelopmental disorder characterized by a distinct behavioral phenotype, intellectual disability, circadian rhythm disorder, obesity, and craniofacial and skeletal anomalies. Most features of SMS arise due to haploinsufficiency of RAI1 due to either intragenic variation or 17p11.2 deletion.

Previous work has shown potential links between SMS, RAI1, obesity, and lipid metabolism abnormalities, including hypercholesterolemia. To better characterize obesity and lipid metabolism alterations observed in SMS, baseline metabolic phenotyping of Rai1+/- mice, which display hyperphagia, early onset obesity, and altered adiposity, was performed to include activity, food consumption, growth, and metabolite and lipid analyses. Prior to onset of obesity, 6-week-old singly-housed mice displayed reduced cage activity, lack of wheel running, modestly shifted circadian activity, increased food intake, and rapid weight gain compared to normal littermates ($p<0.01$). Untargeted metabolomic profiling of livers from 4- and 5-month-old Rai1+/- and wildtype littermates fed a high fat diet identified a total of 962 individual metabolites.

Quantitative enrichment analysis performed using KEGG and HMDB metabolic pathways showed increased levels of multiple triglycerides, and altered alanine, glutathione, and amino sugar metabolism, and lower levels of urea cycle, primary bile acid, and some nicotinamide metabolites. Additionally, the enrichment ratios of D-glutamine, D-glutamate, glycerolipid, and glycerophospholipid metabolism, among many others, were significantly increased in Rai1+/- mice compared to wildtype. Targeted lipidomic profiling of 844 unique lipid species in Rai1+/- and wildtype livers showed markedly higher levels of triacylglycerols, specifically 16 and 18 carbon chain species. Decreased monoacylglycerol esters, diacylglycerols, and phosphoethanolamine lipid species (Welch's two-sample t-test, $P<0.05$) were noted. C16- and C18-containing triacylglycerols and monoacylglycerols were the most significantly altered, with reduction of larger lipid species, suggesting that processing of dietary fats and downstream fatty acid synthesis may be impaired in SMS, supportive of impaired lipid transport and/or processing in the liver. Specifically, processing of dietary fatty acids and downstream lipid synthesis should be further investigated.

Lay Abstract:

Smith-Magenis syndrome (SMS) is a complex neurodevelopment disorders with a distinct phenotype. Most features of SMS arise from haploinsufficiency of RAI1 or deletion of 17p11.2. Previous literature has shown links between SMS, RAI1, obesity and lipid abnormalities in persons and mice. To better characterize and analyze these findings, a mice model of SMS with heterozygosity of Rai1 was created. These mice demonstrate hyperphagia, obesity, and lack of cage activity, and were fed a high-fat diet. Then, these mice were sacrificed and their livers were taken and metabolomic and lipidomic analyses was performed. For the metabolomic analysis, some findings included increased levels of multiple triglycerides, and altered amino sugar and glutathione metabolism. Additionally, lower levels of urea cycle, primary bile acid, and nicotinamide metabolites were noted. For the lipidomic analysis, findings included decreased monoacylglyerol esters and diacylglyerols, and markedly increased triacylglycerols, specifically 16 and 18 carbon chain species. These findings suggest alteration of dietary fat processing and downstream impairment of lipid transport in Rai1 mice livers. These results could help to explain lipid metabolism abnormalities and autophagy in SMS patients, and targeted treatment could be beneficial, including lifestyle and diet modifications.

ABSTRACT

Elucidating the Genetic Basis of Dysphagia in Smith-Magenis Syndrome Through Integrative Network Analysis

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Smith-Magenis Syndrome (SMS) is primarily associated with a microdeletion at the 17p11.2 locus, implicating RAI1 as a crucial gene, though its mechanistic role remains unclear. Neurodevelopmental disorders, including SMS, frequently manifest neural crest anomalies, resulting in dysphagia and pharyngeal abnormalities. We conducted a thorough investigation encompassing clinical assessments of dysphagia in a cohort of 14 SMS patients at the NIH, coupled with SNP sequencing analyses.

By examining the intersection with known genetic factors in schizophrenia, another condition/disorder with swallowing difficulties, our study aimed to understand the genetic basis of dysphagia in SMS. We leveraged a schizophrenia transcription factor binding site (TFBS) database, focusing on the sterol regulatory element-binding transcription factor 1 (SREBF1) located within the critical SMS region on 17p11.2. Through a nearest neighbor query incorporating all genes within this locus against the schizophrenia TFBS database, we identified 249 genes, with a corresponding 4,438 SNPs from our SMS patient cohort exhibiting dysphagia.

Employing a novel gene enrichment analysis utilizing machine learning, we sought to highlight functional similarities between SMS and schizophrenia gene sets, circumventing/bypassing direct gene overlap. This analysis, alongside SNP annotation utilizing multiple databases including FINNGEN and a Type 2 Diabetes (T2D) SNP dataset, annotated 1,084 (24%) of the SMS patient SNPs, with a notable 12% overlap with the T2D dataset. Clinical assessments were systematically translated into Human Phenotype Ontology (HPO) terms, facilitating an integrative network analysis through TFBS network querying and community detection algorithms.

Remarkably, our hierarchical gene enrichment approach identified a pathway involved in oligodendrocyte differentiation and myelination (WP4304), bolstering the significance of SREBF1-target genes in myelinating oligodendrocytes and providing further credence to the previous speculation that genetic perturbations of SREBF1 contribute to hypomyelination. Our multiscale integrative network approach will be presented. This multidimensional analysis underscores the importance of SREBF1 in dysphagia pathogenesis in SMS and illustrates the efficacy of a multiscale network approach for deciphering complex phenotypes in genetic disorders.

Lay Abstract: Like insulation on electrical wires, healthy myelination is crucial for the rapid transmission of nerve impulses. Oligodendrocytes are the specialized neural cells producing the insulating myelin around neurons' axons. Hypomyelination leads to neurological disease, including problems in thinking, sensory processing, and swallowing difficulties (dysphagia). In Smith-Magenis syndrome (SMS) dysphagia can result in a range of nutritional complications including risk of choking and aspiration-induced pneumonia. We conducted a thorough investigation encompassing clinical assessments of dysphagia in a cohort of 14 SMS patients at the NIH, coupled with DNA-based SNP sequencing analyses.

SMS is caused by a microdeletion of the 17p11.2 locus that contains the solitary transcription factor SREBF1, which is known to be involved in regulating lipid metabolism. We chose a schizophrenia transcriptional regulatory network (TRN) database in which the authors thought that SREBF1 played a role in schizophrenia, possibly due to hypomyelination. We queried this TRN database using genes from the SMS 17p11.2 locus to identify nearest neighbor genes. These 1st degree genes were used for identifying corresponding SNPs from the 14 SMS patients studied. Parallel clinical diagnostic assessments by clinical swallowing experts at the NIH were converted into standardized disease phenotypes (observable characteristics) with their known disease genes used to build multiscale networks. The data used in building a multiscale network includes everything from nanometer sized SNPs to the entire nervous system. Using a hierarchical gene enrichment algorithm, we identified an oligodendrocyte differentiation and myelination pathway (WP4304), reinforcing the possibility that hypomyelination caused by microdeletion of the transcription factor SREBF1 plays a role in SMS. We used a knowledge graph trained by machine learning to specifically focus on gene function, rather than traditional gene identity, for developing an SMS focused knowledge graph. Ideally this will provide more nuanced diagnostic criteria that are based on underlying biology, rather than a range of different clinical symptoms that may vary widely among patients.

ABSTRACT

Presence of Birt-Hogg-Dube Syndrome Symptoms in the Smith-Magenis Population and Adherence to Screening Recommendations

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In recent years there has been growing interest in understanding the link between Smith-Magenis syndrome (SMS) and Birt-Hogg Dube syndrome (BHDS). BHDS is composed of a triad of clinical features, including fibrofolliculomas of the skin, lung cysts and pneumothorax, and kidney tumors. Currently, the risk for an individual with SMS to develop symptoms of BHDS is not known. We are designing a questionnaire for deployment through the SMS Patient Registry to gather data regarding knowledge of symptoms, presence or absence of symptoms characteristic of BHDS, family history of cancer, and active screening for BHDS, including individual experiences, recommendations, and outcomes. This investigation will improve knowledge and understanding of both SMS and the co-morbidities associated with BHDS and will guide future recommendations and approaches to education in the SMS community. Appropriate screening will increase understanding of the timing and occurrence of specific symptoms of BHDS and will lead to improved outcomes.

We anticipate data collection during the next 3 months, so that findings may be analyzed and interpreted in time for the SMS Research Symposium and the PRISMS Conference. Plans for the final presentation will include an individual risk algorithm based on age and molecular diagnosis, family cancer history, and survey data from SMSPR participants describing the prevalence and type of BHDS symptoms, prevalence and frequency of screening, types of screenings and available results, recommendations, and outcomes, along with the prevalence of a BHDS diagnosis.

Lay Abstract: In recent years there has been growing interest in understanding the link between Smith-Magenis syndrome (SMS) and Birt-Hogg Dube syndrome (BHDS). BHDS is composed of a cluster of possible clinical features, including fibrofolliculomas of the skin (a specific skin growth, similar to skin tags), lung cysts and collapsed lung, and kidney tumors. Currently, the risk for an individual with SMS to develop symptoms of BHDS is not known. We are designing a questionnaire for deployment through the SMS Patient Registry to gather data regarding multiple aspects of BHDS symptoms, screening, and outcomes. This investigation will improve knowledge and understanding of both SMS and the co-morbidities associated with BHDS, as well as provide guidance for future recommendations and approaches to education within the SMS community. Appropriate screening will increase understanding of the timing and occurrence of specific symptoms of BHDS and will lead to improved outcomes.

ABSTRACT

rAAV-CRISPRa Therapy Corrects RAI1 Haploinsufficiency and Rescues Selective Disease Features in Smith-Magenis Syndrome Mice

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Haploinsufficiency in retinoic acid induced 1 (RAI1) causes Smith-Magenis syndrome (SMS), a syndromic autism spectrum disorder characterized by neurocognitive deficits and obesity. Currently, curative treatments for SMS do not exist. Here we take a recombinant adeno-associated virus (rAAV)-clustered regularly interspaced short palindromic repeats activation (CRISPRa) approach to increase expression of the remaining intact Rai1 allele.

Building upon previous work that found the paraventricular nucleus of hypothalamus (PVH) plays a central role in SMS pathogenesis, we performed PVH-specific rAAV-CRISPRa therapy by increasing endogenous Rai1 expression in SMS (Rai1+/–) mice. We found that rAAV-CRISPRa therapy rescues excessive repetitive behavior, delays the onset of obesity, and partially reduces hyperphagia in SMS mice. Our work provides evidence that rAAV-CRISPRa therapy during early adolescence can boost the expression of healthy Rai1 allele and modify disease progression in a mouse model of Smith-Magenis

ABSTRACT

Disease Burden in Smith-Magenis Syndrome as Identified by Caregivers

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Objective: To identify the most important and frequent symptoms that occur in individuals with Smith-Magenis Syndrome.

Background: Smith-Magenis Syndrome (SMS) is a rare, neurodevelopmental disorder caused by a mutation of the RAI1 gene, resulting in symptoms including but not limited to: impaired behavior, irregular sleeping patterns, intellectual disability, and short stature. Additional information is needed regarding what symptoms have the greatest impact on the lives of patients with this condition.

Methods: We conducted semi-structured, qualitative interviews with caregivers of individuals with SMS to identify the most important symptoms that occur in SMS. Caregivers were recruited through Parents & Researchers Interested in Smith-Magenis Syndrome (PRISMS). Interviews were recorded, transcribed, coded, and analyzed to identify the most common and important symptomatic themes in SMS.

Results: We interviewed seven caregivers of individuals with SMS. These interviews yielded 1695 total quotes representing 86 unique symptoms. Participant quotes predominantly represented three symptomatic domains: Physical (480 quotes), Social (275 quotes), and Behavioral (256 quotes). Within the Physical domain, caregivers most frequently referenced themes related to the individual's "Inability to do activities" (73 quotes) and "Sleep/daytime sleepiness" (67 quotes). Within the Social domain, participants provided 108 quotes related to difficulty communicating. Participants also provided 33 direct quotes related to "Self-injurious behaviors" and 31 quotes describing the effect of "Tantrums" on a SMS patient's life.

Conclusion: This study provides additional insight into the most life altering and common symptoms experienced by individuals with SMS. This information will be used to further inform a planned cross-sectional study designed to explore what generates the greatest disease burden in SMS and the subsequent development of an instrument to measure changes in disease burden in this disease overtime.

Lay Abstract: We asked caregivers of individuals with Smith-Magenis Syndrome (SMS) about the symptoms that most impact the lives of the individuals they care for. This information will be further analyzed and eventually used in the development of a Caregiver Reported Outcome Measure (CRO) to measure disease progression and impact in SMS.

ABSTRACT

Differentiation of Induced Pluripotent Stem Cells (iPSCs) of Smith-Magenis Syndrome (SMS) RAI1 Mutation Carriers Into Neural Cells Reveals Perturbations in Nervous System Development and Synaptic Signaling

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Smith-Magenis syndrome (SMS) is a rare neurodevelopmental disorder associated with diverse clinical presentations including behavioral problems, sleep disturbance, intellectual disability, obesity, and craniofacial defects. In ~90% of cases, the genetic etiology involves an interstitial deletion of chromosome 17p11.2. The rarer, nondeletion subtype shows heterozygous mutations in retinoic acid induced 1 (RAI1), one of ~22 genes located within the region. Animal models have implicated anomalies in neuronal pathways, however, in human neural cells the dysfunctional molecular mechanisms are poorly understood.

To address this question, we reprogrammed somatic cells from SMS cases that carry RAI1 point mutations (herein referred to as SMS-RAI1) and differentiated the iPSC clones into neural progenitor cells (NPCs), and forebrain cortical neurons, representing two stages along the temporal progression of neural cell maturation. Transcriptome profiles for both NPCs and cortical neurons from SMS-RAI1 cases and unaffected controls were generated by performing RNA sequencing. Significantly altered expression of multiple genes was associated with highly enriched gene ontology (GO) terms that included nervous system development, synaptic signaling, cell cycle, and neuron projection. Human phenotype ontology correlated clinically, and was significant for neurodevelopmental abnormality, neurodevelopmental delay, and neuron-to-neuron communication. Expression modules of genes that were differentially expressed during the cellular developmental transition overlapped with modules previously reported for autism spectrum disorder, bipolar disorder, and schizophrenia. This study uncovered distinct cellular mechanisms that help model associated neural defects in SMS-RAI1 and may provide targets for therapeutic development.

Lay Abstract: The neurobiological defects associated with the loss of the RAI1 gene in SMS non-deletion cases are still poorly understood. To address this question, we performed cellular modeling studies using induced pluripotent stem cell (iPSC)-derived neural cells from SMS and unaffected controls. We examined the differential level of gene activity by RNA sequencing in two types of iPSC-neural derivatives, representing two stages of neural cell maturation: early-stage neural progenitor cells (NPCs), and later-stage forebrain cortical neurons. This analysis revealed that the temporal progression of SMS cells deficient in RAI1 into neuronal cell maturation was associated with dysfunction in multiple processes including nervous system development, cell cycle, and abnormality in skull size. Genes that showed altered expression in cases overlapped with those previously associated with autism spectrum disorder, bipolar disorder and schizophrenia. These findings help advance knowledge of perturbed cellular mechanisms in SMS, and could illuminate genetic targets for drug discovery.

ABSTRACT

Growth Standards for Children 0-16 Years of Age With Smith-Magenis Syndrome (SMS)

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F Duncan (5)
AK Leo0nard (5)
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D Moretti-Ferreira (7)
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Smith-Magenis syndrome (SMS) is a rare chromosomal disorder characterized by craniofacial anomalies, intellectual disability, developmental delays, chronic sleep disturbances, and intense behavioral/emotional dysregulation. As a result, siblings of individuals with SMS may demonstrate coping difficulties and challenges identifying benefits of their sibling relationship. Nine adolescents (ages 10-14, 56% male, 78% White/22% Biracial) growing up with a sibling with SMS were paired and met individually with trained mentors (ages 18-25) for an eight-week, sibling-to-sibling, semi-structured online mentorship program aimed at enhancing adaptive coping and benefit finding. Mentees reported increased benefit finding three months after completing the program as compared to prior to starting the program ($t(7) = 4.57$, $p = .002$). Specifically, three months after program completion, mentees were more likely to endorse that having a sibling with SMS has helped them become a stronger person ($t(7) = 4.41$, $p = .003$), know how much they are loved ($t(7) = 4.71$, $p = .002$), learn to better cope with their problems ($t(7) = 5.40$, $p = .001$), be more patient ($t(7) = 4.41$, $p = .003$), and taught them to be more loving of others ($t(7) = 6.48$, p .05), three months after program completion, mentees with higher rates of benefit finding were also more likely to utilize active coping ($r = -.74$, $p = .04$), planning/problem solving ($r = -.92$, $p = .001$), humor ($r = -.83$, $p < .01$), and instrumental supports/seeking advice ($r = -.85$, $p = .008$) as adaptive coping methods. Results suggest benefit finding is a modifiable cognitive state that can be enhanced via sibling-to-sibling mentorship and that may continue to increase several months beyond program completion. Being able to successfully identify benefits of having a sibling with SMS may also relate to use of several teachable and sustainable adaptive coping strategies.

Lay Abstract: Smith-Magenis syndrome (SMS) is a rare chromosomal disorder characterized by craniofacial anomalies, intellectual disability, developmental delays, chronic sleep disturbances, and intense behavioral/emotional dysregulation. As a result, siblings of individuals with SMS may demonstrate coping difficulties and challenges identifying benefits of their sibling relationship. Nine adolescents (ages 10-14, 56% male, 78% White/22% Biracial) growing up with a sibling with SMS were paired and met individually with trained mentors (ages 18-25) for an eight-week, sibling-to-sibling, semi-structured online mentorship program aimed at enhancing adaptive coping and benefit finding. Mentees reported increased benefit finding three months after completing the program as compared to prior to starting the program. Specifically, three months after program completion, mentees were more likely to endorse that having a sibling with SMS has helped them become a stronger person, know how much they are loved, learn to better cope with their problems, be more patient, and taught them to be more loving of others as compared to prior to participating. Although mentees did not modify their coping style preferences significantly over time, three months after program completion, mentees with higher rates of benefit finding were also more likely to utilize active coping, planning/problem solving, humor, and instrumental supports/seeking advice as adaptive coping methods. Results suggest benefit finding is a modifiable cognitive state that can be enhanced via sibling-to-sibling mentorship and that may continue to increase several months beyond program completion. Being able to successfully identify benefits of having a sibling with SMS may also relate to use of several teachable and sustainable adaptive coping strategies.

ABSTRACT

Tethered Cord in Smith-Magenis Syndrome: A Case Series

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Background: Smith-Magenis syndrome (SMS) is a recognizable condition caused by heterozygous (primarily de novo) interstitial deletions at 17p11.2 including RAI1 or pathogenic variation in RAI1. Features include a distinctive neurobehavioral profile, circadian rhythm disturbance, brachydactyly, obesity, and unique craniofacial features. Herein we present three cases of tethered cord, a spinal condition which has not been previously described in SMS. Each case has the deletion form of SMS.

Case Series: Case #1 was diagnosed with scoliosis at 16 months of age that progressed despite serial casting. Spinal fusion with MAGEC rods was performed at age 6 years which was complicated by loss of neuromonitoring signals to bilateral feet. Emergent MRI confirmed no intraspinal injury but revealed a tethered cord. After surgical release the patient achieved daytime continence. Case #2, was clinically diagnosed with tethered cord by SMS clinician at age 3 (waddling lordotic gait) and referred to a neurosurgeon who confirmed diagnosis by magnetic resonance imaging (fibrolipoma of filum terminale). Surgery was declined. He is not yet toilet trained. Case #3 was diagnosed and had neurosurgery for 90-degree scoliosis and tethered cord at age 15. She was seen in SMS clinic age 32, is toilet trained with new onset urinary and stool incontinence.

Discussion: Onset of symptoms for tethered cord occurred concurrently with scoliosis in two cases and lordosis in one case and associated with gait abnormalities, urinary and/or stool difficulties e.g., toilet training difficulties, urinary frequency, and constipation. The variable presenting features highlight the importance for careful examination as well as clinician awareness when evaluating a patient with SMS, particularly as some features common in SMS (e.g. chronic constipation) can also be associated with tethered cord syndrome. We propose MRI of the lumbar spine (including prone positioning) to assess for tethered cord in SMS individuals with refractory constipation, progressive scoliosis or gait abnormalities.

Lay Abstract: Tethered cord is a disorder where the lower spinal cord is fixated (tethered) to the spinal canal, resulting in abnormal stretching of the spinal cord and can be associated with a variety of symptoms including skeletal, neurological, or bowel-bladder abnormalities. The diagnosis can be made by clinical examination and supported with findings on lumbar spine MRI.

We present a series of three individuals with the deletion form of Smith-Magenis syndrome who were diagnosed with a tethered cord. To our knowledge, this has not been described previously in Smith Magenis syndrome. We highlight the variable presenting symptoms and course. We recommend evaluating for tethered cord in patients in patients with suggestive symptoms.

ABSTRACT

Managing Food-Related Behavior in Individuals With Smith Magenis Syndrome —A Compendium of Strategies

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Background: Treating obesity in complex disorders requires individualized health management plans. Individuals with Smith Magenis Syndrome (SMS) often develop obesity in their middle childhood years. However, individuals with SMS also struggle with cognitive impairments, anxiety, behavioral disturbances, and sleep disorder. Thus, treating obesity in the SMS population has multiple inherent barriers. Identifying and understanding beneficial strategies in this rare population is necessary to guide both other caregivers and health providers to successfully treat obesity in individuals with SMS. However, to date, there is no research on what strategies caregivers employ to help individuals with SMS individuals manage their food intake and mitigate associated behaviors.

Methods: Caregivers (n=24) representing 21 individuals with SMS, recruited from the Parents and Researchers Interested in SMS (PRISMS) 2023 national meeting and social media platforms, participated in semi-structured interviews. Interviews were digitally recorded, transcribed verbatim, coded and analyzed using hybrid thematic analysis.

Results: Analysis revealed strategies employed by caregivers focus on mitigating compulsive eating behaviors, selective food preferences, and difficulties with impulse regulation. Strategies spanned concrete actions such as locking food away as well as more intangible strategies like modifying how they communicate. Importantly, strategies were variable from family to family but also changed over time within families and across settings, such as home or school/work environments. One common theme for families whose children initially struggled to put on weight in early childhood was that they wished they could have employed more healthy options early on.

Conclusion: Managing food-related behaviors in SMS requires innovative strategies personalized to the individual. Caregivers and the medical community can use this resource of strategies to identify new ideas to help manage food-related behaviors.

Keywords: Smith Magenis Syndrome, food-related problems/behavior, strategies, hyperphagia.

Lay Abstract: Managing obesity in individuals with Smith Magenis Syndrome (SMS) likely requires unique strategies but these have not been investigated to date. We performed semi-structured interviews with focus groups of caregivers to understand the types of effective strategies employed. These interviews were transcribed, coded, and then analyzed to understand themes in effective strategies. We found that while some similarities existed, such as the need to lock away food, there were often individual variations in how the strategy was employed (only specific foods hidden/locked vs. the entire pantry locked). Additionally, we found that strategies changed over time within families as the individual grew and changed. One common theme for families whose children initially struggled to put on weight in early childhood was that they wished they could have employed more healthy options early on. We now have compiled these strategies so they may be a resource to families and caregivers treating obesity in this unique population.

ABSTRACT

Understanding the Clinical Impact of Copy Number Variants in 17p11.2 Not Spanning the RAI1 Gene

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Copy number variants (CNVs) spanning gene RAI1 cause two distinct neurodevelopmental genomic disorders; Smith Magenis Syndrome (SMS) (MIM: 182290) caused by a deletion of RAI1 and Potocki-Lupski Syndrome (PTLS) (MIM: 610883) caused by a duplication. Approximately 90-95% of individuals diagnosed with SMS have deletions spanning RAI1 with the remaining 5-10% harboring single nucleotide variant alleles in RAI1, particularly exon 3. Two-thirds of individuals with PTLS carry the 3.6 Mb common recurrent duplication with the remaining 1/3 carrying a non-recurrent copy number gains all spanning dosage sensitive gene RAI1. When CNVs are detected surrounding the gene but not overlapping, they are frequently clinically diagnosed without a molecular cause (i.e., confirmed array result).

To better refine our understanding of impact of CNVs within 17p11.2 not spanning RAI1, and in preparation for biomarker clinical studies and potential RAI1 directed therapeutic interventional studies, we ascertained 14 probands with copy-number gains in 17p11.2 that did not include dosage sensitive RAI1; such individuals manifested a broad phenotype of developmental delay/intellectual disability and a presumed diagnosis of PTLS. We performed a combination of high-resolution array CGH (n=14), short-read whole-genome sequencing (sr-WGS, n=7), long-read WGS (ONT; n=7 and PacBio HiFi; n=7) and optical genome mapping (OGM) on a subset. Genomic complexities identified in this cohort include DUP-NML-DUP-NML-DUP(n=1), DEL-DUP(n=1), higher order amplifications(n=2), marker chromosomes (n=3) and simple copy number gains (n=7). Two cases with higher order amplifications (a 4X and a 6x amplification) appear to involve an identically overlapping copy number gain with distal breakpoint mapping within the structurally polymorphic neoplasia associated isodicentric 17q breakpoint cluster, two include a region to which the BHD1 locus maps [MIM: 135150]. Chromosome region 17p11.2 amplification is also associated with some cancers.

Atypical presentations of PTLS/SMS phenotype present opportunity for families and clinical researchers to better delineate the spectrum and warrant deep phenotyping. Furthermore, such gains at 17p11.2 may illuminate structural variant mutagenesis mechanism(s) and provide insight into (i) genomic mechanisms by which copy number gains not spanning RAI1 may hinder its transcription and function; (ii) potential PTLS contributing genes other than the 'driver RAI1 gene'.

Lay Abstract: Two different disorders linked to changes in the amount of DNA surrounding the gene called RAI1. Smith-Magenis Syndrome (SMS) happens when a piece of DNA that includes RAI1 is missing (deletion); and the other, Potocki-Lupski Syndrome (PTLS), occurs when there's an extra copy of the DNA segment including RAI1 (duplication). Sometimes, doctors may find changes in the DNA near RAI1, but not directly affecting it, and it's hard to understand the cause of the disorder in these cases. To understand how DNA changes near but not including RAI1 can affect development, we investigated 14 individuals who had extra DNA in the same general area (17p11.2) but didn't affect RAI1 directly. We used several advanced DNA analysis techniques to study these cases in detail.

We found a variety of DNA changes, including some complex rearrangements and extra copies of DNA segments. Two particular cases showed an increase in DNA copies that were closely related to each other and linked to a region associated with certain types of cancer. This research helps us understand the full range of symptoms and characteristics of these disorders, potentially leading to better diagnosis and treatment. It also sheds light on how DNA changes not affecting RAI1 directly can still impact the gene's activity and contribute to PTLS and SMS.

ABSTRACT

Growth Standards for Children 0-16 Years of Age With Smith-Magenis Syndrome (SMS)

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INTRODUCTION

Smith-Magenis Syndrome (SMS, OMIM 182290) is a complex syndromic diagnosis marked by neurobehavioral differences and dysmorphisms, caused by haploinsufficiency of the retinoic acid-1 (RAI1) gene either by a pathogenic sequence variant or deletion at chromosome 17p11.2 involving a portion or all of this gene. Dysmorphisms may include a broad square face and brachycephaly, heavy eyebrows, full mouth with everted upper lip, and early micrognathia evolving to prognathism after excessive relative mandibular growth. All patients with SMS have variable global cognitive impairment, greatest in speech/language, disturbed sleep patterns and distinct behaviors including self-injury, food foraging and abnormal oral intake regulation, hyperactivity and aggression. Short stature and central obesity are common in patients with SMS and reference curves are needed to assess growth in clinical care and research endeavors.

METHODS

After IRB approval, anthropometry (including length/height, weight, head circumference) were collected via direct patient encounter at the NIH, parental report from external medical encounters, and extraction from medical records. Utilizing polynomial smooth splines with a B-spline basis and variable windows depending on age, sex-specific length/height and weight curves were created including 5th, 50th and 95th percentile lines for 0 through 16 years. Head circumference data were pooled from males and females to create 5th, 50th and 95th percentile lines for 0 through 12 years.

RESULTS

Nearly 6,000 length/height, weight and head circumference measurements from 189 patients with SMS from birth through 18 years of age were gathered. Length/height and weight data were plotted against age from birth through 16 years to create new length/height-for-age and weight-for-age curves by sex. Similar processes were employed to construct head circumference-for-age curves from birth through 12 years, combining data from both sexes into one figure.

DISCUSSION

The curves included in this article represent the first set of standardized growth curves for individuals with SMS. As such they will permit clinicians to monitor and set expectations for linear growth, weight gain and cranial growth in individuals with SMS.

ABSTRACT

Blind to the Perils of Pursuing Food: Behaviors of Individuals With Smith-Magenis Syndrome

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Purpose. Discrepancies exist between the need to lock food away and satiety scores in the Smith-Magenis syndrome (SMS) population. This study sought to uncover food-related behaviors within this unique group of individuals.

Methods. Caregivers (n=24) representing 21 individuals with SMS, recruited from the Parents and Researchers Interested in SMS (PRISMS) national meeting and social media platforms, participated in semi-structured interviews. Interviews were digitally recorded, transcribed verbatim, coded and analyzed using hybrid thematic analysis.

Results. This study identified a global theme of "Blind to the perils while pursuing their goals", supported by five organizing themes: (i) Biology impacting behaviors, (ii) Need for personalized strategies, (iii) Controlling food experiences, (iv) Need for parents to orchestrate life, and (v) Surprising resourcefulness. Subthemes within these organizing themes highlighted that individuals with SMS have unique food-related behaviors, and often fixate on certain types of foods. Their constant obsession with food for many of them is driven by hunger, obsessive characteristics, a need for autonomy, and a need for fairness. Caregivers must put multiple guardrails in place and remain constantly vigilant to prevent overeating in these individuals.

Conclusion. Individuals with SMS often perseverate on food and display unique food related behaviors. Treating obesity in this population is likely to be ineffective without multicomponent, individualized strategies. Additionally, research in this population will likely require targeted instruments for the SMS population to more clearly define the underlying etiologies and to track changes over time in therapeutic trials.

Lay Abstract: Although individuals with SMS may exhibit significantly increased food intake, it is not fully known exactly what causes or exacerbates weight gain in SMS patients, as not all patients develop obesity. Previous research has also shown that over half of caregivers reported needing to lock away food but at the same time reported low to moderate scores for hyperphagia on existing questionnaires. This contradiction points to a need to understand food-related behaviors specific to the SMS population. We performed semi-structured interviews with caregivers of individuals with SMS. Interviews were transcribed and then underwent thematic analysis. We found a global theme "Blind to the perils while pursuing their goals" and five organizing themes. These themes highlighted the unique food-related behaviors in the SMS population and their fixation on specific types of foods. Additionally, we found that individuals with SMS are driven by hunger, obsessive characteristics, a need for autonomy, and a need for fairness. We also found that there was a high burden on caregivers to put up multiple guardrails and remain constantly vigilant.

ABSTRACT

Slight Differences With Similar Language Profiles in Individuals With Smith-Magenis Syndrome (SMS) Due to a Genetic Deletion Versus a Mutation of the RAI1 Gene

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Introduction: Smith-Magenis Syndrome (SMS) is caused by either a deletion within chromosome 17p11.2 or a mutation of the RAI1 gene (known as the RAI1 variant). Approximately 90% of those with SMS have a deletion and 10% have an RAI1 mutation. Results from previous studies reported more mild delays in cognitive and motor skills in those with the RAI1 variant form of SMS. The phenotype of SMS includes delayed speech-language development, but since no previous studies compared language abilities of those with the deletion and those with the RAI1 variant, the full extent of similarities or differences in the communication phenotype is unknown. This study compared the language and communication profiles of individuals with SMS due to a deletion versus an RAI1 mutation to provide clarity about the variability within this syndrome. By comparing these groups, we also aimed to clarify the contributions of the RAI1 gene to language development.

Methods: We analyzed responses about language from the International SMS Patient Registry for 33 individuals (ages 7-22 years). Mode of communication, early speech-language milestones, expressive and receptive language abilities, and literacy skills were analyzed for 23 individuals with a deletion and 10 with an RAI1 mutation. We report descriptive statistics, but due the small number of subjects in each group, no inferential statistics were completed.

Results: Individuals with the RAI1 form of SMS showed a slight advantage for the age that words were first spoken and combined, use of natural speech, comprehension of directions and stories, and the ability to read and write. While small group differences were present, there were notable similarities between groups for all variables.

Discussion: The findings suggest that while there are small differences across all variables, both groups have similar impairment in language abilities. It is not possible to determine if these small differences are clinically meaningful or if they simply reflect the heterogeneity of the phenotype.

This study also aimed to clarity the contributions of the RAI1 gene to language development. Slight differences with clear similarities in the language and communication phenotype between groups supports the hypothesis that haploinsufficiency of the RAI1 gene is responsible for the language phenotype of SMS and suggest that the RAI1 gene is critical for the development of typical language abilities.

ABSTRACT

Longitudinal Outcomes From a Smith-Magenis Syndrome Sibling-to-Sibling Online Mentorship Program: A Focus on Benefit Finding and Coping Mechanisms

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Smith-Magenis syndrome (SMS) is a rare chromosomal disorder characterized by craniofacial anomalies, intellectual disability, developmental delays, chronic sleep disturbances, and intense behavioral/emotional dysregulation. As a result, siblings of individuals with SMS may demonstrate coping difficulties and challenges identifying benefits of their sibling relationship. Nine adolescents (ages 10-14, 56% male, 78% White/22% Biracial) growing up with a sibling with SMS were paired and met individually with trained mentors (ages 18-25) for an eight-week, sibling-to-sibling, semi-structured online mentorship program aimed at enhancing adaptive coping and benefit finding. Mentees reported increased benefit finding three months after completing the program as compared to prior to starting the program ($t(7) = 4.57$, $p = .002$). Specifically, three months after program completion, mentees were more likely to endorse that having a sibling with SMS has helped them become a stronger person ($t(7) = 4.41$, $p = .003$), know how much they are loved ($t(7) = 4.71$, $p = .002$), learn to better cope with their problems ($t(7) = 5.40$, $p = .001$), be more patient ($t(7) = 4.41$, $p = .003$), and taught them to be more loving of others ($t(7) = 6.48$, p .05), three months after program completion, mentees with higher rates of benefit finding were also more likely to utilize active coping ($r = -.74$, $p = .04$), planning/problem solving ($r = -.92$, $p = .001$), humor ($r = -.83$, $p < .01$), and instrumental supports/seeking advice ($r = -.85$, $p = .008$) as adaptive coping methods. Results suggest benefit finding is a modifiable cognitive state that can be enhanced via sibling-to-sibling mentorship and that may continue to increase several months beyond program completion. Being able to successfully identify benefits of having a sibling with SMS may also relate to use of several teachable and sustainable adaptive coping strategies.

Lay Abstract: Smith-Magenis syndrome (SMS) is a rare chromosomal disorder characterized by craniofacial anomalies, intellectual disability, developmental delays, chronic sleep disturbances, and intense behavioral/emotional dysregulation. As a result, siblings of individuals with SMS may demonstrate coping difficulties and challenges identifying benefits of their sibling relationship. Nine adolescents (ages 10-14, 56% male, 78% White/22% Biracial) growing up with a sibling with SMS were paired and met individually with trained mentors (ages 18-25) for an eight-week, sibling-to-sibling, semi-structured online mentorship program aimed at enhancing adaptive coping and benefit finding. Mentees reported increased benefit finding three months after completing the program as compared to prior to starting the program. Specifically, three months after program completion, mentees were more likely to endorse that having a sibling with SMS has helped them become a stronger person, know how much they are loved, learn to better cope with their problems, be more patient, and taught them to be more loving of others as compared to prior to participating. Although mentees did not modify their coping style preferences significantly over time, three months after program completion, mentees with higher rates of benefit finding were also more likely to utilize active coping, planning/problem solving, humor, and instrumental supports/seeking advice as adaptive coping methods. Results suggest benefit finding is a modifiable cognitive state that can be enhanced via sibling-to-sibling mentorship and that may continue to increase several months beyond program completion. Being able to successfully identify benefits of having a sibling with SMS may also relate to use of several teachable and sustainable adaptive coping strategies.

ABSTRACT

Tailoring a Food-Behavior Questionnaire for the Smith Magenis Syndrome (SMS) Population

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Background: Individuals with Smith Magenis Syndrome (SMS) often face complex relationships with food, stemming from sensory sensitivities, compulsive eating behaviors, and metabolic abnormalities. We recently completed qualitative interviews with caregivers of SMS individuals that revealed individuals with SMS displayed unique patterns of food-related issues that were not reflected on currently available food questionnaire. Without accurate assessment of food-related behaviors, it is not possible to capture positive or negative changes over time, especially with regard to interventions and possible clinical trials. Thus, a tailored assessment tool to the SMS population was needed.

Methods: We performed two rounds of semi-structured interviews with caregivers (n=37). In the first round (n=24), caregivers completed the Food-Related Problems Questionnaire (FRPQ) and Hyperphagia Questionnaire for Clinical Trials (HQCT). We reviewed questions individually with caregivers, discussing difficulties in answering existing questions. We modified the FRPQ to the SMS-FRPQ_v1 based on this feedback, which included changes to nine questions and the addition of three new questions. This new questionnaire was then reviewed by three SMS experts for content validation and minor changes incorporated (SMS-FRPQ_v2). The SMS-FRPQ_v2 was further refined through focus groups with additional caregivers (n=15). The finalized SMS-FRPQ is currently undergoing validation by a larger sample of SMS caregivers (n~100).

Results: Focus groups revealed specific nuances of feeding-behaviors in Smith-Magenis Syndrome (SMS) caused difficulties in answering existing questions. Individuals with SMS often fixated or increased intake of selective foods, making questions referring to ‚Äúall food‚Äù difficult to answer. Caregivers also struggled answering questions about sneaking food since many employed external controls preventing access to food. Caregivers agreed with the modifications resulting in the SMS-FRPQ and subjectively had less confusion in answering the questionnaire. Data collection is ongoing, and results will be available in May 2024.

Conclusion: The SMS population needs a tailored questionnaire to assess food related behaviors. The SMS-FRPQ created to fill this gap may fill this gap and provide a comprehensive and nuanced assessment tool to assess changes during interventions. Validation of the SMS-FRPQ is to be completed soon.

Keywords: SMS, food-related problems/behaviors

Lay Abstract: Individuals with Smith Magenis Syndrome do not display the same food-related behaviors as those with Prader-Willi Syndrome. Thus, use of existing questionnaires do not capture the extent or variety of the food-related behaviors exhibited by individuals with SMS. We modified an existing questionnaire, the Food-Related Problems Questionnaire (FRPQ) based on focus groups of caregivers of individuals with SMS. Modifications were made to reflect the focus on specific food choices as well as the presence of external controls locking food away in this population. The modified questionnaire, SMS-FRPQ, underwent content validation by external experts and by additional focus groups of caregivers. Full validation of the new tool is ongoing with results expected by May, 2024. The development of the SMS-FRPQ may provide a unique tool for this population to assess changes during therapeutic interventions.

ABSTRACT

Life as an Adult With Disabilities in Germany in Theory and Practice —Experience Report From a Mother of a 32-Year-Old Daughter With Smith-Magenis Syndrome

Astrid Diederichs

Mother and legal guardian, volunteer head of the scientific advisory board of SIRiUS e.V. - the German self-help organization for Smith-Magenis syndrome

With Germany's "Wirtschaftswunder" (economic miracle) in the 1960s, considerable resources were available to expand the welfare state and strengthen political will among citizens. Under the Federal Association for Life Support (Lebenshilfe e.V.), interests of people with disabilities became more of a social focus. A disability policy with corresponding laws was created with the primary goal of (re)establishing work activity and (re)integrating into working life. A comprehensive network of workshop facilities for disabled people (WfbM) emerged from local craft facilities outside of institutions for the disabled. The aim today to maintain, develop, improve, or restore the performance or earning capacity of disabled people, to further develop their personality, and to enable or secure their employment.

The practice for those affected by SMS is much more difficult. Given the level of emotional development relative to cognitive disability, self-determined or even autonomous decisions are almost impossible for an individual with SMS. Government agencies/insurance providers often only approve applications in the cases of significant physical impairments. This makes the search for suitable places for an adult with SMS to live that offers 24/7 close support, but also offers intellectually appealing daily structures or a combination with a visit to the WfbM extremely challenging.

Before our daughter was confirmed to have SMS at age 25years, she was considered an atypical autistic. After good support and workshop preparation at school, she moved to a new Asperger's home for young adults in Berlin when she was 19. She also started in a WfbM. Both together were probably too much: the team of carers at the home were completely overwhelmed by this situation, unable to act on our daughter, leading to her expulsion. Due to the lack of the system-related possibility of 1:1 additional support in the WfbM, this measure also had to be cancelled, to the regret of everyone who saw the potential in our daughter.

Thanks to a motivated provider of autism facilities and our willingness to fight for the application of disability rights to those affected by SMS in court, our daughter has lived for the past 10 years 1.5hr away in a place in the country. For the past 5 years, she also visits the local WfbM. We all see her as clearly stabilized and satisfied, and regularly taken surveys about her emotional development demonstrate the success of her current living environment.

ABSTRACT

Clinical and Molecular Biomarker Studies in RAI1-Related Disorders Toward Future Gene Therapies

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The RAI1 gene, located at the chromosome 17p11.2 locus, plays a pivotal role in regulating gene transcription through chromatin remodeling. Deletions (>90%) and loss-of-function mutations (<10%) in RAI1 lead to Smith Magenis syndrome (SMS), characterized predominantly by developmental delay/intellectual disability (DD/ID), neurobehavioral manifestations (e.g., overeating, self-mutilation, and aggression), congenital kidney and heart abnormalities, and sleep disturbances. Conversely, Potocki-Lupski Syndrome (PTLS) results from reciprocal duplication of the SMS region, featuring infantile hypotonia, DD/ID, oropharyngeal dysphagia leading to failure to thrive, neurobehavioral traits such as autism, obstructive sleep apnea, and structural cardiovascular anomalies. While current management of SMS and PTLS remains primarily symptomatic, recent advancements in genetic-based therapies have transformed the landscape of possible treatments. However, we must be cautious as excessive use of genetic-based treatments can potentially convert SMS to PTLS and vice versa. Conversely, inadequate dosing may fail to reverse the phenotype, resulting in trial failure. Thus, the development of safety biomarkers reflecting target engagement holds significant promise for the success of future trials.

To this end, we propose to examine a comprehensive panel of clinical, neurophysiological (sleep/EEG), and molecular biomarkers in patients with SMS and PTLS. Our overarching goal is to delineate a selection of candidate biomarkers that exhibit specificity and sensitivity in distinguishing between SMS and PTLS individuals. Specifically, we aim to identify biomarkers in both syndromes that reliably respond to genetic-based therapies, indicate whether dosing is right, and are stable over time. To identify such biomarkers, we will conduct a study of patients with SMS and PTLS, and neurotypical participants (N=20 each) including their physical exam, collection of blood and skin biopsy, and an overnight sleep study. These data will be compared between the SMS, PTLS and neurotypical groups to derive integrated biomarkers for future clinical trials. The study will take place at Texas Children's Hospital and will entail no cost to patients or families for their participation. We anticipate completing enrollment within the next three years and extend our invitation to families nationwide to join our study.

Lay Abstract: The RAI1 gene, found on chromosome 17p11.2, is crucial for controlling how genes are turned on and off through a process called chromatin remodeling. Problems with this gene, like deletions, duplications or simple mutations, can cause two different syndromes: Smith Magenis syndrome (SMS) and Potocki-Lupski Syndrome (PTLS).

SMS is characterized by things like developmental delays, behavioral issues (like overeating or aggression), kidney and heart problems, and sleep troubles. On the other hand, PTLS happens when there's a duplication of the same region, leading to issues like weak muscles in babies, developmental delays, trouble swallowing, behavioral traits like autism, sleep problems, and heart defects.

While treatments for SMS and PTLS mainly focus on managing symptoms, new genetic therapies offer hope for more targeted treatments. However, using these therapies too much or too little could potentially switch someone from having SMS to PTLS or vice versa. So, it's crucial to find ways to measure how well these treatments are working and if they're safe.

Our plan is to study a range of different markers, like clinical signs, brain activity during sleep (using EEG), and molecules in the blood and skin, in people with SMS and PTLS, as well as in those without these conditions. By comparing these markers between groups, we hope to find ones that can tell us if a treatment is working correctly and if it's safe over time. This study will happen at Texas Children,Äôs Hospital, and families won't have to pay to take part. We're aiming to finish enrolling participants within the next three years and welcome families from across the country to join us in this important research.

ABSTRACT

Smith-Magenis Syndrome Patient Registry: A Resource for Researchers

Theresa A. Wilson
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The Smith-Magenis Syndrome Patient Registry (SMSPR) is a natural history database with over 130 participants. Participants are 50% female, range in age from 1.5 - 73 years, and 83% have a deletion on chromosome 17p11.2. Participants reside in 10 countries, across 5 continents, with 90% in North America. The SMSPR collects data on demographics, medical history, birth measurements, body type, sleep, medications, eating behaviors, and speech and language development. New questionnaires are currently under development and requests for specific topics for inclusion are readily considered. To researchers with a specific research question, this dataset is available through a straightforward approval process managed by PRISMS. Additionally, a researcher may submit a new questionnaire for the SMSPR and have it sent to all participants, with approval. We will share the process for data access and survey development to support and encourage use of this a data-rich, ready resource to enhance the study of Smith-Magenis syndrome.

Lay Abstract: The Smith-Magenis Syndrome Patient Registry (SMSPR) is a natural history database with over 130 participants. Participants are 50% female, range in age from 1.5 ‚Äì 73 years, and 83% have a deletion on chromosome 17p11.2. Participants reside in 10 countries, across 5 continents, with 90% in North America. The SMSPR collects data on demographics, medical history, birth measurements, body type, sleep, medications, eating behaviors, and speech and language development. New questionnaires are currently under development and requests for specific topics for inclusion are readily considered. The focus of this abstract is to highlight the SMSPR for use by researchers as a tool to help expand the understanding of SMS and inform treatment options. Participation in the registry by those with SMS is critical to the success of this resource.

ABSTRACT

A Coordinated Model for Assessment and Intervention for Severe Behavior

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Kacie McGarry

University of Florida

We are developing a model of behavioral assessment and intervention that includes direct and repeated behavioral observation, behavioral observation under specific environmental contexts, and collection of data relating to possible sources of pain and discomfort. Pain and discomfort are known to influence the occurrence of severe behavior including self-injury, property destruction, and aggression. In this presentation we will show data from various components of the model as it develops, both from published and ongoing studies. Although we have not applied this model to Smith-Magenis Syndrome, specific features of the syndrome suggest that an integrated and coordinated assessment model would be useful.

Lay Abstract: We are currently developing an approach to track the occurrence of severe behavior such as self-injury, property destruction, and aggression. We are finding that such behavior occurs under identifiable environmental contexts, but also escalates during periods when the individual is experiencing pain or discomfort (such as fatigue or illness). We will show results of prior and ongoing studies to support this model and its potential application to Smith-Magenis Syndrome

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Parents and Researchers Interested in Smith-Magenis Syndrome

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