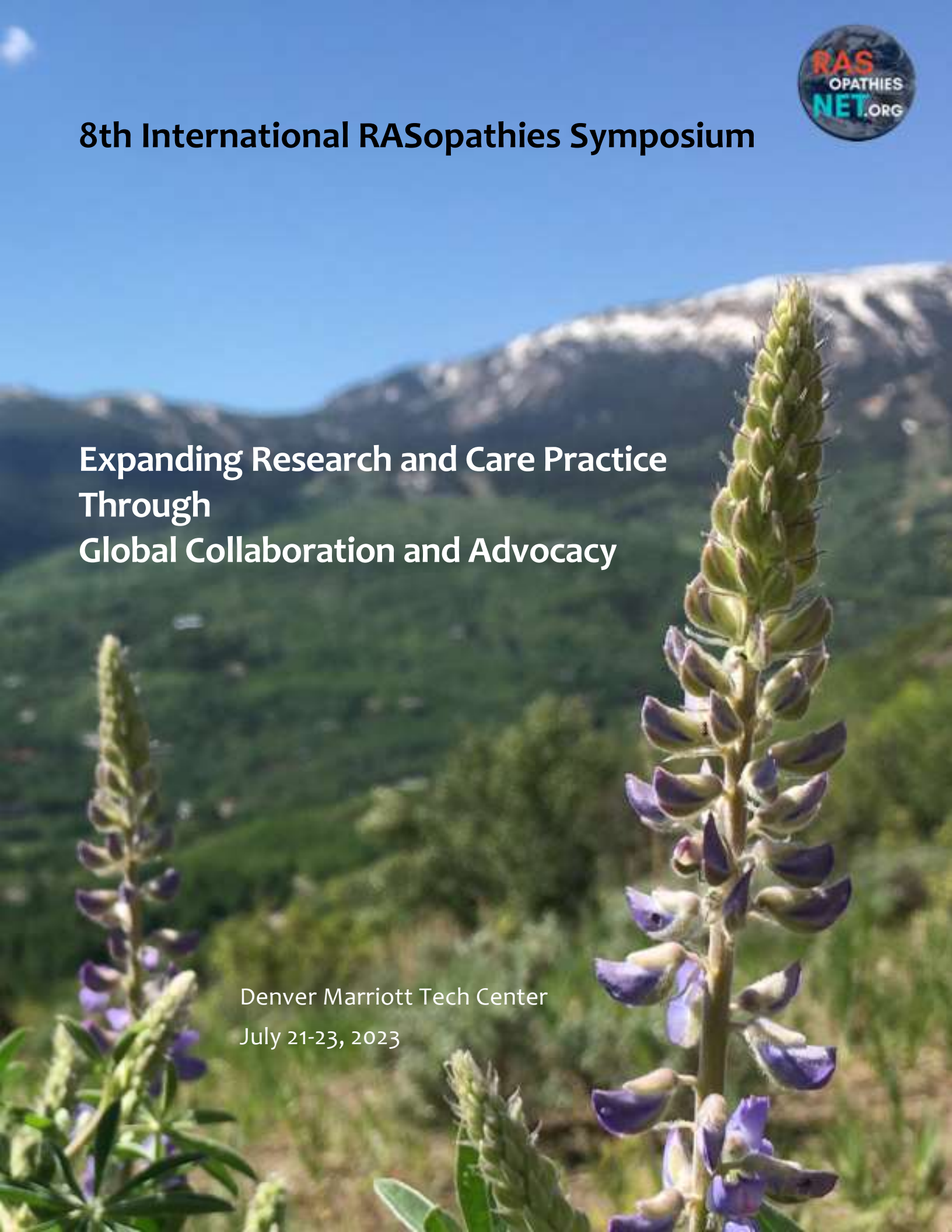

8th International RASopathies Symposium

Expanding Research and Care Practice Through Global Collaboration and Advocacy

Denver Marriott Tech Center

July 21-23, 2023

RASOPATHIES NETWORK

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* Funding for this conference was made possible (in part) by **R13TR004509** from the National Center for Advancing Translational Sciences, the National Institute of Neurological Disorders and Stroke, the Eunice Kennedy Shriver National Institute of Child Health & Human Development, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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~ WELCOME ~

Thank you for joining us for our *8th International RASopathies Symposium: Expanding Research and Care Practice Through Global Collaboration and Advocacy*!

Despite COVID, in planning this hybrid in-person and virtual symposium, we learned that the bloom of RASopathies research continues to advance at a lively rate.

We would like to thank all who helped us pull this symposium together, including the Chairs, Gregor Andelfinger, MD, PhD, CHU-Sainte Justine, Montreal, Canada; Anton Bennett, PhD, Yale University, New Haven, CT, USA; and Rene Pierpont, PhD, University of Minnesota, Minneapolis, MN, USA.

On behalf of the RASopathies Network, we hope this event engages and inspires you as we continue forward toward a better understanding of the RASopathies.

Yours in Friendship,

Lisa Schoyer, MFA, PI
Beth Stronach, PhD
Co-Organizers
and
The RASopathies Network Board

The RASopathies are a group of rare genetic conditions, including Noonan, Neurofibromatosis type 1, Costello and Cardiofaciocutaneous syndromes, which are caused by mutations in the DNA that makes the Ras/MAPK cellular signaling pathway. This pathway is turned on or off by various methods to make the cell grow, specialize, divide, and die properly. In affected people, the mutation keeps the pathway stuck in the ON position. We hope to find therapeutic interventions to help unstick the switch.

The RASopathies Network USA is an exempt organization under 501(c)(3). Our EIN number is 27-3775851.

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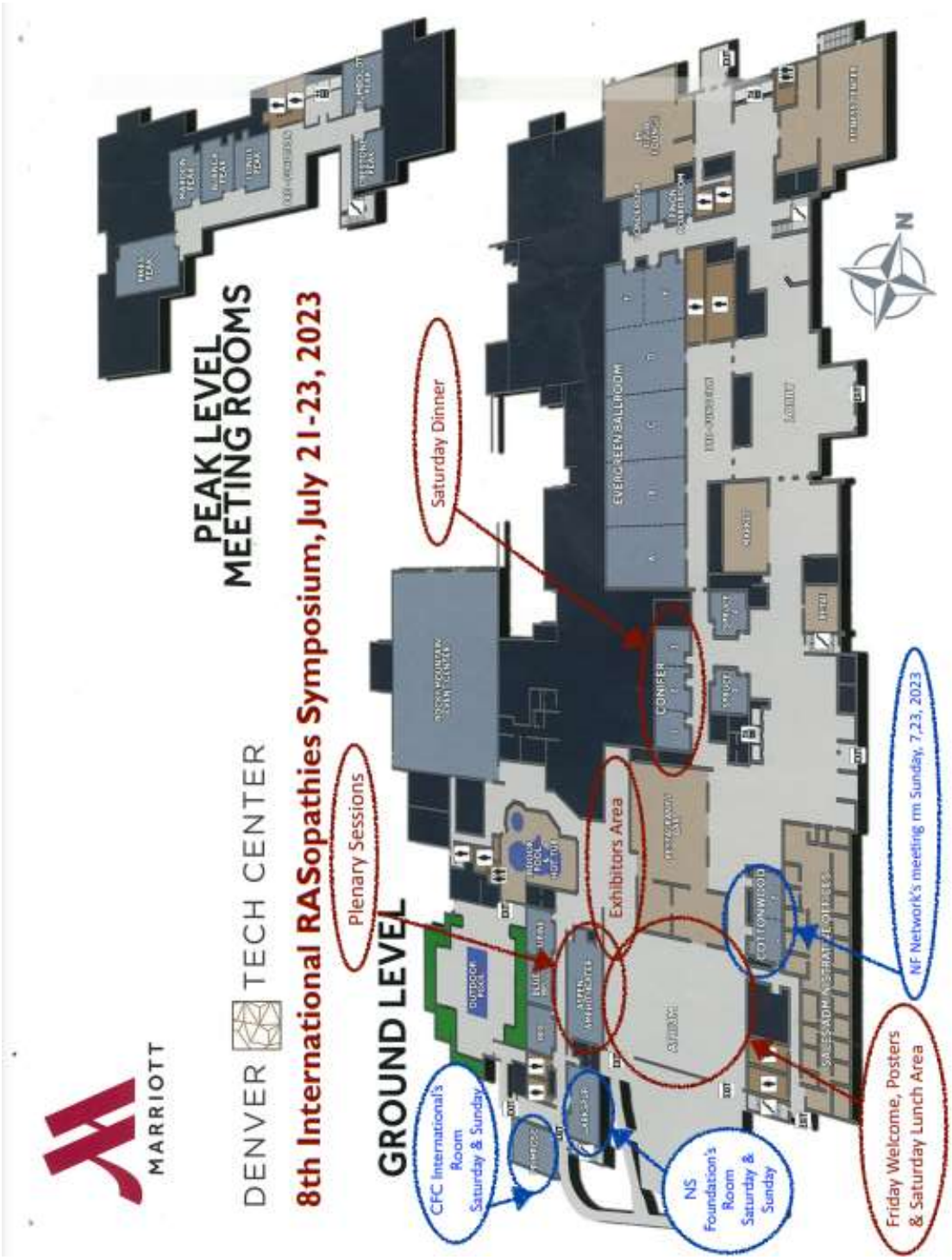

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The Heart Institute at Children's Hospital Colorado is nationally ranked for heart care and surgery by U.S. News & World Report and treats more than 20,000 patients from across the country each year. Here, hundreds of cardiac experts work together to provide care for a variety of congenital and childhood heart diseases. As the largest heart institute in the region and one of only eight stand-alone pediatric research centers in the country, we are a leader in pediatric heart care and are committed to improving the lives of all kids with heart disease.

To do this, we are working together to address complex conditions and improve treatment. For example, our multidisciplinary Noonan Syndrome and RASopathy Clinic is held monthly and is staffed by a team of experts from cardiology, genetics, endocrinology, hematology/oncology, ENT, audiology and genetic counseling. We also work closely with other medical specialties including GI/nutrition, neurology, orthopedics, dermatology and ophthalmology, among others. The clinic provides comprehensive evaluation, genetic counseling, developmental monitoring and individualized treatment plans for patients with RASopathy disorders and aims to address the diverse needs of individuals affected by these conditions throughout their lives. We also provide opportunities for patients and families to participate in research that advances our understanding of RASopathy-associated medical conditions and explores targeted therapies.

We hope to connect with you during your visit and share more about our program and recent innovations.

Making a difference starts with connection

We're looking forward to connecting with you during your visit because we know our work is only as strong as the people and partnerships behind them. By developing new approaches to treatment and finding avenues for improving outcomes and widening the pool of knowledge together, we can ensure that kids locally and globally can live longer, healthier lives.

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What to do and where to eat

We're here to help make the most out of your stay! Consider us your tour guide. We've put together a curated list of recommendations, so whether you're looking for coffee, a sweet treat, happy hour or a mile high adventure — we've got you covered.

FOOD

Denver Biscuit Company | Becky Hill
El Five | Jessica Stansauk
Mercantile Dining and Provision | Leslie McCallen
Rioja | Kelly Wolfe
Safta | Sarah Gitomer

COFFEE

Glissade Coffee Company | Kelly Wolfe
Ink Coffee | Becky Hill
Kaladi Coffee Roasters | Leslie McCallen
Lucille's Creole Cafe | Kathryn Chatfield
Rosebud Cafe | Kally Czapla

SWEETS

D Bar | Becky Hill
Little Man Ice Cream | Kathryn Chatfield, Sarah Gitomer
Sweet Action | Leslie McCallen
The Yard Milkshake Bar | Kally Czapla

HAPPY HOUR

The Cooper Lounge | Kelly Wolfe
Logan Street Restaurant and Bar | Becky Hill
Los Chingones | Leslie McCallen
Postino | Kathryn Chatfield
Terminal Bar Union Station | Kally Czapla

ACTIVITIES

Elitch Gardens Theme Park | Jessica Stansauk
Lookout Mountain | Leslie McCallen
Denver Zoo | Kathryn Chatfield
Museum of Nature and Science | Kelly Wolfe
Red Rocks | Sarah Gitomer

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AGENDA

8th International RASopathies Symposium
July 21-23, 2023, Denver Marriott Tech Center

** = Penn Orphan Disease Center Million Dollar Bike Ride RASopathies Research Grant Awardee
Green = Early Stage Investigator
= Family-Friendly Sessions

Schedule	*Description*	*Speaker*	*Duration*
FRIDAY 7:30-9:00pm	**Opening Night Dessert Reception and Presentations:** Self-Advocacy Success Stories to Stimulate Discussion on Improving QoL *Moderator:* **Michelle Ellis**, Noonan UK		**1h 30m**
Atrium	Welcome and Mixer; **ESI meet-up**	Meeting Organizers and Chairs	30m
	Living and thriving with a BRAF RASopathy	**Christine & Gigi Sevilla**, Chicago, IL	20m
	Managing Noonan syndrome as an adult	**April Anschutz**, Austin, TX	20m
	Innovating better solutions to manage my child's medically complex care	**Ryan Sheedy**, Bentonville, AR	20m

SATURDAY 7:00-8:00am	***Breakfast*** - Atrium		**1h**
Sat 8:00-9:50am	**1: Clinical Session:** Awareness of Clinical Indications & Recent Progress *Moderator:* **Karen Gripp, MD**, Nemours Children's Hospital, Wilmington, DE		**1h 50m**
Aspen Amphitheater	Hematological indications in RASopathies: Need for more research and education	**Benjamin Briggs, MD PhD,** Rady Children's Hospital, Navy Medical Center San Diego, CA	20m
	Targeting the Ras/MAPK pathway in JMML with trametinib	**Elliot Stieglitz, MD,** UCSF Benioff Children's Hospital, CA	20m
	Cell cycle defects underlie NS-associated cardiomyopathy suggesting potential new mechanisms	**Cordula Wolf, MD,** German Heart Center, Technical University of Munich, School of Medicine & Health, Munich, DEU	20m
	A molecular hypothesis to solve feeding problems, a substantial problem in RASopathy patients	**Dagmar Tiemens, PhD candidate & parent advocate,** RadboudUMC, Nijmegen, NLD	20m
	MEKi Treatment effects and QoL in diverse patients with NF1 tumors	**Christopher Moertel, MD,** University of Minnesota Medical Center, Minneapolis, MN	20m

	ESI Selected Abstract: Hypertrophic neuropathy: a possible cause of pain in children with Noonan syndrome and related disorders	**Fieke Draaisma,** RadboudUMC, Nijmegen, NLD	10m
Sat 9:50-10:00am	***Break***		**10m**
Sat 10:00-11:30am	**2: Neuro Session:** Neurodevelopmental Focus- From Brain to Behavior *Moderator*: **Rene Pierpont, PhD LP**, University of Minnesota, Minneapolis, MN		**1h 30m**
Aspen Amphitheater	Intersecting Neuroscience and Genetics: Utilizing Multivariant Brain Analysis for Understanding Genetic Mutations and Neuropsychiatric Outcomes in Children with Noonan Syndrome	**Tamar Green, MD,** Stanford Medicine, Stanford, CA	20m
	Information processing in NSSDs: correlation with genotype and social cognitive intervention approach for adults with Noonan syndrome	**Renée Roelofs, PhD, Ellen Wingbermühle, PhD,** Van Gogh Institute for Psychiatry, Venray, NLD, Donders Institute, Radboud University, Nijmegen, NLD	20m
	Telehealth intervention to support social skill development in adolescents with NF1	**Bonnie Klein-Tasman, PhD,** University of Wisconsin, Milwaukee, WI	20m
	Social behavioral phenotypes in a Spred1 knockout mouse RASopathy model, impact of MEKi	**Sarah C Borrie, PhD,** KU Leuven, Leuven, BEL	20m
	ESI Selected Abstract: Brain-restricted Somatic Variants Activating Ras-MAPK Signaling Cause Focal Drug- Resistant Epilepsy	**Sattar Khoshkhoo, MD,** Brigham and Women's Hospital, Boston MA	10m
Sat 11:30-12:15pm	***Lunch*** - Atrium		**45m**
Sat 12:15-1:30pm	**3: Poster Session** - Atrium Learning from each other	Families, Advocates, Scientists, Doctors, Industries	**1h 15m**
Sat 1:30-3:00pm	**4: Physiology Session:** Causes and Impacts of Disordered Metabolism and Energy Homeostasis *Moderator:* **Gregor Andelfinger, MD PhD**, CHU-Sainte Justine, Montreal, CAN		**1h 30m**
Aspen Amphitheater	Using inducible pluripotent stem cells to delineate the molecular mechanisms that cause gastrointestinal difficulties in RASopathy patients	**Maria I Kontaridis, PhD**,** MMRI, Utica, NY	20m
	HRAS germline mutations impair LKB1/AMPK signaling and mitochondrial homeostasis in Costello syndrome models	**Rodrigue Rossignol, PhD,** Bordeaux University, FRA	20m
	Adipose tissue atrophy in Costello syndrome - intrinsically dysregulated gene expression augmented by stressors	**Ion C Cirstea, PhD,** Ulm University, Ulm, DEU	20m

	Costello syndrome: bone homeostasis and metabolic profiling	**Chiara Leoni, MD PhD,** Fondazione Policlinico Universitario A. Gemelli IRCCS, ITA **Elisabetta Flex, PhD,** Istituto Superiore di Sanità, ITA	20m
	ESI Selected Abstract: Vosoritide improves growth in children with Noonan syndrome	**Nadia Merchant, MD,** Children's National Hospital, Washington DC	10m
Sat 3:00-3:15pm	***Break***		**15m**
Sat 3:15- 4:30pm	**5: Molecular Session:** Advances in Drug Discovery *Moderator:* **Pau Castel, PhD,** NYU Grossman School of Medicine, New York, NY		**1h 15m**
Aspen Amphitheater	Exploring drug candidates in RASopathies using bioinformatic integration of data from drug screening, transcriptomics, and gene regulatory networks	**Daochun Sun, PhD,** Medical College of Wisconsin, Milwaukee, WI	20m
	Molecular mechanisms and potential therapeutic strategies for RIT1-driven Noonan syndrome	**Pau Castel, PhD,** NYU Grossman School of Medicine, New York, NY	20m
	Advancing novel therapies for the RASopathies using cell and animal models	**Bruce Gelb, MD**,** Icahn School of Medicine at Mount Sinai, New York, NY	20m
	ESI Selected Abstract: Investigation of cardiac valve disease mechanisms in Noonan syndrome with an iPSC model	**Clifford Z. Liu, MD/PhD candidate,** Icahn School of Medicine at Mount Sinai, New York, NY	10m
Sat 4:30-4:45pm	***Break***		**15m**
Sat 4:45-5:45pm	**6: Discussion Panel 1:** Current Treatment Landscape and New Therapeutic Developments *Moderator:* **Anton M. Bennett, PhD**, Yale School of Medicine, New Haven, CT		**1h**
Aspen Amphitheater	*Topics*: Proteomics, Pathway inhibitors (MEK, SHP2, Pan-RAS/RAF), Paradoxical Circuit Breakers, Trials	*Panelists*: **Forest White, PhD,** MIT, Boston, MA **Gregor Andelfinger, MD PhD,** CHU-Sainte Justine, Montreal, CAN **Mark W. Kieran, MD, PhD,** VP Clinical Development, DayOne Biopharmaceuticals	
Sat 6:30-8:00pm	***Networking dinner*** - Conifer Ballroom		**1h**

SUNDAY 7:30-8:30am	***Breakfast*** - Atrium	**1h**
Sun 8:30-9:20am	**7: Genetic Session:** Genotype-Phenotype Correlations *Moderator*: **Katherine A. Rauen, MD, PhD,** UC Davis, CA	**50m**

Aspen Amphitheater	Understanding RASopathies expression signatures to better inform diagnosis and treatment	**Vanessa Fear, BSc (Hons), PhD**,** University of Western Australia, Perth, AUS	20m
	Updates on the NCI RASopathies Natural History Study and Preliminary Genome-First Results	**Megan Frone, MS, CGC,** NIH/NCI, Rockville, MD	20m
	ESI Selected Abstract: Myocardial tissue engineering: A powerful tool to study hypertrophic cardiomyopathy in RIT1F82L/+ associated Noonan syndrome and its potential treatment by trametinib in vitro	**Karolin Kleeman, PhD candidate,** University Medical Centre Goettingen, DEU	10m
Sun 9:20 - 9:30am	***Break***		**10m**
Sun 9:30-10:30am	**8: Keynote**		**1h**
Aspen Amphitheater	Building and maintaining multinational rare disease networks/collaborations	**Martin Zenker, MD,** Institute of Human Genetics, University Hospital Magdeburg, DEU	
Sun 10:30-11:30am	**9: Discussion Panel 2:** Global Perspectives and Collaborations *Moderator*: **Pilar Magoulas, MS CGC**, Houston, TX		**1h**
Aspen Amphitheater	*Topics*: • Syndrome Commonalities across Ethnicities • International Collaborations in Practice • Standards, Guidelines, and Updates for RASopathies Diagnosis and Treatment • Establishing Collaboration among Advocacy Networks • Modeling Euro NS Clinical Practice Surveys	*Panelists*: **Rene Pierpont, PhD, LP,** UMinn, MN **Carlos Prada, MD,** Lurie Children's, Chicago, IL **Paul Kruszka, MD, MPH,** GeneDx, Gaithersburg, MD **Emma Burkitt-Wright, MBChB PhD MRCP,** Manchester Ctr Genomic Medicine, UK	
	Closing Remarks		**10m**
Sun 11:45am-4pm	**Post-Symposium Summary Sessions:**		**1h**
11:45am-1:00pm Primrose	for CFC Families - Hosted by CFC International	**Katherine A. Rauen, MD, PhD; Rene Pierpont, PhD, LP**	1h
12:30-1:30pm	for CS Families - Hosted by CSFN	**Karen Gripp, MD; Suma Shankar, MD, PhD; David Stevenson, MD**	1h
1:00-2:00pm Larkspur	for NS and NSML Families - Hosted by Noonan Syndrome Foundation and Noonan Syndrome Association	**Bruce Gelb, MD; Tamar Green, MD, PhD; Pilar Magoulas, MS, CGC**	1h
12:00-4:00pm Cottonwood	for NF1 Families - Hosted by NF Network	**Bruce Korf, MD, PhD; Bonnie Klein-Tasman, PhD; Christopher Moertel, MD**	4h

SPEAKER ABSTRACTS

Introductory Remarks:

Chairs
Gregor Andelfinger, MD, PhD, CHU-Sainte Justine, Montreal, Canada
Anton Bennett, PhD, Yale University, New Haven, CT, USA
Rene Pierpont, PhD, University of Minnesota, USA

Organizers
Lisa Schoyer, MFA, Board President RASopathies Network, Principal Investigator
Beth Stronach, PhD, Board Secretary RASopathies Network, Co-Investigator

Opening Night Dessert Reception and Presentations: Self-Advocacy Success Stories to Stimulate Discussion on Improving Quality of Life

Moderator: Michelle Ellis, Noonan UK

Welcome and Mixer - ESI Meet-Up
Meeting Organizers and Chairs

Living and thriving with BRAF RASopathy
Christine and Gigi Sevilla, *Chicago, Illinois*

Managing Noonan syndrome as an adult
April Anschutz, *Austin, Texas*

Innovating better solutions to manage my child's medically complex care
Ryan Sheedy, *Bentonville, AR*

Session 1: Awareness of Clinical Indications & Recent Progress

Moderator: Karen Gripp, MD, Nemours Children's Hospital, Wilmington, DE

Hematological indications in RASopathies: Need for more research and education
Benjamin Briggs, MD PhD, *Rady Children's Hospital, Navy Medical Center San Diego, CA*

RASopathies are a group of conditions that share phenotypic and molecular overlap resulting from pathogenic variants of the genes within the RAS-MAPK signaling pathway. It has been well described that some patients with RASopathies have bleeding disorders, particularly those with Noonan syndrome or Noonan-like phenotypes placing them at risk for post-surgical or post-traumatic bleeding complications. Data on the prevalence and cause of bleeding disorders within this population varies widely, likely due to a lack of a consistent definition for a bleeding disorder and the type of laboratory

testing and clinical characterization performed. Despite this, an attempt to answer these questions to protect individuals with RASopathies remains important, as we present data to suggest that 16 patients would need to be screened or treated to prevent a surgical bleeding complication.

One reason for the slow progress in the field is the definition of a bleeding disorder, whether it be abnormal laboratory results, bleeding symptoms, or both. A challenge to answering this question is that many of the clinical studies have incomplete evaluation in retrospect, given newer studies have suggested that all components of coagulation (primary hemostasis, secondary hemostasis, and fibrinolysis) may be involved. A second challenge is that laboratory findings are milder than symptoms would suggest, but more than one defect is often found, and perhaps it is the aggregate impact of these deficiencies that explains the bleeding phenotype. Thromboelastography is a graphical representation of all aspects of coagulation and we present data suggesting that, unfortunately, this may not be more effective in detecting the bleeding phenotype. This underscores the importance of obtaining a comprehensive clinical history for bleeding symptoms as we present data showing a strong correlation between symptoms and surgical bleeding complications. One challenge, however, to relying on symptoms alone is that it takes time for them to develop and would be unreliable in a small child.

Considering these challenges, we propose a roadmap for future efforts in the field to include continued research, quality improvement initiatives, and clinical and social education. Research efforts should focus on the clinical characterization of subjects to include comprehensive laboratory workup and clinical bleeding symptoms to determine a more reliable definition for a bleeding disorder, as well as, investigating newer more accurate laboratory testing technologies. Research is also needed to answer whether the bleeding disorder is a dynamic or static process and whether it might be modifiable. Certainly, any clinical trials using MEK inhibitors should investigate the impact on other elements of the condition including bleeding disorders. Until these questions are answered we propose a new clinical approach to patients with RASopathies namely comprehensive investigation using clinical history and laboratory workup buttressed with continual re-evaluation for any change in symptoms over time.

Targeting the RAS/MAPK pathway in JMML with trametinib

Elliot Stieglitz, MD, *UCSF Benioff Children's Hospital, CA*

Juvenile myelomonocytic leukemia (JMML) is an aggressive myeloproliferative disorder of childhood. The biochemical hallmark of JMML is aberrant signaling through the Ras pathway caused by initiating mutations in *NF1, NRAS, KRAS, RRAS, RRAS2, SH2B3, PTPN11* and *CBL*. While hematopoietic stem cell transplantation (HSCT) can be curative, 5-year event free survival after transplant is only ~50%. Recently, several studies have identified mutational burden and DNA methylation as being predictive of outcome in JMML. In this trial, we propose that lower-risk patients are defined as those with 1 somatic alteration AND low DNA methylation while high-risk patients are defined as those with more than 1 somatic alteration OR intermediate/high DNA methylation.

Trametinib is an orally bioavailable, reversible, highly selective allosteric inhibitor of MEK1/2 which is downstream of Ras/MAPK signaling. Trametinib is FDA-approved for the treatment of adults with advanced melanoma with a BRAF V600E or V600K mutation. It is currently being investigated in an ongoing phase 2 clinical trial for patients with relapsed or refractory JMML. Four of nine patients enrolled on that trial had an objective response.

Azacitidine was recently tested in a phase 2 clinical trial for newly diagnosed JMML patients. Eighteen patients enrolled and after 3 courses of azacitidine monotherapy, 11/18 patients achieved an objective response, 17 patients proceeded to HSCT and 82% were leukemia-free at a median follow-up of 23.8 months (range, 7.0-39.3 months) after HSCT. Azacitidine is now FDA approved for patients with newly diagnosed JMML.

An upcoming clinical trial conducted through the Therapeutic Advances in Childhood Leukemia (TACL) consortium, will risk stratify patients based on DNA methylation and mutational burden to receive different therapies. Lower-risk patients will receive trametinib and azacitidine for up to 12 courses and will only proceed to HSCT in the event of progressive disease. High-risk patients will receive trametinib and azacitidine in combination with cytarabine and fludarabine for up to two courses and then will proceed to off-protocol HSCT.

Cell cycle defects underlie NS-associated cardiomyopathy suggesting potential new mechanisms

Cordula Wolf, MD, ***German Heart Center, Technical University of Munich, School of Medicine & Health, Munich, DEU,***
*Presenting data from: Meier AB, Raj Murthi S, Rawat H, Toepfer CN, Santamaria G, Schmid M, Mastantuono E, Schwarzmayr T, Berutti R, Cleuziou J, Ewert P, Gorlach A, Klingel K, Laugwitz KL, Seidman CE, Seidman JG, Moretti A, Wolf CM. Cell cycle defects underlie childhood-onset cardiomyopathy associated with Noonan syndrome. iScience 2022;**25**(1):103596.*

Childhood-onset myocardial hypertrophy and cardiomyopathic changes are associated with significant morbidity and mortality in early life, particularly in patients with Noonan syndrome, a multisystemic genetic disorder caused by autosomal-dominant pathogenic variants in genes of the RAS-MAPK pathway. Although the cardiomyopathy associated with Noonan syndrome (NS-CM) shares certain cardiac features with the hypertrophic cardiomyopathy caused by mutations in sarcomeric proteins (HCM), such as pathological myocardial remodeling, ventricular dysfunction, and increased risk for malignant arrhythmias, the clinical course of NS-CM significantly differs fromHCM. This suggests a distinct pathophysiology that remains to be elucidated. Here, through analysis of sarcomeric myosin conformational states, histopathology, and gene expression in left ventricular myocardial tissue from NS-CM, HCM, and normal hearts complemented with disease modeling in cardiomyocytes differentiated from patient-derived PTPN11N308S/+ induced pluripotent stem cells, we demonstrate distinct disease phenotypes between NS-CM and HCM and uncover cell cycle defects as a potential driver of NS-CM.

Systematic approach to feeding difficulties, GERD and vomiting in NS spectrum disorders

Dagmar Tiemens, PhD, Candidate and Parent Advocate, *RadboudUMC, Nijmegen, NLD*

Background: We have studied the needs of patients with a Noonan Syndrome Spectrum Disorder (NSSD) and their relatives, to help inventory and prioritize among the wide variety of their needs. This way we aim to help evaluate focus in research, medical care and policy. We used the participatory and interactive Dialogue method to inventory and prioritize patient group specific problems/needs or topics. These topics were categorized into themes. Each respondent subsequently prioritized and ranked the themes and topics within the themes by putting them in order of importance, generating a number per topic and average scores per topic and theme. 80 NSSD patients and relatives mentioned 53 different topics that were categorized into eight themes. Nineteen topics were physical problems. According to the total group of respondents, the top 3 prioritized topics within theme number one

were: Coagulation problems, heart problems, and feeding problems. Data stratified by age groups, phenotype (NS and other NSSDs) and gender, showed some needs / topics that were surprisingly highly prioritized by patients. For instance, feeding problems were prioritized as the most important topic of the highest prioritized theme, according to patients aged 0-12 years. Similar results were found on the topics regarding coagulation, neuropsychology and musculoskeletal issues. This may indicate, amongst others, a need for subsequently more clinical management on coagulation, (educational) tools to support patients at school or at work and a need for more physiotherapy or occupational therapy.

To focus on the needs of NSSD patients regarding feeding problems, we aimed to develop a hypothetical relationship between a Rasopathy and vomiting / gastroesophageal reflux disease (GERD). Additionally we aimed to clarify why the, up to date, most effective therapeutical option (ondansetron) turns out to be so highly effective in stopping the vomiting / GERD in NSSD patients.

Method: Using review research, we searched for cell specific targets of the RAS/MAPK/ERK pathway, that are known to play a role in cells within components of the vomiting cascade. Upregulation of these pERK targets should change their cellular and anatomical functioning and contribute to GERD / vomiting. As we have found one highly effective and specific drug to stop the vomiting in these patients, we searched for a mechanism that connects its cellular effects to the downregulation of these pERK targets.

Results: We have found two anatomical sites in the vomiting cascade that seem to meet these conditions. In the dorsal motor nucleus of the n. vagus in the brainstem, upregulation of the RAS/MAPK/ERK pathway results in a significant extra release of Substance P, which induces vomiting and nausea. In the gastro-intestinal (GI) tract, pERK target caldesmon, stimulates relaxation of its smooth phasic muscle cells. Hyperactivation of caldesmon (as a result of a Rasopathy) may contribute to too much relaxation, resulting in delayed gastric emptying, GERD and vomiting.

We used a similar combination of cellular mechanisms and functions anatomically, to substantiate how ondansetron can be so effective in inhibiting vomiting in patients with NSSD.

Conclusion and further research: When we focus on one of their most important needs, especially in young children with NSSD (feeding problems), it is remarkable that both current Clinical Guidelines and NS diagnostic criteria pay little to no attention to it. This indicates that feeding problems tend to be a blind spot in both medical care and research and that treatment of feeding problems (and vomiting) in NSSDs according to general standards does not seem to help sufficiently. Therefore it is important not only to evaluate the Guidelines regarding feeding problems, but also that specialized institutions help validate our hypotheses and the effectiveness of ondansetron. Also, it is necessary to improve the distribution of these new insights in the medical field as well as to patients with NSSD. Enhancing the accessibility of current management knowledge and effective therapeutical options can improve clinical management, meet these patients' indicated high need and may prevent the sometimes long term multidisciplinary and costly care of patients with NSSD and feeding problems.

MEKi Treatment effects and QoL in diverse patients with NF1 tumors

Christopher Moertel, MD, *University of Minnesota Medical Center, Minneapolis, MD*

The development of MEK inhibitors (MEKi) as a therapy for patients with NF1-associated tumors represents an extraordinary shift in the management of people living with this condition. Those who develop plexiform neurofibromas or optic gliomas now have an effective drug to turn to for help in

managing these tumors. As clinicians have gained more experience with MEKi, we are better able to adjust dosing and manage side effects to preserve and maintain the best quality of life in patients receiving the drug. At the University of Minnesota, we have gained significant experience with selumetinib, trametinib and mirdametinib, three MEKi that have proven to be effective in the management of NF1-associated neoplasia. Working in concert with our colleagues in pediatric dermatology, we have developed guidelines for skin side effect management of MEKi. As experience grows, comfort with the monitoring and management of gastrointestinal, eye and cardiac side effects develops.

ESI Selected Abstract: Hypertrophic neuropathy: a possible cause of pain in children with Noonan syndrome and related disorders

Fieke Draaisma, *RadboudUMC, Nijmegen, NLD*

Fieke Draaisma[1], Corrie Erasmus[2], Hilde Braakman[2], Melanie Burgers[1], Erika Leenders[3], Tuula Rinne[3], Nens van Alfen[4], Jos Draaisma[1].

1: Department of Pediatrics, Radboud Institute for Health Sciences, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, The Netherlands.

2: Department of Pediatric Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, The Netherlands.

3: Department of Human Genetics, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands.

4: Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands.

Purpose: Hypertrophic neuropathy: a possible cause of pain in children with Noonan syndrome and related disorders

Methods: This retrospective cohort study over a period of six months was conducted in the NS expert center of the Radboud University Medical Center in the Netherlands. Patients were eligible if they were younger than 18 years, clinically and genetically diagnosed with NS or an NS related disorder and experienced pain in their legs. Anamneses, physical examination and high-resolution nerve ultrasound, to assess nerve hypertrophy, were performed in all children. If needed, complemented spinal magnetic resonance imaging (MRI) was performed.

Results: Over a period of six months four children, three with NS and one child with NS with multiple lentigines, were eligible for inclusion. All children experienced pain, most predominantly localized in the lower extremities resulting in exercise intolerance to a greater or lesser extent. In two of them this was accompanied by muscle weakness. High-resolution nerve ultrasound showed (localized) hypertrophic neuropathy in all children. One child underwent an additional spinal MRI as she experienced disabling pain and muscular weakness in both upper and lower extremities. At the age of ten, she fully depends on her parents for daily life activities. *Figure 1* shows ultrasonographic features of the proximal sciatic nerve of this patient compared with a control individual showing profound nerve hypertrophy. Additional spinal MRI showed thickening of the nerve root and plexus.

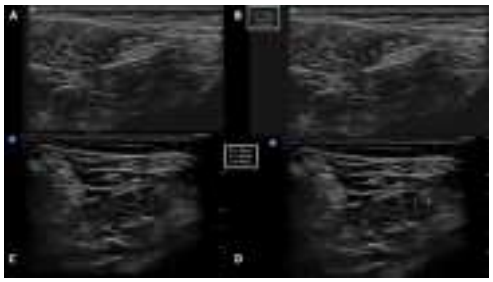

Figure 1: the proximal sciatic nerves without (A and C) and with (B and D) cross sectional areas. A and B are the healthy control (24 mm^2) and C and D the patient (128 mm^2) respectively.

Conclusions: In the four children included with a NS and related disorders pain was concomitant with nerve hypertrophy, which suggests an association between these two findings. The use of high-resolution nerve ultrasound imaging might result in better understanding of the nature of this pain and the possible association to nerve hypertrophy in patients with NS and related disorders.

Session 2: Neuro Session: Neurodevelopmental Focus - From Brain to Behavior

Moderator: Rene Pierpont, PhD LP, University of Minnesota, Minneapolis, MD

Intersecting Neuroscience and Genetics: Utilizing Multivariant Brain Analysis for Understanding Genetic Mutations and Neuropsychiatric Outcomes in Children with Noonan Syndrome

Tamar Green, MD, *Stanford Medicine, Stanford, CA*

This talk explores the usability of topological data analysis (TDA) in neuroscience, specifically in children with Noonan Syndrome (NS). We focus on the application of the TDA-based Mapper approach as a tool for multivariant analysis of brain characteristics, specifically surface area, cortical thickness, and volume, to better understand the structural configurations in genetically assigned participants. Our research uncovers distinctive neuroimaging patterns associated with NS, with an emphasis on the SOS1 and PTPN11 gene mutations. Furthermore, our findings reveal a marked distinction between NS and typically developing (TD) groups, reflected by a high modularity score, underlining the role of multivariant structural brain configurations in genetically assigned participants at the group level. Additionally, we probe the predictive value of these patterns for cognitive abilities.

In the subsequent segment, we delve into a comprehensive neuropsychiatric evaluation of children with NS. We compare their outcomes with typically developing children and account for overall cognitive abilities. Our results show an increase in symptoms across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and oppositional defiant disorder (ODD) symptom clusters in children with NS. These results remain significant even after adjusting for variations in intellectual functioning, implying that neurodevelopmental symptoms are not solely driven by overall intelligence.

Collectively, these investigations offer critical insights into the complex relationship between multivariant brain structure analysis, genetic mutations, and neuropsychiatric outcomes in children with Noonan Syndrome. This research paves the way for future exploration and potential treatment modalities.

Information processing in NSSDs: correlation with genotype and social cognitive intervention approach for adults with Noonan syndrome

Renée Roelofs, PhD & Ellen Wingbermühle, PhD, *Van Gogh Institute for Psychiatry, Venray, NLD, Donders Institute, Radboud University, Nijmegen, NLD*

Problems in information processing and psychological functioning are frequent in patients with Noonan syndrome spectrum disorders (NSSDs), although there is much variation at the individual level, and patients with variants in PTPN11 are overrepresented in the scientific literature. We present an overview of cognitive strengths and weaknesses, as well as behavioral and emotional characteristics per genetic variant, based on the current literature. We will illustrate our own findings on these topics, and we will elaborate on treatment options, especially focusing on the (online) social cognitive training for Dutch adult patients with NSSDs that we have developed in our center.

Telehealth intervention to support social skill development in adolescents with NF1

Bonnie Klein-Tasman, PhD, *University of Wisconsin, Milwaukee, WI*
Glad, D., Pardej., S. K., Olszewski, E., & Klein-Tasman, B. P.

Introduction: While children and adolescents with neurofibromatosis type 1 (NF1) have elevated rates of social difficulties in comparison to same-aged peers, there is little research about how best to support the development of their social skills and peer relationships. The Program for Education and Enrichment of Relational Skills is an evidence-based intervention to improve social functioning that has been used with teens with autism spectrum disorders, ADHD, and other neurogenetic conditions and has recently been demonstrated to be useful using a telehealth format. This pilot study aimed to examine the effectiveness of the telehealth PEERS® intervention for teens with NF1.

Method: Adolescents with NF1 (12-17 years; M_{age} = 13.79 years, *SD* = 1.32; N=19) with social skills difficulties and at least one caregiver from each family participated. Study activities took place virtually via phone and/or online video conferencing platforms. Caregivers and adolescents completed several measures of social outcomes at pre-test (T1), post-test (T2), and at a 14-week follow-up (T3). Social outcome measures include *Social Skills Improvement System Social-Emotional Learning* (*SSIS-SEL;* Gresham & Elliott, 2017), *Social Responsiveness Scale – Second Edition* (*SRS-2;* Constantino & Gruber, 2012), *Friendship Qualities Scale* (*FQS;* Bukowski et al., 1994), *Quality of Socialization Questionnaire* (*QSQ*; Frankel & Mintz, 2008), and *Test of Adolescent Social Skills Knowledge* (*TASSK;* Laugeson et al., 2009). The PEERS® intervention was administered according to the PEERS® manual (Laugeson & Frankel, 2010) in conjunction with the CARD telehealth manual (*PEERS Remote Manual*, n.d.) and telehealth materials provided by UCLA. The PEERS® intervention involves separate caregiver and adolescent sessions that meet for 90 minutes each week for a 14-week period. This study was approved by the university's Institutional Review Board.

Results: Paired samples t-tests were computed to compare performance on the five outcome measures from T1 to T2 and from T1 to T3. Caregiver-reported SSIS-SEL (T1-T2: $t(18) = -2.25$, $p = .018$, $g = -.51$; T1-T3: $t(17) = -2.44$, $p = .013$, $g = -.56$) and SRS-2 (T1-T2: $t(18) = 2.85$, $p = .005$, $g = .64$; T1-T3: $t(17) = 2.54$, $p = .011$, $g = .59$) were significantly better at T2 and T3 compared to T1 with medium effect sizes. TASSK (T1-T2: $t(18) = -8.34$, $p < .001$, $g = -1.87$; T1-T3: $t(16) = -1.87$, $p < .001$, $g = -1.55$) and caregiver-reported QSQ (T1-T2: $t(18) = -3.85$, $p < .001$, $g = -.86$; T1-T3: $t(16) = -2.81$, $p = .006$, $g = -.67$) were also significantly better

at T2 and T3 compared to T1 with medium to large effect sizes. Self-reported SSIS-SEL, FQS, and adolescent-reported QSQ were not significantly different from T1 to T2 or T3.

Discussion: Following the intervention, caregiver-reported social-emotional skills, social impairment, caregiver-reported number of adolescent get-togethers, and teen social knowledge showed improvement. The pilot data from this investigation show the promise of the specific social skills intervention, PEERS®, implemented using telehealth, to support the social and friendship skills of adolescents with NF1 who have social difficulties.

Social behavioral phenotypes in a Spred1 knockout mouse RASopathy model, impact of MEKi

Sarah C. Borrie, PhD, *KU Leuven, Leuven, BEL*

Sarah C. Borrie[1], Ellen Plasschaert[1], Ype Elgersma[2], Steven A. Kushner[2], Alexa E. Horner[3], Maksym V. Kopanitsa[3], Akihiko Yoshimura[4], Eric Legius[1], Hilde Brems[1]

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RASopathies are a group of disorders that result from mutations in genes coding for proteins involved in regulating the Ras-MAPK signaling pathway, and have an increased incidence of autism spectrum disorder (ASD). Legius syndrome is a rare RASopathy caused by loss-of-function mutations in the SPRED1 gene. SPRED1 protein negatively regulates activation of Ras by inhibiting RAS/RAF and by its interaction with neurofibromin, a Ras GTPase-activating protein (RAS-GAP). The patient phenotype is similar to, but milder than, Neurofibromatosis type 1—another RASopathy caused by loss-of-function mutations in the NF1 gene. RASopathies exhibit increased activation of Ras-MAPK signaling and commonly manifest with cognitive impairments and ASD. Here, we examined autism-linked behaviors in *Spred1-/-* mice as a model for Legius syndrome, and probed the mechanisms underlying the behavioral phenotypes. *Spred1-/-* mice have deficits in social dominance in the automated tube test, and social communication deficits in their ultrasonic vocalizations, seen both in early postnatal stages and in adult mice. Assays of novelty investigation behaviors showed that *Spred1-/-* mice exhibit reduced nesting behavior, marble burying and investigation of a novel object. Additionally, associative learning in an operant touchscreen battery was impaired in *Spred1-/-* mice. Targeting the RAS-MAPK pathway by treating adult mice with the specific MEK inhibitor PD325901 could reverse the deficits in social dominance and novelty investigation behaviors, but could not rescue the cognitive impairments. Together these findings demonstrate the specificity of dysregulation of Ras-MAPK pathway activity in mediating ASD-like social behavior and novelty investigation deficits in *Spred1-/-* mice, and indicate the critical role of the Ras-MAPK signaling for the regulation of social behaviors. These results suggest that targeting the Ras-MAPK pathway has novel therapeutic potential for ASD phenotypes in Legius Syndrome.

ESI Selected Abstract: Brain-restricted Somatic Variants Activating Ras-MAPK Signaling Cause Focal Drug Resistant Epilepsy

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S Khoshkhoo[1,2], Y Wang[2], Y Chahine[2], S Robert[3], E Kiziltug[3], E Damisah[3], C Nelson Williams[3], G Zhu[4], W Kong[4], AY Huang[2], E Stronge[2], W Phillips[2], B Chhouk[2], S Bizzotto[5], MH Chen[2], T Adikari[6], Z Ye[6], T Witkowski[6], D Lai[7], N Lee[2], J Lokan[8], I Scheffer[6,9,8], S Berkovic[8,6], S Haider[10], M Hildebrand[8,6], E Yang[2], M Gunel[3], RM Richardson[11], I Blümcke[12], S Alexandrescu[2], A Huttner[3], E Heinzen[7], J Zhu[4], A Poduri[2], N DeLanerolle[3], D Spencer[3], EA Lee[2], K Kahle[11], C Walsh[2]

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Background: Mesial temporal lobe epilepsy (MTLE), characterized by seizures arising from the hippocampus, is the most common focal epilepsy subtype and often refractory to anti seizure medications. Recently, post-zygotic (i.e., somatic) variants have emerged as a major cause of pediatric focal epilepsies like focal cortical dysplasia, but the contribution of somatic variants to MTLE pathogenesis is unknown. Here we test the hypothesis that somatic variants in the hippocampus are an important pathogenic mechanism underlying drug-resistant MTLE.

Methods: We performed high-coverage whole-exome sequencing (WES, depth >500X) of DNA derived from the hippocampus, and paired brain tissue and/or blood when available, of 104 surgically-treated MTLE patients and 30 neurotypical individuals. We performed additional gene-panel sequencing (depth >1000X) on cases without candidate pathogenic somatic variants. Candidate somatic variants were validated with amplicon sequencing and/or droplet digital Polymerase Chain Reaction (ddPCR). A subset of the novel MTLE associated somatic variants were evaluated experimentally using cellular and molecular assays.

Results: Using WES we detected 9 pathogenic variants all predicted to constitutively activate Ras-MAPK signaling, in patients with MTLE and none in the neurotypical controls. Follow up gene-panel sequencing identified 21 additional pathogenic somatic Ras-MAPK variants in MTLE, and none in the controls, suggesting a strong and likely causal role for these variants in MTLE pathogenesis. All but 4 patients had no evidence of dysplasia or neoplasia on histopathology and imaging. Immunohistochemical studies of hippocampal tissue harboring pathogenic somatic variants demonstrated increased phosphorylation of Erk1/2, confirming Ras-MAPK overactivation. Molecular assays showed abnormal liquid-liquid phase separation for the PTPN11 variants as a possible dominant gain-of-function mechanism, similar to Noonan syndrome.

Conclusion: Somatic variants activating Ras-MAPK signaling likely cause MTLE in a significant subset of patients with sporadic, drug-resistant disease. Our findings provide a novel genetic mechanism for MTLE and strongly suggest that focal drug-resistant epilepsy in the temporal lobe of the brain is a somatic RASopathy.

Session 3: Poster Session: Learning from Each Other

Families, Advocates, Scientists, Doctors, Industries

Session 4: Physiology Session: Causes and Impacts of Disordered Metabolism and Energy Homeostasis

Moderator: Gregor Andelfinger, MD PhD, CHU-Sainte Justine, Montreal, Quebec, CAN

Using inducible pluripotent stem cells to delineate the molecular mechanisms that cause gastrointestinal difficulties in RASopathy patients

Maria I. Kontaridis, PhD,**

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RASopathies are a group of rare genetic disorders caused by mutations in the Ras-MAPK signaling cascade. While individually rare, collectively, this group of diseases is considered one of the most common types of congenital disorders worldwide. The nonreceptor protein tyrosine phosphatase SHP2 is a critical component of the Ras-MAPK pathway, serving as a positive regulator to induce activation of downstream signaling. Mutations in SHP2 are pathogenic, causing both Noonan Syndrome (NS, ~50%) and Noonan Syndrome with Multiple Lentigines (NSML, formerly LEOPARD, ~90%). Intriguingly, though NS and NSML patients have similar clinical characteristics, including developmental delays, cardiac abnormalities, and gastrointestinal difficulties, individual mutations in each disorder are unique, resulting in opposing catalytic functions of SHP2; whereas NS mutations in SHP2 are gain-of-function, NSML-associated SHP2 mutations are loss-of-function and behave as dominant negatives. In mice, deletion of SHP2 specifically in the intestine and colon was recently found to affect the development of secretory lineages, disrupting goblet and paneth cell differentiation. However, SHP2 mediated molecular mechanisms that mediate these defects remain poorly understood. Here, we focused on understanding the mechanistic causes of the gastrointestinal defects in NS and NSML patients using iPSC-derived gastrointestinal organoids, organ-on-a-chip technology, and mouse models for NS and NSML to elucidate the aberrant functional and mechanistic alterations consequent to SHP2 mutations in the gut. Our data show that iPSC-derived gut organoids from NS (D61Y) proliferate faster, are smaller in size, and generate smaller goblet cells that produce less MUCIN. In contrast, NSML (Q510E) organoids proliferate slower, but have hyperplastic and enlarged goblet cells that produce more MUCIN, suggesting a phosphatase-dependent function of SHP2 in goblet cell fate. Interestingly, expression of the paneth cell marker LYSOSYME was shown to be ectopically upregulated in both NS and NSML iPSC-derived organoids, suggesting that differentiation of these cells, in contrast to goblet cell regulation, may be phosphatase-independent. Molecularly, while the NS organoids have increased ERK and decreased AKT activity, NSML organoids have decreased ERK but increased AKT activation, suggesting differential signaling between GOF and LOF mutations in SHP2 in the gut. Organ-on-a-chip and NS (D61Y) and NSML (Y273C) mouse gut epithelia confirm these results, which together, suggest that SHP2 is an important regulator of the secretory function of the intestine, which is mediated through both phosphatase-dependent (goblet cells) and -independent (paneth cells) signaling mechanisms.

HRAS germline mutations impair LKB1/AMPK signaling and mitochondrial homeostasis in Costello syndrome models

Rodrigue Rossignol, PhD, *Bordeaux University, FRA*

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Germline mutations that activate genes in the canonical RAS/MAPK signaling pathway are responsible for rare human developmental disorders known as RASopathies. Here, we analyzed the molecular determinants of Costello syndrome (CS) using a mouse model expressing HRAS p.G12S, patient skin fibroblasts, hiPSC-derived human cardiomyocytes, a HRAS p.G12V zebrafish model and human fibroblasts expressing lentiviral constructs carrying HRAS p.G12S or HRAS p.G12A mutations. The findings revealed alteration of mitochondrial proteostasis and defective oxidative phosphorylation in the heart and skeletal muscle of Costello mice that were also found in the cell models of the disease. The underpinning mechanisms involved the inhibition of the AMPK signaling pathway by mutant forms of HRAS, leading to alteration of mitochondrial proteostasis and bioenergetics. Pharmacological activation of mitochondrial bioenergetics and quality control restored organelle function in HRAS p.G12A and p.G12S cell models, reduced left ventricle hypertrophy in the CS mice and diminished the occurrence of developmental defects in the CS zebrafish model. Collectively, these findings highlight the importance of mitochondrial proteostasis and bioenergetics in the pathophysiology of RASopathies and suggest that patients with Costello syndrome may benefit from treatment with mitochondrial modulators.

Adipose tissue atrophy in Costello syndrome - intrinsically dysregulated gene expression augmented by stressors

Ion C. Cirstea, PhD, *Ulm University, Ulm, DEU*

RASopathies are developmental disorders arising from germline mutations in genes that encode for RAS-MAPK components. Among RASopathies, the Costello syndrome (CS) is triggered by activating mutations in HRAS gene that occur mostly at the oncogenic hotspots. Major CS pathophenotype

features are a failure to grow, skin, craniofacial and skeletal abnormalities, cardiac defects, neurological impairment, and a predisposition to cancer. However, clinical data in CS patients reported metabolic abnormalities such as reduced adiposity, increased energy expenditure and basal metabolism, which may contribute to the failure to grow. Experimental data using cellular and mouse models also revealed that HRAS mutations affect energy metabolism in CS. Studies performed in CS $Hras^{G12S}$ mice showed a reduced weight gain in response to high fat diet, impaired fatty acids oxidation, and an impaired mitochondrial proteostasis as well as an increased oxidative phosphorylation. We performed a long-term study in the $Hras^{G12V}$ mouse model, which harbors a stronger mutation than G12S substitution. We monitored the expression of a selected set of critical metabolic genes in the inguinal white adipose tissue (iWAT). We were able to identify age- and gender-related changes in the selected genes. Furthermore, we identified an increased energy expenditure in response to stress, proved by the severe reduction of fat pads in mice that undergo skin wound healing assay or were treated with β3-adrenergic receptor agonists. We consider that the CS resembles a metabolic wasting syndrome and that the basal dysregulation of metabolic genes is enhanced by stressors, and ultimately leading to a severe impairment of adipose tissue homeostasis.

Costello syndrome: bone homeostasis and metabolic profiling

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***Elisabetta Flex, PhD**, Instituto Superiore di Sanità, ITA*

Costello syndrome (CS) is a rare disorder, caused by activating dominantly acting germline variants in the *HRAS* gene. CS has a clinical phenotype characterized by a distinctive facial gestalt with aged appearance, failure to thrive, developmental delay, congenital heart defects, skin and muscle-skeletal anomalies and increased risk to develop tumors. A number of studies recently investigated the consequences of RAS/MAPK signaling dysregulation on bone metabolism as well as on glucose/lipid metabolism.

Starting from the clinical characterization of failure to thrive and skeletal malformations in the cohort of individuals affected by CS followed in our Institution, we focused the research activity of last year in studying bone assessment and metabolic profile of individuals with CS.

In a pilot study published in 2014 involving 9 individuals with CS and 29 controls, we demonstrated that the CS group had significantly lower mean values of all bone mineral density (BMD) parameters measured by Dual-energy X-ray absorptiometry (DXA) compared to the control group ($p \leq 0.01$). Moreover, low 25-OH vitamin D concentration was documented in all individuals with CS. Based on these findings we prospectively enroll a larger cohort of CS patients (n=16) in a study evaluating the efficacy of a 4-year vitamin D supplementation on bone health. Dosages of bone metabolism biomarkers in blood and DXA scan parameters were collected at baseline (T0) and, when available, after 1 year (T1), 2 years (T2) and 3 years (T3) of vitamin D supplementation administered to reach a serum level of 25(OH)vitD of ≥50 ng/ml. Following the 4-year time interval, despite vitamin D supplementation therapy, no significant improvement in BMD was observed. None of our pediatric patients reached the diagnosis of osteoporosis and no fractures were reported in the total sample.

Our workgroup also demonstrated the presence of an increased resting energy expenditure measured by indirect calorimetry together with an alteration in serum glucose/lipid values. In particular, asymptomatic hypoglycemia has been detected in 9/21 (42.8%) subjects with CS (monocentric cohort)

and elevated cholesterol level in 7/21 (33.3%). These preliminary findings suggested the involvement of a still uncharacterized and unappreciated metabolic dysfunction as a driver event characterizing the disorder.

Mass spectrometry-based analysis and ^{1}H-NMR spectroscopy revealed a significantly altered metabolic profile in CS primary fibroblasts compared to control cells, supporting accelerated glycolysis. Notably, this was uncoupled with defective mitochondrial activity, but found to be caused by an altered redox balance due to increased intracellular ROS levels promoting AMPKα and p38 activation, augmented expression and constitutive plasma membrane translocation and activation of the GLUT4 glucose transporter, resulting in an increased glucose uptake into cells. We also show that besides glycolysis, the glucose excess promotes fatty acid synthesis and their storage as lipid droplets, which are significantly more abundant in CS cells. Moreover, in line with evidence supporting the hypothesis of a redox regulation of autophagic signaling, CS cells displayed an accelerated autophagic flux in a steady state condition.

Our findings provide a mechanistic link between upregulated *HRAS* function, defective growth and increased resting energetic expenditure in CS.

ESI Selected Abstract: Vosoritide improves growth in children with Noonan syndrome

Nadia Merchant, MD, *Children's National Hospital, Washington, DC*
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[1]Division of Endocrinology, [2]Department of Biostatistics, [3] Division of Cardiology, Children's National Hospital, Washington, DC

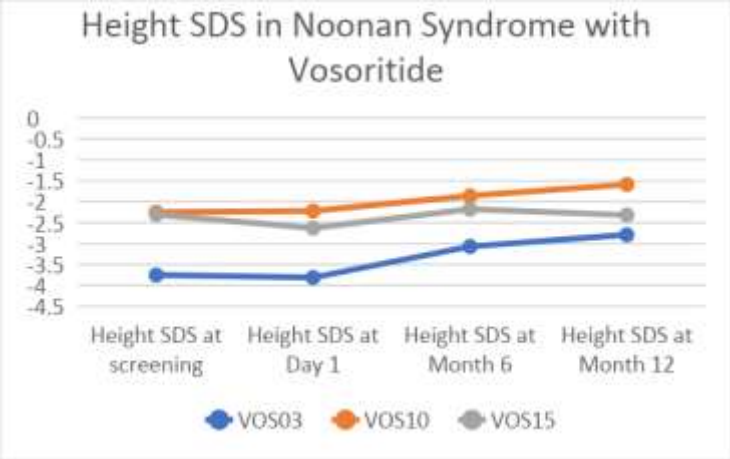
Objective: Vosoritide is a C-type natriuretic peptide (CNP) analog which binds to natriuretic peptide receptor-B (gene *NPR2*) on chondrocytes, leading to increased chondrocyte proliferation and differentiation via inhibition of the ERK1/2-MAPK pathway. Vosoritide was approved in November 2021 in the US to increase linear growth in children with achondroplasia age greater than 5. Our study aims to assess the safety and efficacy of vosoritide in children with selected genetic causes of short stature including patients with RASopathies (Noonan syndrome, Costello syndrome, Cardiofaciocutenous syndrome, neurofibromatosis type 1).

Methods: This is a prospective, Phase II study. All subjects must have a genetic variant causing a RASopathy, be prepubertal between the ages of 3 and 11 for boys and 3 and 10 for girls, and have a height less than -2.25 SD. Subjects are followed for a 6-month observation period to establish a baseline annualized growth velocity (AGV) and then receive daily subcutaneous vosoritide (15 mcg/kg/day) for 12 months. The primary outcomes are rate of AEs and change in annualized growth velocity (AGV) from baseline.

Results: Currently, we have four children with Noonan syndrome enrolled. All 4 children have *PTPN11* variants, and three have completed 12 months of vosoritide therapy. Two of the treated children were previously treated with growth hormone (GH) with inadequate responses. AGV for the 3 subjects during the observation period was 4.1, 2.7 and 5.9 cm/yr and increased to 9.9, 6.8, and 8.9 cm/yr respectively. Thus, the increase in AGV for the three subjects were 5,8, 4.1, and 3 cm/yr. Height standard deviation score (SDS) improved during the first year of therapy by 1.02, 0.31, and 0.63 SDS, respectively. Vosoritide was well tolerated with a similar safety profile as patients with achondroplasia. Mild to moderate injection site reactions were common with no intervention needed. There were no episodes

of symptomatic hypotension and no significant bone age advancement. No subjects dropped out of the study.

Conclusion: This is the first clinical trial of vosoritide for children with genetic short stature due to Noonan syndrome. Vosoritide led to significant improvements in growth in all 3 children treated to date without any significant adverse effects. Vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAPK pathway. Vosoritide may have a better safety profile compared to growth hormone for children with RASopathies.



Session 5: Molecular Session: Advances in Drug Discovery

Moderator: Pau Castel,PhD, NYU Grossman School of Medicine, New York, NY

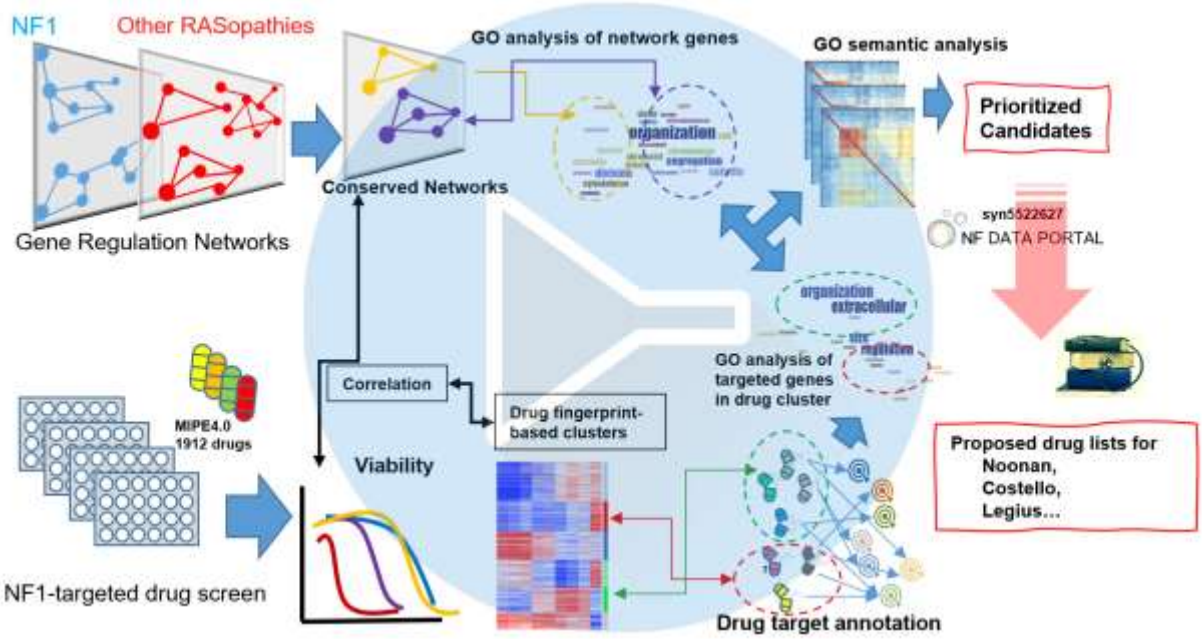
Exploring drug candidates in RASopathies using bioinformatic integration of data from drug screening, transcriptomics, and gene regulatory networks

Daochun Sun, PhD, *Medical College of Wisconsin, Milwaukee, WI*

Data reuse and drug repurposing are key solutions to enhance treatment discovery for rare diseases. As the collection of multiple rare syndromes resulting from RAS/MAPK signaling dysfunction, RASopathies have very limited FDA-approved treatment options. Novel therapeutic strategies are demanded. Although each syndrome has unique characteristics, the overlapped clinical features, genetic alterations, and molecular signaling embrace these syndromes and implicate that the targeted treatments for one syndrome can be repurposed among RASopathies with scientific rationales. We hypothesize that the conserved gene regulation networks can help to identify and prioritize drug candidates among RASopathies. We take advantage of the drug screen data in Neurofibromatosis Type 1(NF1)-associated plexiform neurofibroma and aim to explore and prioritize potential drugs for preclinical study in other RASopathies, including Noonan, Costello, and Legius syndromes.

The customized algorithm implemented here was awarded in Hack4Rare 2021 data mining competition organized by Children's Tumor Foundation and RASopathies Networks. We use the R programming environment to integrate high-throughput data such as transcriptomes and drug screen responses and

step-wisely identify the shared essential gene regulation networks among RASopathies with consideration of biological relevance using gene ontology (GO) semantic analysis (graphic abstract below). The conserved gene regulation networks may reveal insights into the disease mechanisms, and the proposed drugs can provide an actional list for preclinical studies with the biological rationales to target each RASopathies.



Molecular mechanisms and potential therapeutic strategies for RIT1-driven Noonan syndrome

Pau Castel, PhD, *NYU Grossman School of Medicine, New York, NY*

Pathogenic gain-of-function variants in RIT1 are found in the germline of a subset of individuals with Noonan syndrome, the most common RASopathy. RIT1 encodes for the non-classical RAS protein RIT1, which is a poorly understood GTPase that exhibits unique molecular properties. Our lab recently demonstrated that, in contrast to classical RAS proteins, RIT1 appears to be mostly regulated through proteasomal degradation by interacting with a protein complex formed by the substrate adaptor protein LZTR1 and the RING E3 Ubiquitin Ligase Cullin3. We found that this complex is conserved in lower organisms and is necessary for the proper regulation of RIT1 protein levels and variants in RIT1 result in the dysregulation of this mechanism, leading to increased RIT1 protein levels and signaling. In addition, we have recently investigated the mechanisms that underlie RIT1-dependent RAF-MEK-ERK activation and have developed genetically-engineered mouse models that recapitulate clinical features of RIT1-associated Noonan syndrome. Finally, using our preclinical models, we have identified potential therapeutic strategies for cardiac hypertrophy associated with RIT1 variants. Overall, our work provides novel insights into the regulation, function, and pathogenesis of the RAS-like protein RIT1 in Noonan syndrome.

Advancing novel therapies for the RASopathies using cell and animal models

Bruce Gelb, MD,** *Icahn School of Medicine at Mount Sinai, New York, NY, USA*

With the genetic etiologies of the RASopathies established, albeit incompletely, our understanding of disease pathogenesis is enabling the development of mechanistic therapies for various morbidities for these traits. Initial promising efforts have focused primarily on MEK inhibitors (MEKis), premised initially with pre-clinical data and now with emerging information from uncontrolled use in affected individuals. Those experiences are revealing that MEKis will not resolve RASopathy-related issues in all patients and that MEKi side effects may limit use, particularly for less severe RASopathy co-morbidities. To develop novel therapeutics for the RASopathies, our group has developed a robust platform using Drosophila and human induced pluripotent stem cell models of RASopathies. We have used that for both repurposing of known drugs and discovery of novel compounds. For this presentation, Dr. Gelb will provide an update on the status of those RASopathy drug development efforts.

ESI Selected Abstract: Investigation of cardiac valve disease mechanisms in Noonan syndrome with an iPSC model

Clifford Z. Liu, MD/PhD candidate, *Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Clifford Z. Liu[1,2,5], Aditi Prasad[1,5], Elizabeth Kahn[5], Shrey Patel[1,5], Bruce D. Gelb[1,3,4]
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Noonan syndrome (NS) is primarily an autosomal dominant disorder that results from gain-of-function germline variants in the RAS/MAPK pathway. One of the main features of NS is congenital heart disease, with cardiac valve stenosis estimated to occur in over 50% of NS patients. However, progress towards a mechanistic understanding of this pathology has been hindered by a lack of access to human valve cells. To circumvent this limitation, we have developed a novel feeder-free human induced pluripotent stem cell (iPSC) differentiation strategy that allows us to recapitulate the steps of valvulogenesis *in vitro.* This strategy allows us to generate endocardial cells that are transcriptionally and functionally distinct from vascular endothelial cells. These endocardial cells can then be induced to undergo endothelial to-mesenchymal transition (EndMT) to form valvular interstitial cells (VICs), the resident cell of the cardiac valve leaflet that is responsible for the production and maintenance of extracellular matrix (ECM).

To investigate the underlying valve pathology in NS, we then applied this differentiation strategy to iPSCs that have been CRISPR edited to carry pathogenic NS variants. Using this model, we found that NS-iPSCs exhibit increased specification towards a mesodermal lineage and subsequently have increased differentiation efficiency into endocardial cells. Interestingly, we found that these NS endocardial cells exhibit defective EndMT, specifically towards VICs that belong to the fibrosa layer, but not to those of the spongiosa layer. We then performed single cell RNA sequencing on these populations and found that fibrosa NS-VICs exhibit dysregulation of numerous genes involved in the ECM, such as *COL6A3, COL8A1, COL12A1, LUM, BGN,* and *POSTN.* Gene set enrichment analysis identified numerous putative signaling pathways that are upregulated in NS-VICs, including RAS-MAPK, TGF-beta, and PI3K-AKT-mTOR signaling pathways. By applying our model of generating iPSC-derived VICs

to NS-iPSCs, we have gained valuable insights into the underlying mechanisms driving valve stenosis in NS. These findings may help pave the way for developing novel therapeutics to resolve or slow progression of valvular stenosis in NS.

Session 6: Discussion Panel 1: Current Treatment Landscape and New Therapeutic Developments

Moderator: Anton M. Bennett, PhD, Yale School of Medicine, New Haven, CT

Panelists: Forest White, PhD, *MIT, Boston, MA*; **Gregor Andelfinger, MD PhD**, *CHU-Sainte Justine, Montreal, CAN;* **Mark W. Kieran, MD, PhD**, *VP Clinical Development, Day One Biopharmaceuticals*

Topics:
Proteomics, Pathway Inhibitors (MEK, SHP2, Pan-RAS/RAF), Paradoxical Circuit Breakers, Trials

Session 7: Genetic Session: Genotype-Phenotype Correlations

Moderator: Katherine A. Rauen, MD, PhD, UC Davis, CA, USA

Understanding RASopathies expression signatures to better inform diagnosis and treatment

Vanessa Fear, BSc (Hons), PhD,** *University of Western Australia, Perth, AUS*

The RASopathies are a set of syndromes that include cardiofaciocutaneous (CFC) Syndrome, Noonan Syndrome (NS), Noonan Syndrome with lentigines, and Costello Syndrome. RASopathies develop from mutations in genes of the RAS/MAPK pathway. The syndromes are characterized by overlapping disease phenotypes including short stature, unusual facial features, developmental delay, congenital heart disease, gastric problems, and increased risk of cancer. There is a need to distinguish the different RASopathies to facilitate accurate, early patient diagnosis, and provide a better understanding of these overlapping yet distinct diseases.

The BRAF protein is part of the Ras-MAPK pathway and genetic variants in the BRAF gene are the most common cause of CFC syndrome and are also a cause of Noonan syndrome and/or Noonan-related conditions. In this study we use CRISPR gene editing and inducible pluripotent stem cell disease modeling to derive neural and cardiac tissue from genetically engineered stem cells, and healthy matched control cells. We have derived BRAF_CFC, BRAF_NS, and BRAF_VUS stem cells that harbor a pathogenic CFC genetic variant, a pathogenic NS genetic variant, and a BRAF patient genetic variant of uncertain significance. We have performed neural disease modeling to identify any changes in neural differentiation in these cells. Next, we will perform cardiac cell differentiation to form cardiomyocytes and determine any functional changes in cellular and molecular pathways.

The project goal is to shorten the time to patient diagnosis for RASopathies, CFC and Noonan Syndrome, and will characterize functional cellular changes specific to each disease condition. Importantly, future application of this approach can be applied to other RASopathies to build a data set to readily classify these phenotypically overlapping syndromes.

Updates on the NCI RASopathies Natural History Study and Preliminary Genome-First Results

Megan Frone, MS, CGC, *NIH/NCI, Rockville, MD*

Megan N. Frone[1], Gina Ney[1], Jung Kim[1], Margarita Aryavand[1], Andrea M. Gross[2], Marielle E. Yohe[2,3], Alex Pemov[1], Esteban Astiazaran-Symonds[4], Jeremy S. Haley[5], Uyenlinh L. Mirshahi[5], Gretchen Urban[5], H. Shanker Rao[5], Mariya Shadrina[6], David J. Carey[5], Brigitte C. Widemann[2], Sharon A Savage[1], Bruce D. Gelb[6,7], Douglas R. Stewart[1].

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The RASopathies are a spectrum of clinical syndromes characterized by a range of clinical features including cardiac anomalies, neurological conditions, and failure to thrive caused by germline variants in genes encoding components of the RAS/mitogen-activated-protein kinase (RAS/MAPK) pathway. Some RASopathies are also associated with increased cancer incidence in childhood. Little is known about cancer risk later in life for these individuals. The IRB-approved RASopathies study at the National Cancer Institute aims to collect a large prospective longitudinal cohort of pediatric and adult individuals with clinical RASopathy diagnoses to study the prevalence of cancer; to assess the spectrum of benign and malignant clinical findings; to describe novel phenotypes associated with germline RAS/MAPK pathway variation; and to create a biospecimen repository for use in subsequent translational research projects. The RASopathies study opened in July of 2021 and currently has 61 individuals enrolled. Fifty-three carry a diagnosis of a RASopathy: 28 with Noonan syndrome (NS); two NS with multiple lentigines; one NS with loose anagen hair; one with a dual diagnosis of NS and Neurofibromatosis type 1; eight Costello syndrome (CS) including one individual with attenuated CS; six Cardiofaciocutaneous syndrome (CFC); three Legius syndrome; one Capillary Malformation-Arteriovenous Malformation; and three without formal diagnosis. To assess cancer incidence associated with germline pathogenic or likely pathogenic (P/LP) RASopathy variants in an unascertained population, a genotype-first approach was taken to analyze exome sequencing and phenotypic data from electronic health records from 1) Mount Sinai's BioMe (n=32,340), 2) the UK Biobank (UKB, n=469,802), and 3) the DiscovEHR subset cohort of the Geisinger MyCode Community Health Initiative (n=167,060). RASopathy genes associated with NS were the most prevalent (1:2,669 in UKB, 1:1,321 in DiscovEHR, and 1:1,406 in BioMe) with P/LP variants in *PTPN11* accounting for approximately 45% of cases. P/LP variants associated with CFC were relatively frequent in the cohorts (1:46,978 in UKB; 1:28,418 in DiscoverEHR, absent in BioMe). P/LP variants in *SPRED1*, associated with Legius syndrome, were also observed (1:19,574 in UKB; 1:42,626 in DiscovEHR; absent in BioMe). With the exception of carriers of P/LP variants in *SPRED1,* cancer incidence in these individuals was similar to non-carriers. A 4-fold increased cancer incidence was observed in *SPRED1* P/LP carriers in UKB (OR 4.54; p=4.61E-4) with earlier cumulative cancer occurrence than in non-carriers. Individuals with P/LP germline variants in NS-associated genes were found to have higher all-cause mortality compared to non-carriers with a decrease in mean age of about two years (Cox regression = 0.006), after removing individuals who had ever developed a hematological malignancy. This genome-first analysis in a large unascertained cohort of adult individuals suggests that individuals with P/LP *SPRED1* variants may have increased cancer risk. Carriers of P/LP NS genes do not appear to have increased cancer incidence in adulthood; however, they do appear to have increased all-cause mortality.

ESI Selected Abstract: Myocardial tissue engineering: A powerful tool to study hypertrophic cardiomyopathy in RIT1F82L/+ associated Noonan syndrome and its potential treatment by trametinib in vitro

Karolin Kleeman, *University Medical Centre Goettingen, DEU*

*Karolin Kleemann[1,2], Helena R. Szallies[1,2], Fereshteh Haghighi[1,2], Alexandra V. Busley[1,2], Jan Patrick Pietras[1,2], Leonie Böhmker[1,2], Louisa Habich[1,2], Julia Dahlmann[1,2], Tony Rubio[1,2], Fitzwilliam Seibertz[1,2], Wiebke Möbius[3], Sarah Nourmohammadi[1,2], Marianne Volleth[4], Michael Hofbeck[5], Niels Voigt[1,2], Martin Zenker[3], Ingo Kutschka[1,2], Lukas Cyganek[1,2], George Kensah[1,2]**

[1]University Medical Center Goettingen, Germany; [2]DZHK-German Center for Cardiovascular Research, Goettingen, Germany; [3]Max Planck Institute of Multidisciplinary Sciences, Goettingen, Germany; [4]University Medical Centre Magdeburg, Germany; [5]University Children's Hospital Tübingen, Germany

Corresponding author

RIT1-associated Noonan syndrome (NS) is known to be associated with a severe cardiac phenotype resulting mostly in hypertrophic cardiomyopathy. For patients suffering from RASopathies no targeted treatment is available yet, so for many very young patients heart transplant is the last resort. In 2019, Andelfinger *et al.* published a promising compassionate use case, in which two patients with RIT1 mutation were treated with the MEK1/2 inhibitor trametinib (TB). In the presented study, the gain-of-function mutation p.F82L in RIT1 of one of the NS patients is further investigated by employing induced pluripotent stem cells (iPSCs), derived from the patient to generate 3D bioartificial cardiac tissues (BCTs). CRISPR/Cas9 gene-corrected iPSCs served as Isogenic controls. In addition to characterizing the distinct (electro-)physiological phenotype, we also investigated changes on morphological, histological, ultrastructural and molecular level in the engineered myocardium.

In the presented study we mimicked the clinical situation of the patient by starting TB treatment only after manifestation of the distinct phenotype using concentrations similar to TB levels measured in the patient's serum. Our *in vitro* disease model is copying the clinical phenotype in terms of severe myocardial thickening along with increased myocardial stiffness and impaired contractility. Interestingly, histological analysis revealed that over the course of culture cardiac remodeling processes lead to fibrosis. When treating the tissues with TB, fibrosis was attenuated, compliance was increased and the contractility was rescued towards control levels reflecting the regression of HCM and improvement of cardiac status in the patients.

In conclusion, our study recapitulates the clinical observation of beneficial effects of TB on HCM in $RIT1^{F82L/+}$-associated NS and supports the therapeutic potential of targeting the hyperactivated RAS/MAPK pathway. Therefore, our disease model is a powerful tool to gain insights in underlying myocardial pathomechanisms in RASopathies and for drug testing to support the development of novel therapeutic options.

This work was supported by grants of the European Union (NSEuroNet, 01GM1807) and the German Federal Ministry of Education and Research (GeNeRARe; 01GM1902D).

Session 8: Keynote: Building and maintaining multinational rare disease networks/collaborations

Martin Zenker, MD, *Institute of Human Genetics, University Hospital Magdeburg, DEU*

Session 9: Discussion Panel 2: Global Perspectives and Collaborations

Moderator: Pilar Magoulas, MS CGC, Houston, TX

Panelists: Carlos Prada, MD, *Lurie Children's, Chicago, IL*; **Paul Kruszka, MD, MPH,** *GeneDx, Gaithersburg, MD*; **Emma Burkitt-Wright, MBChB PhD MRCP,** *Manchester Ctr Genomic Medicine, UK*

Topics:

Syndrome Commonalities across Ethnicities
International Collaborations in Practice, Standards, Guidelines and Updates for RASopathies Diagnosis and Treatment
Establishing Collaboration among Advocacy Networks
Modeling Euro NS Clinical Practice Surveys

Closing Remarks

Chairs

Gregor Andelfinger, MD, PhD, CHU-Sainte Justine, Montreal, Canada
Anton Bennett, PhD, Yale University, New Haven, CT, USA
Rene Pierpont, PhD, University of Minnesota, USA

Organizers

Lisa Schoyer, MFA, Board President RASopathies Network, Principal Investigator
Beth Stronach, PhD, Board Secretary RASopathies Network, Co-Investigator

POSTER ABSTRACTS

NF Research Tools Database: A disease-specific knowledgebase of experimental tools

Robert J. Allaway[1], Ashley Clayton[1], Mialy DeFelice[1], Brynn Zalmanek[1], Jay Hodgson[1], Caroline Morin[2], Stockard Simon[1], James A. Eddy[1], Milen Nikolov[1], Christina Conrad[1], Kenneth Chan[3], Felicia Sabatino[3], Dzmitry Fedarovich[3], Adam Lafontaine[3], Laura Brovold[3], Jineta Banerjee[1], Kalyan Vinnakota[4], Marco Marasca[1], Kevin J. Boske[1], Bruce Hoff[1], Ljubomir Bradic[1], James Goss[2], YooRi Kim[4], Julie A. Bletz[1]

[1]Sage Bionetworks, Seattle, WA, USA, 98121 ; [2]No affiliation; [3]Rancho Biosciences, Santa Fe, CA, USA, 92067; [4]Gilbert Family Foundation, Detroit, MI, USA, 48226

Research tools like mouse models and antibodies are crucial for conducting biological studies and are often shared among researchers to support scientific progress. However, with the fast pace of research, keeping track of available and emerging tools can be challenging, particularly for those new to a specific disease research area. Our experience in the neurofibromatosis (NF) field has shown that researchers struggle to identify the research tools available to them, determine where tools can be acquired, and understand what tools are best-suited for which experiments. While a variety of databases exist to help researchers find useful research tools, these databases often are specific to one type of research tool while being disease-agnostic, provide only high-level information, do not contain information about in-development models, and do not contain observational data for the research tools.

To address these limitations, we created the NF Research Tools Database, a user-friendly, open-access database and companion portal designed to help the NF research community easily find, obtain, and use NF-relevant research tools. This prototype database catalogs a wide variety of NF-relevant research tools using databases such as Cellosaurus, AntibodyRegistry, and the RRID Portal, among others, as well as information provided in literature and from the research community. We aggregated and curated metadata for NF-relevant animal models, cell lines, genetic reagents, antibodies, and biobanks. The database includes core metadata for all tools, e.g., name, type of tool, synonyms, developer, as well as tool type-specific metadata, e.g., for cell lines or animal models, the type of cancer that the model recapitulates. The database is also designed to store observational data contributed directly from the research community. Our companion web portal allows users to search and filter this database interactively and easily explore these tools. This website is available at tools.nf.synapse.org. Community members can actively contribute to the growth of the database and portal by submitting information about the reliability, biology, usage, and other observations on each research tool.

While the pilot project currently includes NF-relevant research tools, we plan to expand to include tools related to other RASopathies. This expansion could help researchers discover and repurpose useful tools from biologically adjacent syndromes, or to identify gaps where new tools are needed. By collating and curating this information and surfacing it in an open-access exploration portal, we anticipate that this database will serve as a valuable resource to help the RASopathy community discover, understand, and use research tools.

LZTR1 A new predisposition gene in acute lymphoblastic leukaemia? ▲

Adeline Bonnard[1], *Yoann Vial[1], Chloé Arfeuille[1], Séverine Drunat[1], Aurélie Caye[1], Hélène Cavé[1]*

1.Hôpital Robert Debré (AP-HP), Paris, France, and INSERM UMR_S1131, Institut de Recherche Saint-Louis, Université Paris Cité, Paris, France.

Background: LZTR1 is a negative regulator of the RAS proteins family, of which it promotes ubiquitination and degradation by the proteasome. Germline loss-of-function mutations in *LZTR1* activate the RAS signaling pathway and cause schwannomatosis and Noonan syndrome (NS). Among the few cases of LZTR1-NS reported so far, three developed acute lymphoblastic leukemia (ALL) during childhood, suggesting that germline inactivation of LZTR1 may act as a predisposing factor. However, there are still few data regarding the role of LZTR1 in normal and malignant hemopoiesis. Our objective was to evaluate the link between germline mutation of *LZTR1* and ALL, and determine which RAS proteins are targeted by LZTR1 in ALL.

Methods: Between 2018 and 2023, 1608 patients with childhood ALL were referred to our laboratory. *LZTR1* variants were screened using NGS. Only variants with a population allele frequency $<5.10^{-4}$(GnomAD V2.2) were considered. Germline or somatic status was assessed on blood at complete remission. LZTR1 was inactivated in TF-1 and Jurkat cell lines using CrispR-Cas9. Protein expression was measured by capillary Western (Jess, Protein Simple). Statistical significance was determined by two-tailed unpaired Fisher test and one-way ANOVA and multiple comparisons test.

Results: We identified 54 *LZTR1* variants in 46/1608 (2.9%) ALL. Of these, 34 were germline, representing a frequency of 2.1% versus 1.7% in the general population (p=0.25). The remaining 20 variants were somatic. In addition, somatic CNVs (loss of chromosome 22 or 22q mitotic recombination) caused loss of heterozygosity (LOH) of the *LZTR1* variant in 9 cases. Somatic *LZTR1* alterations were significantly enriched in patients with a germline *LZTR1* variant (9/34; 26%) versus others (12/1574; 0.76%) (p<.0001). Though mostly displaying 'good risk' ALL, 8/21 (38%) patients with somatic *LZTR1* alterations relapsed and the somatic *LZTR1* event was maintained at relapse in 7 of them. In order to identify LZTR1 targets in hematopoietic cells, we performed RAS protein dosage in a LZTR1 KO myeloid (TF1) and lymphoid (Jurkat) cell line. No significant variation was found for the canonical NRAS, KRAS and NRAS proteins whereas MRAS and more importantly RIT1 showed major increase in both cell lines. This points to RIT1 as a major LZTR1 target in hematopoietic cells. We then investigated LZTR1 expression in ALL with wild type LZTR1 (n=17) in comparison with matched non leukemic bone marrow samples. A clear LZTR1 expression was observed in all ALL samples only, while none of the RAS protein studied was detected. In contrast, ALL with biallelic LZTR1 inactivating alteration (n=4) showed a strong protein expression of RIT1+/- HRAS.

Conclusion: Although we do not show enrichment of germline *LZTR1* variants in ALL patients, their significant association with somatic alterations (second variant or LOH) and persistence at relapse highlight a driver role for LZTR1 in leukemia development. The link between LZTR1 and ALL is supported by the recent report of ALL in a mouse KO model (PMID: 35904492). The penetrance of the predisposition is low but remains of concern, since, as observed in schwannomatosis, it could be increased in families with an affected child. The high expression of LZTR1 evidenced in leukemic cells suggests that it has a regulatory role in ALL, possibly in response to abnormal stimulation of the RAS pathway. Loss of LZTR1 in some patients abolishes this regulation, leading to aberrant expression of RIT1, a protein whose role in ALL has never been described before, thus pointing to new therapeutic strategies.

A Poignant Chronicle of Struggles of a Toddler with Costello Syndrome

Omar Brijawi, MD

Cincinnati Children's Hospital, Ohio, USA

We report the case of a two-year-old male patient with Costello Syndrome. Antenatally, noted to be macrosomic at 20 weeks gestation, the mom developed hypothyroidism and severe polyhydramnios requiring amnioreduction (x3). He was born at 35 weeks gestation with a birth weight of 4.2 kg, born via c/section, required PPV and CPAP in the delivery room, and admitted to NICU due to severe respiratory distress and critical airway. Diagnosed with "fetal overgrowth syndrome" and noted to have a large tongue and nystagmus. MLB showed tracheobronchomalacia, and he was intubated at birth to establish a patent airway. At one month of age, he had Laparoscopic Nissen fundoplication and G tube placement with tongue and upper lip tie release and circumcision. He was fed exclusively via his G tube initially. At 3 months, ECHO revealed hypertrophic cardiomyopathy with LVOT obstruction and the patient was started on MEK1 (trametinib) and propranolol. He responded well with resolution of heart failure. Genetic testing at 4 months revealed heterozygous mutations in genes HRAS and RB1, consistent with Costello Syndrome and Retinoblastoma. At 10 months his brain MRI revealed slight increase in size of supratentorial ventricles. At 14 months, the family reported decreased leg function and bladder dysfunction, which prompted imaging showing a small filar lipoma with borderline low conus. Neurosurgery performed tethered cord release at 15 months. Post-surgery, the patient has continued issues with his gait, but had improvement in his urinary symptoms.

He was seeing a multidisciplinary feeding team for problems with feeding intolerance and poor oral motor skills. There has been an improvement in the patient's oral motor skills and has slowly increased oral intake by tasting baby food and swallowing. At 16 months, he was noted to have signs of wasting, loss of subcutaneous fat/muscle mass around the limbs and buttocks, despite meeting adequate caloric goals. He developed abdominal distension, loose stools/diarrhea and cramping. MEK1 was discontinued as a precaution for this reason. EGD/flex sigmoidoscopy and biopsies were normal. Duodenal fluids showed growth of both GPC and GPR on quantitative cultures, and low levels of disaccharides and pancreatic enzymes. At 18 months, he was evaluated for a possible bladder mass, which was not seen on lumbar MRI or screening abdominal US approximately a month prior. PET imaging was done to evaluate the mass, which showed FDG uptake in the mass as well as a lymph node. Intraop, the tumor was retroperitoneal, arising from an urachal remnant, connected to the dome of the bladder and right umbilical artery remnant. He underwent surgical excision of the embryonal rhabdomyosarcoma, with partial bladder resection and urachal remnant excision and started on a combination of Vincristine, Dactinomycin, and Cytoxan.

Multiple attempts at weaning him off the ventilator have been unsuccessful. He was recently admitted to the Trach Unit for acute chronic respiratory failure due to Parainfluenza 3 viral infection and bacterial tracheitis. He developed pneumatosis intestinalis with portal vein gas, and his feeds have been stopped, started on antibiotics and transitioned to full TPN via a central line. He is now completely ventilator dependent.

Role of endocytic trafficking in SPRED1-mediated, NF1-independent Ras activity control

Sarah Bühler*, *Stephanie Morgner*, Zumer Naeem#, Ignacio Rubio**

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Spred1, and more recently Spred2, mutations have been identified as the cause of the rasopathy syndrome Legius. Legius shows a very similar clinical picture to Neurofibromatosis type 1, caused by loss of neurofibromin 1 (NF1), but manifests as a milder form. Due to the lack of intrinsic enzymatic activity of Spred1, the similarity to NF1 and the finding that Spred1 and neurofibromin directly interact with each other, it has been hypothesized that Spred1 exerts inhibition of the Ras/Erk pathway by recruiting neurofibromin 1 to the membrane for Ras inactivation. Using NF1 deficient cells we observed that Spred1 can down-regulate the Ras pathway independently of NF1 (Figure 1). Further investigation disclosed a prominent trafficking phenotype in cells with overexpression of SPRED1. SPRED1 overexpression caused the internalization of plasma membrane resident H-Ras (Figure 2), an effect that was also observed in NF1-deficient cells. This led us to the hypothesis that besides interaction with neurofibromin 1, Spred1 also regulates endocytic Ras trafficking. In order to decipher the precise function of SPRED1 in this context we performed proximity biotinylation screens to identify interacting and neighbor proteins of SPRED1. We will present the results of this screen, highlighting in particular proteins genuinely involved in early endocytic trafficking control. In summary, we will report on a function of SPRED1 as a negative regulator of Ras that appears to be largely independent of its role as a neurofibromin 1 recruitment factor.

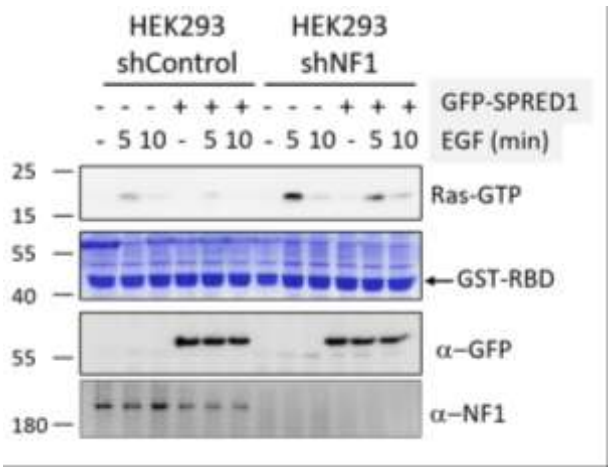

*Figure SEQ Figure * ARABIC 1 - Spred1 down-regulates Ras activation in the absence*

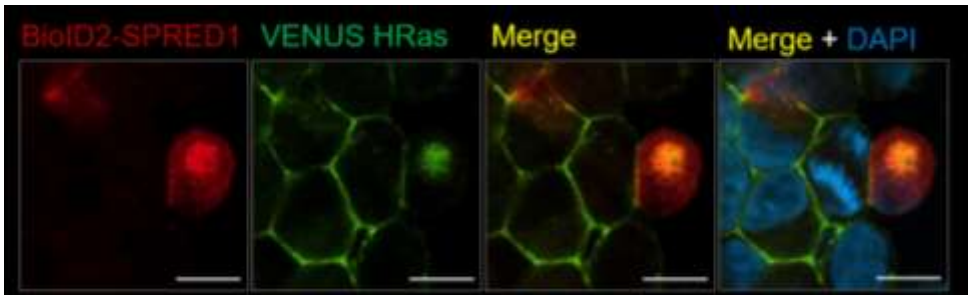

Figure 2 - Spred1 overexpression triggers Ras redistribution to endosomal vesicles

Developmental defects in zebrafish Noonan syndrome models

Jeroen den Hertog[1,2], Daniëlle Woutersen[1], Maja Solman[1] and Jisca Majolée[1]

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Noonan Syndrome (NS) belongs to the RASopathies, a group of syndromes that have partially overlapping symptoms and are characterized by activated RAS/MAPK signaling. NS symptoms include short stature and defects in the heart, in the lymphatic vasculature and in hematopoiesis as well as in formation of the head and face. Many factors of the RAS/MAPK signaling pathway have been found to be associated with NS, including the protein-tyrosine phosphatase, SHP2 and the guanine nucleotide factors SOS1 and SOS2. We use zebrafish to study NS in vivo and we have generated knock-outs lacking functional Shp2, Sos1 and Sos2. Moreover, we have generated knock-in lines using CRISPR/Cas9 technology and homology-directed repair, expressing variants of Shp2 and Sos that were identified in human NS patients. Recent work focuses on defects in lymphangiogenesis and we found that our zebrafish models phenocopy the defects observed in human patients. These observations and pharmacological interventions to ameliorate the defects in zebrafish models will be discussed.

Using Noonan Syndrome as a lens to reveal brain-basis of neuropsychiatric phenotypes

Naomi Fuhrmann, Manish Saggar, Tamar Green

Stanford University, Stanford, CA, USA

Background: Noonan syndrome (NS) is the most common (1:2000) neurodevelopmental genetic syndrome associated with the Ras/MAPK pathway. It is associated with effects on brain morphometry. Brain-wide association between brain and neuropsychiatric outcomes is typically performed using mass univariate linear models; potentially missing out on revealing multivariate nonlinear relationships. Here, we use Topological Data Analysis based Mapper approach to uncover multivariate nonlinear brain-wide associations in NS.

Methods: We collected sMRI from n=38 children with NS (age:8.70±2.03) and n=37 age- and sex-matched typically developing (TD) controls (age:9.48±1.29). We fed the cortical data(volume, surface area, thickness) into Mapper. Mapper embedded participants into a low-dimensional graph, preserving local neighborhood structure from high-dimensional feature space. We calculated the modularity score measuring separation between TD and NS and participation coefficient (PC) measuring distribution of each subject's connections among the communities (diagnosis).

Results: NS and TD groups were segregated on the Mapper-generated graph (Q_mod = 0.18; p=0; significance tested using 10,000 shuffled diagnosis labels). We observed lower PC in NS (F=10.58 , p=0.0017), suggesting low heterogeneity within the NS group.

Conclusion: We provide preliminary results from a multivariate nonlinear embedding approach to examine differences in sMRI data between NS and TD. The nonlinear approach differentiated between the groups and provided evidence for higher homogeneity within the NS group. Next, using the NS-based embedding, we aim to examine the brain-basis of heterogeneous neuropsychiatric phenotypes.

Modulating RAS-MAPK pathway as a potential treatment for strain-induced cardiac arrhythmias caused by RAF1 mutation in Noonan syndrome. ▲

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The gain of function mutation RAF1$^{S257L/+}$, accounting for more than 50% of Noonan syndrome (NS) cases, results in a hyperactive RAS-MAPK pathway. Individuals suffer from myocardial dysfunction including electrophysiological abnormalities. Resulting arrhythmias may be potentially life-threatening, if sinus rhythm is not restored expeditiously. Intensive research has provided insights into structural anomalies. However, electrophysiological abnormalities contributing to arrhythmia initiation and maintenance in affected NS patients have not yet been investigated in-depth.

To delineate the role of RAF1$^{S257L/+}$ in cardiac rhythm disturbance *in vitro*, we used cardiomyocytes differentiated from NS patient-derived (RAF1$^{S257L/+}$) and isogenic gene-corrected (RAF1$^{corr/+}$) iPS cells to generate 3D bioartificial cardiac tissues (BCTs).

In a custom-made bioreactor system, we applied mechanical preload to BCTs to resemble an *in vivo* physiological stress condition. Here, in RAF1$^{S257L/+}$ BCTs, we observed a high susceptibility to arrhythmias compared to RAF1$^{corr/+}$ myocardium. This abnormality came alongside with a severely stiffened myocardium, and an impaired myocardial relaxation, pointing towards a diastolic dysfunction. Moreover, RAF1$^{S257L/+}$ cardiomyocytes in BCTs dedifferentiated into vimentin^{pos} fibroblast-like and α-SMA^{pos} myofibroblast-like cells most likely as the contributors to develop a stiffened myocardium. These non-cardiomyocytes populations were not observed in RAF1$^{corr/+}$ BCTs. Electrophysiological analysis revealed a potentially arrhythmogenic shortening in action potential duration in RAF1$^{S257L/+}$ BCTs. Furthermore, the presence of spontaneous ectopic foci resulted in unstable excitation patterns. Long-term modulation of the hyperactive RAS-MAPK pathway by treatment with a MEK inhibitor, significantly reduced these arrhythmogenic parameters accompanied with a normalization of RAF1$^{S257L/+}$ BCT compliance, eventually stabilizing beating rhythm significantly.

For the first time, our study provides an in-depth characterization of the RAF1$^{S257L/+}$-associated arrhythmogenic phenotype *in vitro*. Shortened action potential durations, unstable pace maker regions and a stiffened myocardium may contribute to the initiation and maintenance of severe cardiac rhythm anomalies. Moreover, our model revealed a distinct genotype-phenotype correlation by using isogenic gene-corrected myocardium and we successfully rescued this distinct phenotype by pharmacological intervention. Our findings may have implications for future preventive treatment strategies for NS patients.

Caregivers of Children with RASopathies: A Pilot Feasibility Study for Parent Stress Intervention

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RASopathies are neurodevelopmental genetic conditions that impact physical, cognitive, and emotional development. Parenting children with a RASopathy diagnosis can be associated with numerous challenges and stressors related to these children's medical, developmental, and learning needs. The rarity of these diagnoses can exacerbate these stressors**.** This pilot study assessed the feasibility and acceptability of a fully remote Acceptance and Commitment Therapy (ACT) intervention to improve caregiver stress; data will inform an upcoming randomized controlled trial (RCT). Parents of a child with a RASopathy (e.g., neurofibromatosis type 1 (NF1), Noonan Syndrome (NS), or another RASopathy) who had moderate parenting stress on a screener were eligible. The 8-week intervention consisted of three individual ACT coaching sessions and prerecorded videos delivered weekly via the Catalyst app (Metricwire Inc.). Parents completed baseline questionnaires including the Parental Stress Scale (PSS; possible scores range 18-90 with higher scores indicating more stress). PSS changes of ≥5 points were determined a priori to be clinically meaningful. Throughout the intervention, participants responded to ecological momentary assessments (EMAs) through the app to assess stress five days a week at random times.

Our sample included 8 parents: 7 mothers and 1 father; 7 non-Hispanic white, 1 Hispanic. Three out of 8 caregivers had a history of anxiety and/or depression**.** Parent baseline PSS scores ranged from 37-56 (mean=48). Children (ages 3-13 years, median=11.5) were diagnosed with NS (n=3), NS with multiple lentigines (n=1) and NF1 (n=4). Four children had a parent-reported intellectual or developmental disability (2 mild, 1 moderate, 1 severe); 6 children had a parent reported learning disability (3 mild, 2 moderate, 1 severe). There was a range in caregiver ratings of child physical health [fair (n=3), good (n=3), excellent (n=4)]. Seven of the 8 caregivers rated their child's physical health as impacting their daily lives at least somewhat.

With respect to feasibility, 7/8 participants completed the intervention, with one parent withdrawing due to their child's medical emergency**.** PSS scores decreased (improved) for 3 participants, were stable for 3, and increased for 1 participant. There was a high level of engagement with EMAs, with parents completing an average of 92% of surveys. Post intervention, participants rated EMA use as very easy (n=1), somewhat easy (n = 3), neither easy nor hard (n=1), somewhat hard (n = 1), or very hard (n=1). Further data from EMA scores are forthcoming. Parents reported liking the study "a lot" (n=3) or "pretty much" (n=4). All (n=7) participants found the initial coaching session very helpful, and we received qualitative feedback asking for more and longer coaching sessions. To our knowledge, in parents of children with RASopathies, this is the first study to employ a psychological intervention targeting parenting stress and the first to examine EMA use in this population. Participant feedback reflected a high level of satisfaction and engagement in the study, as well as some areas for improvement to be incorporated in the RCT.

Children with RASopathies (Noonan and NF-1) present contrasting neuroanatomical effects on the developing brain ▲

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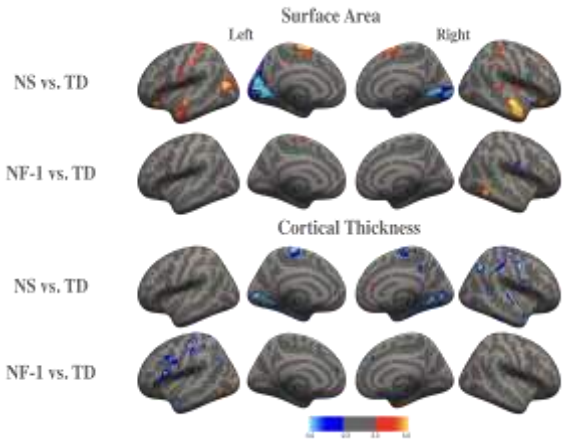
Background: Noonan Syndrome (NS) and Neurofibromatosis type 1 (NF-1) are genetic conditions of the Ras-mitogen-activated protein kinase (Ras-MAPK) signaling pathway associated with neuropsychiatric morbidity and brain development. NS is caused by alterations to genes encoding proteins that have an inhibitory effect on the Ras-MAPK signaling pathway. Whereas NF1 is caused by dysregulation of the proteins involved in the Ras-MAPK pathway, creating an excitatory effect. Prior studies have focused mostly on total brain volume (TBV), separately compared NS or NF-1 to typically developing controls (TD) and used a broad age range that captures several pubertal stages. This study examines whether NS and NF-1 affect surface area (SA) and cortical thickness (CT) differently, suggesting genotype-brain phenotype correlations. In addition, this study aims to uncover how NS and NF-1 affect the developing brain in a converging or diverging way.

Methods: We compared structural T1-weighted images of individuals with NS (n= 57, 35 females) and NF-1 (n= 22, 9 females) to sex- and age-matched TD controls (n= 62, 36 females) across Freesurfer's vertices. We used Freesurfer's, mri_glmfit to run vertex-based analyses (controlling for sex, age, and TBV), and Cohen's *d* to compare effect sizes given NF-1's smaller cohort.

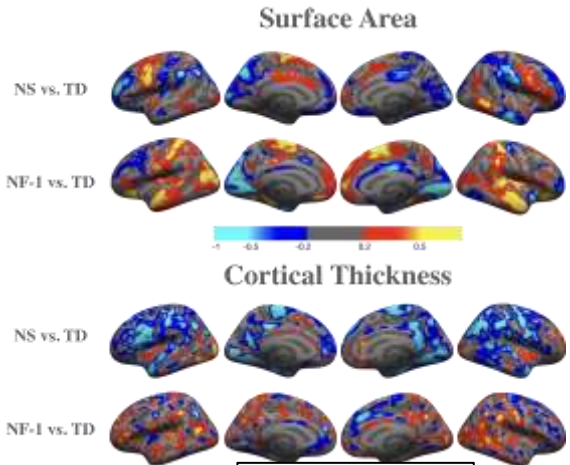
Results: For SA, compared to controls, NS had significant differences ($p < 0.05$ fdr-corrected, d= -1.0 to 0.92); specifically, expanded frontal and temporal regions, and contracted occipital regions. For NF-1 we detected expansion in the precentral gyrus ($p < 0.05$ fdr-corrected) and a medium effect size (d= -0.6 to 0.6) compared to TD. For CT, NS had a pervasive effect ($p < 0.05$ fdr-corrected, d= -0.88 to 0.67), with reduced thickness in frontal and temporal regions. NF-1 had an opposing effect ($p < 0.05$ fdr-corrected, d= -0.7 to 0.6), with increased thickness in posterior occipital regions and medial temporal regions.

Conclusions: NS and NF-1 have contrasting neuroanatomical differences relative to TDs, specifically on CT. This proposes a translational framework to understand how differing cellular mechanisms of NS and NF-1 on the Ras-MAPK pathway lead to differences in neuroanatomy.

Keywords: Noonan syndrome; RASopathies; Neurofibromatosis type 1; Neuroimaging; Neuroanatomical.



Significance Plot ($p<0.05$)



Cohen's D Plot

Deciphering the pathogenicity of *LZTR1* variants in Noonan Syndrome ▲

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Purpose of study: We have previously shown that leucine zipper-like transcription regulator 1 (LZTR1) functions as an adaptor protein for cullin-3 mediated proteasomal degradation of small guanosine triphosphate hydrolases, RIT1 and MRAS. Germline variants of the *LZTR1* gene are associated with Noonan syndrome. Many *LZTR1* variants have been identified in this rare genetic disorder, which include single nucleotide variants (SNVs) which are generally considered loss-of-function, however the significance of SNV variants is unknown and many of these remain classified as variants of unknown significance (VUS). These variants span along different domains of LZTR1, which play important functional roles. For instance, it has been suggested that the Kelch and BTB-BACK domains are required for substrate and cullin-3 binding, respectively. Therefore, it is possible that VUS located in these different domains can ultimately impair the function of LZTR1. To understand the underlying molecular mechanism of Noonan syndrome in the context of LZTR1, we established a biochemical pipeline to characterize a large panel of *LZTR1* Noonan syndrome-associated SNVs to determine their pathogenicity.

Method: Using site-directed mutagenesis, we produced a catalog of Noonan syndrome associated *LZTR1* variants and these were expressed ectopically in mammalian cells. We developed different biochemical assays that assessed the interaction between LZTR1 variants and their substrates, such as RIT1 and MRAS, their ability to degrade these substrates, as well as their capacity to interact with the ubiquitin ligase, cullin 3. We quantitatively analyzed the effect of these VUS in our assays and used a structural model of LZTR1 developed with AlphaFold to assess the effects of each variant.

Result: Characterization of the different *LZTR1* variants using our experimental pipeline demonstrated that most VUS result in their inability to bind and/or degrade the substrates: RIT1 or MRAS, and/or fail to engage with cullin 3. Therefore, our experimental approach suggests that the majority of germline *LZTR1* VUS found in Noonan syndrome act as loss-of-function variants through mechanisms consistent with the role of LZTR1 in the degradation of RIT1 and MRAS substrates.

Event Related Potentials as Predictors of Real-World Difficulties in School Age Children with Neurofibromatosis Type 1: A Pilot Study

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Children with neurofibromatosis type 1 (NF1) have difficulties with various aspects of attention (Casnar & Klein-Tasman, 2017; Isenberg et al., 2013). While some children with NF1 have attention difficulties consistent with a diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD), many children with NF1 have difficulties that do not meet that threshold, yet still demonstrate marked difficulties with attentional processes, such as sustained attention (Mautner et al., 2002). Research in other populations, such as ADHD, has begun elucidating specific biomarkers of attention difficulties using electroencephalography (EEG) Event Related Potentials (ERPs). However, no studies have used EEG methodology to examine the relations between ERPs and behavioral indicators of attention difficulties in children with NF1.

Participants were 11 children with NF1 between the ages of 7 and 11 years. The study battery included parent questionnaires, performance-based measures, and Flanker and Go/Nogo tasks to elicit select ERPs (N2, P3). Regressions were conducted with parent questionnaire indicators of attention problems as the dependent variable (Conners-3 Inattention and Hyperactivity scales, BRIEF-2 Working Memory and Global Executive Composite scales, ADHD-5 Rating Scale Inattention and Hyperactivity symptoms) as well as norm-referenced performance-based measures (NEPSY-II Auditory Attention/Response Set, DAS-2 Digits Forward and Working Memory Index). Hierarchical regressions were calculated to estimate the contribution of age (step 1), cognitive ability (IQ estimate; step 2) and ERP component amplitude and latency (step 3) on behavioral indicators of attention difficulties for each group. Only ERP component amplitudes and/or latencies that were identified with medium to large effect size differences between children with NF1 and an unaffected group in preliminary work were included in the model for parsimony (i.e., Go/Nogo: P3 latency at Pz, N2 latency at Fz, N2 amplitude at Cz; Flanker: N2 latency at Cz).

In the model predicting ADHD-RS-5 Inattention symptoms, age (step 1) was a significant predictor ($F(1, 7)=18.56$, $p=.004$) and age and IQ together (step 2) were significant predictors ($F(2, 6)=8.07$, $p=.020$). Furthermore, the addition of ERP components into the model resulted in statistical significance as well, ($F(6, 2)=45.53$, $p=.022$), though there was no statistically significant increase in variability predicted ($\Delta R^2=.264$, $p=.053$). In the model predicting Conners 3 Inattention symptoms, step 3, which included age, IQ, and ERP components, was significant ($F(6,4)=12.25$, $p=.015$) and resulted in a significant increase in total variability accounted for in Conners-3 Inattention scores ($\Delta R^2=.633$, $p=.016$). In the model predicting DAS-2 Digits Forward scores, step 3, which included age, IQ, and ERP components, was significant ($F(6,4)=8.77$, $p=.027$) and resulted in a significant increase in total variability in Digits Forward scores predicted ($\Delta R^2=.511$, $p=.041$). No other models had significant ERP findings.

Our findings demonstrated that age, IQ, and selected ERP components (P3 latency, N2 amplitude and latency) together significantly predicted parent ratings of inattention difficulties (but not hyperactive/impulsive difficulties) on two different parent report measures. The hierarchical model predicting performance on a Digits Forward task, which likely measures aspects of both attention and working memory for children with NF1 (Casnar & Klein-Tasman, 2017) was also significant. Both inattention (Lidzba et al., 2012; Payne et al., 2011) and working memory (Beaussart et al., 2018) have been identified as central cognitive concerns in NF1. Overall, these findings point to the promise of EEG methodology for identification of biomarkers of attention in NF1. Further clinical implications are discussed.

Sensory and Neurologic Features Associated with Challenging Behaviors Among Individuals with Cardiofaciocutaneous Syndrome ▲

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Introduction: Hallmark features of cardiofaciocutaneous syndrome (CFC) include developmental disability and seizures. The pathogenic variants that cause CFC are well researched and are critical for understanding the role of the RAS-MAPK signaling pathway. However, the behavioral phenotype and the potential associated challenging, sensory, and pain behavior experienced by individuals with CFC has received considerably less attention. Given prior research recognizing that behavioral health

concerns are one of the most widespread features of CFC, a focused investigation that helps to uncover the underlying sensory and neurological needs that perpetuate repetitive and challenging behaviors is needed to move toward effective treatment options. The purpose of this preliminary analysis was to assess the relation between repetitive, sensory, and challenging behavior among individuals with CFC syndrome.

Method: We recruited caregivers at the CFC family advocacy conference and via CFC International to complete electronic questionnaires using RedCAP. We administered the following instruments: the *Repetitive Behavior Scale – Revised* (RBS-R; Bodfish et al., 2000), *Behavior Problems Inventory-Short Form* (BPI-S; Rojahn et al., 2012), *Questions about Behavioral Function* (QABF; Matson & Vollmer, 1995), the *Modified Brief Pain Inventory* (m-BPI-sf; American Pain Society Quality of Care Committee, 1995), and the *Short Sensory Profile* (SSP; Dunn, 1999). Information regarding demographics, genotype, neurologic functioning, comorbid diagnoses, adaptive behavior, and service receipt were also analyzed in relation to behavioral features and quality of life. We evaluated trends using descriptive analyses, Spearman rank correlations, and examined mean differences across genotypic and seizure status groups using independent samples T- tests and One- way ANOVA.

Results: Caregivers of 59 individuals (60% male, 80% White, age range 2-30 years) completed the questionnaires. The cohort consisted primarily of individuals with BRAF mutations (61%) followed by MEK1 (29%) and MEK2 (10%) mutations. Over half (55%) endorsed seizure activity and required support with almost all aspects of life. Additionally, intellectual disability (79%) and speech language impairment (66%) were common along with endorsement of sensory processing disorder (46%) and anxiety disorder (39%). Sensory and challenging behavior were highly rated and severe. Stereotyped behavior was rated as the most severe followed by aggressive/destructive behavior and self- injurious behavior. Repetitive behavior was statistically significantly correlated with sensory behavior ($r(58) = .74$, $p < .001$). Mean pain intensity ratings were significantly higher among individuals with seizures ($M=32.76$, $SD=36.76$) in comparison to those without ($M=14.28$, $SD=24.18$), $t(56) = -2.18$, $p=.007$. Finally, escape (negative reinforcement) was the primary behavioral function for self-injurious behavior and aggression endorsed. No statistically significant differences were noted by genotype.

Discussion: Overall, caregivers highly endorsed challenging and repetitive behavior with over half requiring assistance with daily life and communication. Stereotyped and pain behavior was rated as highly interfering and an area of needed support to increase quality of life. A limitation of this study is that we used a cross-sectional design. Future research should focus on longitudinal design to better assess and evaluate the developmental trajectories of these behaviors over time.

Vision related Quality of Life in Children with RASopathies

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Purpose: Vision problems are common among individuals with RASopathies. Although many vision issues are amenable to treatment, given the multiple systemic issues that are often found in these children, vision dysfunction may go unrecognized in many children. In this study, we evaluated vision related quality of life in children with RASopathies.

Methods: We collected data on 49 individuals using Children's Visual function Questionnaires (CVFQ), one targeted to children under 3 years of age and the second to children 3 years and above from parents of children with Costello, Cardiofaciocutaneous and Noonan syndromes at Family support conferences 2009 – 2022. The CVFQ evaluated General Health, General Vision, Competence, Personality, Family Impact, and Treatment. The subscale scores for children 3 years and above were calculated and compared for significance with treatment.

Results: Forty-five individuals were 3 years or older and only 4 individuals were less than 3 years old. The subscale score ranges for each category General Health, General Vision, Competence, Personality, Family Impact, and Treatment ranged from 0.5 to 1, 0.4 to 1, 0.09 to 1, 0.44 to 1, 0.18 to 1 and 0.13 to 1 respectively with a score of "1" indicating the best and "0" indicating the worst. Individuals with better treatment scores correlated with better Competence and Personality scores and were statistically significant (Table 1).

Conclusions: Vision impairment impacts competence and personality of an individual with RASopathy. Early initiation of treatment improves the QoL and has an overall positive impact on the individual. This questionnaire can serve as a measure for evaluating treatment efficacy in individuals with RASopathies and can serve as a valuable tool in clinical trials.

Table 1: t-Test: Two-Sample Assuming Unequal Variances

	Treatment	**Competence**
Mean	0.611742424	0.762954545
Variance	0.119409942	0.067556184
Observations	44	44
P(T<=t) two-tail	0.022907753	
	Treatment	Personality
Mean	0.60266667	0.84074074
Variance	0.12073364	0.01825196
Observations	45	45
P(T<=t) two-tail	7.1393E-05	

Germline RASopathy mutations provide functional insights into the RAF cysteine-rich domain (CRD)

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The RAS-MAPK pathway is a hotspot for somatic mutations in human cancer and for germline mutations in the RASopathy developmental syndromes. Understanding the regulatory mechanisms that govern this pathway is critical for identifying new drug targets and establishing effective therapeutic approaches for RASopathy and cancer patients alike. Given that RASopathy mutations

must be tolerated during development, they tend to be distinct from oncogenic mutations in terms of their location within the protein or in which family member or isoform they occur, potentially identifying new regulatory regions and druggable targets in pathway members. In the case of the RAF kinase, BRAF, oncogenic mutations occur overwhelmingly in the catalytic (CAT) region, whereas RASopathy mutations are also frequently reported in cysteine-rich domain (CRD) and are frequently associated with cardiofaciocutaneous syndrome. The CRD is a zinc stabilized lipid and protein binding domain in the RAF regulatory (REG) region. Previous studies have shown that the CRD plays roles in RAS activation of RAF by interacting with phosphatidylserine (PS) in the plasma membrane and by bindings directly to RAS GTPases. Conversely, the CRD also plays a role in the autoinhibitory interactions of the REG and CAT domains under quiescent conditions. However, the relative importance of these functions and the residues which mediate them were not well understood. Through the characterization of a panel of RASopathy CRD mutations we show that they can be grouped into three distinct classes based on their abilities to relieve autoinhibition and/or enhance PS binding. Critically, we found that the CRD and autoinhibition are required to maintain BRAF in a non-signaling state and mutations which disrupt this function result in elevated RAS-dependent and RAS-independent BRAF function. Moreover, relief of autoinhibition was the major factor determining mutation severity in zebrafish developmental studies and these findings correlated well with patient reports, indicating the utility of our approaches as prognostic indicators of mutation severity in RASopathy patients. Finally, our studies indicate that stabilizing CRD-mediated autoinhibition may be a viable approach to reduce the aberrant BRAF activation found in many cancers and the RASopathy syndromes.

Finding and treating hidden Rasopathies among *Drosophila* models with habituation deficits

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Habituation, a fundamental form of learning, is the decrement of a response to repeated irrelevant stimuli. It protects from sensory overload, is indispensable for higher cognitive processes, and is affected in neurodevelopmental disorders (NDDs). Habituation is conserved across all species and can be measured in patients and in the fruit fly, *Drosophila*. Previous work of the lab has identified defective habituation in >150 *Drosophila* models of monogenic Neurodevelopmental Disorders (NDDs), underlining the potential of habituation as translational biomarker for NDDs.

Strikingly, numerous habituation-deficient genes act in a few related signaling pathways, including Ras/MAPK, PI3K-Akt, and cAMP signaling. More specifically, various genetic conditions characterized by overactivated Ras/MAPK signaling (= Rasopathy models) show disrupted habituation, and we indeed find that restoring this balance pharmacologically rescues habituation deficits. We hypothesize that apart from the classic Rasopathies, there might be additional disease models among the 150 habituation defective ones that are affected by disbalanced Ras/MAPK signaling.

Profiling these disease models systematically, we have identified a few rare genetic disease models with disbalanced Ras/MAPK signaling and habituation defects, and refer to these as hidden Rasopathies. The novel hidden Rasopathies might be treatable by approaches being developed for classic Rasopathies (e.g. MEK-inhibitors) and reversely, may provide new treatment options for classic

Rasopathies (e.g. drugs targeting molecular basis of the hidden Rasopathy and thus downstream Ras signaling). In addition to pharmacological interventions, we are investigating environmental and behavioral treatment regimens as modifiers of habituation learning mediated by Ras/MAPK. First data will be presented.

Taken together, using *Drosophila* as an efficient model to generate and screen many genetic models, we have identified NDD with a previously undescribed link to Ras/MAPK signaling, potentially underlying defective habituation learning.

Craniofacial Phenotypic Polymorphism in ERas Knockout all-ESC Mice

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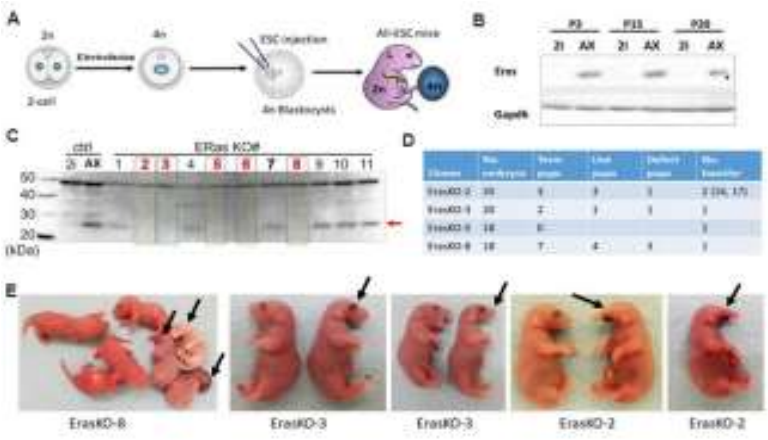
Abstract: The ERas gene, located on the X chromosome, comprises two exons and encodes a 227-amino acid protein that is localized at the cytoplasmic membrane. While ERas is not essential for mouse embryonic stem cell (ESC) maintenance, it is a significant transforming oncogene. ESCs null for ERas retain pluripotency but exhibit notably reduced growth and tumorigenicity (Takahashi et al., Nature, 2003). In this study, we observed that ERas-null all ESC mice, generated through tetraploid complementation, exhibited craniofacial abnormalities in approximately 50% of the pups. Interestingly, ERas expression is specifically induced when ESCs are cultured in 2i/LIF (2iL) medium supplemented with lipid-rich albumin, AlbuMAX (2iLA) (Zhong, et al., Protein & Cell, 2023). ERas-null all-ESC mice derived from ESCs cultured in lipid-rich 2i/LIF medium manifested the craniofacial abnormalities, while those derived from ESCs cultured in lipid-free 2i/LIF medium appeared normal. Our findings suggest that ERas is implicated in lipid metabolism during early development, and disruption of ERas function may lead to craniofacial abnormalities during embryogenesis. These results underscore the potential role of lipid metabolism in craniofacial development and the importance of ERas in this process.

Figure 1. (A) Pure ES cell derived mice (all-ESC mice) are efficiently generated through a process called tetraploid complementation, which involves injecting ground state ESCs into tetraploid blastocysts. This process ensures that the host 4n cells contribute exclusively to the extra-embryonic tissue and do not participate in the formation of somatic tissues. (B) ERas expression is induced when ESCs are cultured in a lipid-rich 2iLA (2i/LIF/AlbuMAX) medium, but remains inactive in a lipid-free 2iL medium. (C) The ERas gene is deleted using CRISPR/Cas9/gRNA (indicated as "del"), causing a shift in the reading frame and resulting in the depletion of the ERas protein. Western blots confirm that the ERas protein is successfully depleted in five clones. (D) All-ESC pups, derived from four confirmed ERas KO ESC clones cultured in 2iLA medium, show that approximately 50% of the pups exhibit craniofacial abnormalities. (E) ERas KO all-ESC pups display varying degrees of craniofacial abnormalities; those with abnormalities typically die shortly after birth, while the others appear normal and are able to survive into adulthood and remain fertile. Notably, all-ESC pups derived from ERas KO ESCs cultured in lipid-free 2iL medium are normal and do not exhibit craniofacial abnormalities (data not shown).

Echocardiographic strain analysis reveals concentric basilar cardiac hypertrophy in an Hras^{G12S} mouse model for Costello syndrome



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Costello syndrome (CS) is an autosomal dominant disorder that is usually caused by the p.G12S variant of HRAS. Children with CS have clinical features that can include hypotonia, congenital heart disease, profound cognitive impairment, and an increased risk of cancer development. There are currently no approved therapies for individuals with CS, which represents a significant unmet medical need. Global expression mouse models have been used to further our understanding of the pathogenesis of CS and can be used to determine the preclinical efficacy of potential CS therapeutics. Mice derived from the first *Hras*$^{G12S/+}$ model of CS have craniofacial abnormalities, increased heart weight to body weight ratio, and impaired metabolism. In this study, we attempted to further define the neurological, muscular, and cardiac phenotypes in these Hras$^{G12S/+}$ mice. We observed an increase in brain weight in the Hras$^{G12S/+}$ mice compared to littermate controls at 4 weeks, 17 weeks, and 28 weeks of age. This weight increase was accompanied by a decrease in GFAP positive astrocyte precursor cells in the Hras$^{G12S/+}$ brains at 4 weeks, but an increase in GFAP positive cells at 17 and 28 weeks. We observed a decrease in NeuN positive mature neurons in the Hras$^{G12S/+}$ brains at each of the three time points. We observed a decrease in mean myofiber size of the gastrocnemius muscle at 4 weeks and 17 weeks but not at 28 weeks. Hras$^{G12S/+}$ mice did not differ from wild type littermate controls in latency to fall in the rotarod test performed at 9 and 15, and 24 weeks. The Hras$^{G12S/+}$ mice also had similar grip strength to littermate controls at 8 weeks. Interestingly, the Hras$^{G12S/+}$ mice did have a shorter latency to fall in the inverted screen test at 15-16 weeks but not at 19-20 weeks. Finally, we showed that the Hras$^{G12S/+}$ had an increased heart weight to body weight ratio at 17 weeks and 28 weeks, but not at 8 weeks, suggestive of progressive cardiomegaly. The cardiomegaly was accompanied by an increase in myocardial collagen deposition, myofibrillar disarray, and cardiac vessel hypertrophy. To further define the cardiomegaly observed in this mouse model, observed we used speckle tracking–based strain echocardiography. In female mice, we observed increased end-diastolic and end-systolic mass at 24 weeks that was not present at 8 weeks. In male mice, an increase in end-diastolic and end-systolic volumes and longitudinal and radial strain of the posterior basal wall were observed at 24 weeks but not at 8 weeks. In conclusion, Hras$^{G12S/+}$ mice have increased glial cells, decreased neurons, a mild and transient myopathy, and progressive cardiomegaly.

Functional characterization of novel germline HRAS variants

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Costello syndrome (CS) is an autosomal dominant disorder that is caused exclusively by germline pathogenic variants in the RAS family GTPase, HRAS. In most cases of CS, the causative HRAS variant is p.G12S. Several rare alterations at G12, including p.G12V, p.G12D, p.G12C, and p.G12E, are associated with the development of a more severe form of CS that is lethal in infancy. Additional variants in HRAS have been identified in patients with CS, including some designated as likely pathogenic, such as p.S89C and p.A59L. In addition, we have identified several HRAS variants using a population genomics approach, such as p.R123C and p.L133H, which are characterized as variants of unknown significance. In this study, we describe our multi-disciplinary approach toward functional characterization of these novel germline HRAS variants. The effects of the variants on HRAS intrinsic and SOS1-catalyzed guanine nucleotide exchange, as well as on intrinsic, NF1- and RASA1-catalyzed GTP hydrolysis are assessed with purified protein in fluorescence-based assays. MAPK and PI3K pathway signaling effects are evaluated in lysates of serum starved HEK293T cells transiently transfected with the variants, using AlphaLISA assays for pERK1/2, pMEK1/2, and pAKT1/2/3. The effect on cell proliferation is determined in "RASless" MEFs stably expressing only the variant HRAS. Similarly, the effect on myogenic differentiation is assessed in C2C12 mouse myoblasts. The impact of the variants on the ability of HRAS to engage effectors such as RAF1, PI3 kinase, and RALGDS is measured using live cell nanoBRET assays. Finally, the impact of HRAS variant expression on zebrafish development including early convergence and extension (CE) at the gastrulation stage is assessed using inducible transgenic lines. The results of these experiments will aid in refining the genetic classification of novel HRAS variants and provide prognostic information for patients diagnosed with CS.

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CFC Syndrome - KRAS

SHANE BAILEY

Reported by Mary Beth Bailey, Mother

Age: 12
Peru, VT, USA

Profession:
Student, 6th Grade

IN 5 WORDS:
- Funny
- Sweet
- Energetic
- Empathetic
- Curious

HOBBIES:
Being outside biking, taking walks with Daisy (dog), skiing, doing errands, anything that involves movement and being on the go!!














How Others Can Include Shane Better:

By listening. Shane's language is his own unique blend of words (some unintelligible), signs (some made up), body language and facial expressions. Shane is persistent in his communication and will not stop trying until he knows he has been understood. This can be hard for peers or people that don't know Shane and his communication style and can often lead to Shane not being heard or being left out. Also, Shane's vision is a real challenge for him so getting onto his level and allowing him to be close enough so that he can see others really benefits him. Again, this can be hard for peers and people who don't know Shane. But wow! Listening, presence and getting on the same level are probably things we all need and all could do better!!

Most Challenging Neurocognitive Issue:

Shane developed craniosynostosis, hydrocephalus and Chiari malformation as a baby. He had multiple surgeries for the Chiari, a shunt placement and 2 cranial expansions to help with the extreme pain and high pressure in his head. After 11 surgeries, Shane has been pretty much stable and headache free for over a year.

Cognitively, Shane's biggest challenge is his inability to focus, his low endurance and his short attention span, all compounded by his visual impairment. Shane is a really bright kid but we just haven't found the environment yet that suits him best and that is the most conducive for him to learn and thrive. But, I know in my heart of hearts that one does exist!

Most Challenging Cardio Issue:

Clinically Shane presents with mildly dilated left atrium, mildly aneurysmal atrial septum, mitral valve prolapse with mild regurgitation, tricuspid valve prolapse with trivial regurgitation and mild aortic regurgitation.

Things are pretty quiet on the cardio front for Shane right now. Let's leave it at that!!

Most Challenging GI/Feeding/Swallowing/Speech Issue:

For a long time when Shane was young, he didn't eat by mouth. Shane had a g-tube placed at 5 months old and he still has it. However, Shane eats everything by mouth now and he has the g-tube for hydration as needed and supplement/medications. Shane loves good food and is my constant companion in the kitchen and garden.

Shane's speech has come such a long way too. Shane had a tracheostomy when he was 14 months old and was decannulated at 4 years old. Even with the trach, Shane was not deterred from trying to speak and communicate. His communication style is his own and he still struggles with speech in general, but continues to add new words and sentences all of the time.

Most Challenging Gross Motor/Rehab Issue:

Balance and coordination are challenges for Shane as well as spatial/body awareness. His visual impairment compounds this.

Most Challenging Sleep Issue:

Shane's sleep cycle for the first 6-7 years of his life was very much like an infants - waking every 2-3 hours to be soothed or fed. After his tracheostomy, his sleep improved a bit. After his shunt placement, it improved even more. After his cranial expansion, we saw even more improvement. For the most part now, Shane sleeps well compared to the past. However, he only has a few hours of sound sleep per night and is quite restless for the remainder of the night. And... he wakes up REALLY early!

Most Unique Challenge:

extremely large, oblong eye balls making him a high risk for retinal detachment. Two years ago, Shane had a retinal detachment in his left eye followed by a spontaneous choroidal detachment in the same eye. Shane had 3 retinal reattachment surgeries which have all been unsuccessful. Shane lost the vision in his left eye and at this point relies solely on his right eye, which had been the weaker of the two. Shane's risk for retinal detachment in the right eye remains quite high.

Medical Success Story:

Shane's whole 12 year journey is a success story. Like many RAS kiddos, Shane has had 30+ surgeries (11 craniosynostosis), weeks in the hospital, countless procedures, way too many blood draws and x-rays and scans and doctor's appointments and so on... But the success of it is the pure joy and happiness that he exudes. When Shane is feeling good, he is a beacon of light and hope and joy that is contagious. People can't help but fall in love with him and his laugh and his smile. Even after 12 years of really hard medical intervention, Shane still approaches most days with an open heart, a big smile and lots of energy!!

Strengths Gained by Previous Failure:

Shane has learned how to adapt really well in certain situations. For example, how to advocate for himself in certain settings (blood draws, surgery prep) even though he has language/communication difficulties. Additionally, learning how to navigate his world with low vision and then losing vision in one eye. He didn't really seem to be affected by the loss of vision.

For me, I have learned to become a fierce advocate for Shane and to listen to and trust my intuition much more. I don't know how many times I've heard in a doctor's office, "It's probably just a bug or something" when my inner voice was telling me to press on, it's not just a bug. For a long time I ignored that voice putting my trust in docs more than myself as Shane's mom.

How Having CFC Helped Navigate Life:

Shane is extremely empathetic towards people who are sick or emotional. I am not sure if this is because of his medical history and CFC or if it is just who he is. Probably a combination of both. Shane's persistence in communication shows just how determined he is to have his voice and opinions heard and to be included in whatever is happening.

Top 3 Things that Affect Quality of Life on a Daily Basis:

1. ADHD - inability to focus, low attention span, inability to settle or take a break.
2. Skin issues - itchiness, rashes, redness/inflammation, sun allergy
3. General aches/pain (head or limbs) and fatigue

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:

We use a lot of supplementation and "food as medicine" in our house. Using these things help to make the day-to-day struggles a bit better. I would like to see this approach more accepted and supported by doctors/therapists.

How Has Having Your Child with CFC Changed Your/Your Family's Life for the Better?

Shane has opened our eyes to the beauty of being rare and the wonder of diversity and difference. We have all become more patient and accepting, more present and aware. Our days have become slower and more meaningful as we have tried to see the world through Shane's eyes and his experiences.

I would like to see treatment available for ___ because ___.

This is a really hard question to answer because every system of Shane's body has been affected at some point during his life. As with many RASopathies, it's been management of systems and symptoms.

Medications:
Shane is on no medications but does take supplements.

Medical Consultants:

- CFC Specialist/Geneticist
- Cardiologist
- Neurologist
- Neurosurgeon
- Craniofacial/Plastic Surgery Specialist
- Orthopedist
- Immunologist/Allergist
- Complex Care Specialist
- Ophthalmologist
- Retinal Specialist
- Low Vision Specialist
- PT/OT/SLP

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CFC Syndrome – MEK1

HAILEY CHAPMAN

Reported by Beth Chapman, Mother

Age: 13
Castle Rock, CO, USA

IN 5 WORDS:
- Affectionate
- Clever
- Stubborn
- Silly
- Happy














How Others Can Include Hailey Better:
Hailey loves to just be present with others. She doesn't need to play the game or do the activity, she just wants to be with people and be acknowledged by them.

Most Challenging Neurocognitive Issue:
Impaired or lack of communication

Most Challenging Cardio Issue:
Hailey's heart conditions have minimal impact on her daily life

Most Challenging GI/Feeding/Swallowing/Speech Issue:
Hailey is 100% g-tube fed and non-verbal. Lack of communication is one of the biggest challenges.

Most Challenging Gross Motor/Rehab Issue:
Hailey uses a wheelchair and has a lot of muscle tightness. It is hard to stretch her legs and keep her range of motion.

Most Challenging Sleep Issue:
Hailey has severe sleep apnea requiring Bi-PAP, and nocturnal seizures so she struggles to sleep soundly.

Most Unique Challenge:
Hailey has a lot of sensory issues and it is really challenging to regulate her sensory systems. This causes a lot of behaviors and self-injurious behavior.

Medical Success Story:
Gaining some seizure control

What new issues have cropped up in adulthood?
With puberty came seizures, increasing behaviors and self-injurious behavior, increased trouble with sleep, and generally a larger person that needs full assistance with all tasks.

How has having a RASopathy negatively impacted your life and your other family members?
In nearly every way. Having a child with such a significant disability makes everything so much more challenging. Going to the grocery store means having to push a wheelchair and a grocery cart. Going to a swimming pool means we have to hold Hailey and can't play catch with her siblings. A vacation means an entire carload or more of medical supplies.

HOBBIES:
- Snuggling
- Music
- Reading
- Dancing
- Watching Elmo

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. Lack of communication
2. Seizures
3. Self-injurious behavior

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
Self-injurious behavior and the anxiety, sensory issues and pain that cause the behaviors

How Has Having CFC Syndrome Changed Your/Your Family's Life for the Better?
Hailey has taught all of us so much patience and empathy. Hailey sees the good in everyone and loves everyone, which helps all of us see people as she does.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for CFC syndrome because Hailey deserves to feel less pain and live more comfortable.

Medications:
- Estradiol
- Norethindrone
- Glycopyrrolate
- Benzac
- Clobazam
- Trazodone
- Iron
- Baclofen
- Senna
- Melatonin

Medical Consultants:
- Cardiologist
- Ear-Nose-Throat Specialist
- Neurologist
- Endocrinologist
- Orthopedist
- Pulmonologist
- Physiatrist
- Audiologist
- Optometrist/Ophthalmologist
- Gastroenterologist
- Dermatologist

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CFC Syndrome – MAP2K2

CLIFFORD CONGER

Reported by Brenda Conger, Mother

Age: 30
Travelers Rest, SC, USA

IN 5 WORDS:
1. Helpful
2. Happy
3. An eating machine
4. Loves to dance
5. An Eating Machine

Pastime:
Attending a local Day Hab program and the YMCA RECESS Program













HOBBIES:
Riding my 3-wheel recumbent bike, going to downtown Greenville, SC to dance on Friday nights to the music on MOMA Square, hanging out with my friends from the Furman University Best Buddies Program, going out to restaurants

How Others Can Include Me Better:
I have great neighbors and local friends who do include me with their activities. My parents have taken me everywhere and actually moved to the Greenville, SC area after reading about an awesome program at the YMCA for post high school adults with diverse abilities.

Most Challenging Neurocognitive Issue:
Weak muscle tone in my legs and this prevents me from walking long distances. My balance is also poor.

Most Challenging Cardio Issue:
I am monitored every 2 years for non-progressive hypertrophic cardiomyopathy.

Most Challenging GI/Feeding/Swallowing/Speech Issue:
The weak muscles have affected my speech. I tend to slur my words and now that speech therapy ended with the school years my speech has gotten worse.

I had a feeding tube at birth and a great deal of reflux but as I aged this issue was resolved and the feeding tube was removed before I was 6 months old.

Most Challenging Gross Motor/Rehab Issue:
I have such weak leg muscles and walking for long distances or any physical activity really tires me out.

Most Challenging Sleep Issue:
As a baby I kept my parents up a great deal with sleep problems. We never really figured out what made me cry out so much and wake up. As an adult I often talk in my sleep and roll around.

Most Unique Challenge:
I have very poor vision and often cannot see well enough to get around safely in unfamiliar environments unless I have assistance.

Medical Success Story:
My parents had me tested for growth hormone deficiency and I was deficient. I was on growth hormone injections for a little over 10 years and this helped me tremendously! As I was growing up, I grew taller than my sister and mother and this helped me feel really good about myself.

Strengths Gained by Previous Failure:
As parents we really cannot answer this one. Every step along the way has been a great deal of work to ensure that Clifford's medical, educational and recreation needs are met to the fullest. It has been totally exhausting but Clifford has become a caring adult who is loved by so many people in our community.

As an adult, what do you wish the researchers to know about having CFC syndrome?
My family wishes to thank all the researchers who continued their work on CFC syndrome! They never gave up and since there is now genetic testing, more children can be identified at a younger age. The syndrome has had more recognition since the gene discoveries. Thank you!

What new issues have cropped up in adulthood?
My hearing loss has gotten worse in the past year and I will need hearing aids. The process to obtain them through the state of SC Medicaid waiver program is very difficult and there are now very few providers left that will take my Medicaid plan for this. Housing for our son has also been a huge challenge. The only reason Clifford obtained a spot in a group home was because my husband has been critically ill.

How has having your RASopathy helped you navigate life?
I am very caring and compassionate and love to help people in need.

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. My weak muscle tone
2. My vision & hearing
3. Callous growth on the bottoms of my feet


Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
Making sure that individuals with CFC syndrome are treated like a senior citizen with medical care since CFC is an advanced aging syndrome.

How has having a RASopathy changed your/your family's life for the better?
Clifford has made us better people. More caring and compassionate. We've met so many wonderful families, doctors, and community individuals because of him.

How has having a RASopathy negatively impacted your life and your other family members?
Advocating for Clifford with all his needs has taken a toll on his mother's health. The stress has resulted with medical problems. His sister has also been impacted with his near-death experiences.

Clifford will need care for life. His medical needs to be monitored as well as his programs. He does not have the adequate skills with cognition, vision, fine and gross motor to live on his own. This has created stress for his older sister who lives 12 hours away. After we are gone someone will need to check in on Clifford to make sure that his medications are administered, clothing needs are met as well as doctor and social programs are indeed being administered. We have learned that staff at the group homes do not always care to reach out to the families when things need to be updated.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for CFC syndrome because Clifford's overall quality of life would be better and he might be able to hold down a part time job.

Medications:
- Vitamin D3
- Amoxicillin 500mg prior to dental work
- Triamcinolone cream for bug bites
- XYZAL for seasonal allergies
- Flonase nasal spray for seasonal allergies

Medical Consultants:
- Dermatologist
- Primary Care Physician
- Ophthalmologist
- Cardiologist
- Ear-Nose-Throat Specialist
- Audiologist

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Costello Syndrome – G12S

CHRIS COATES

Compiled by Heather Coates Hamblin, Sister

Our family is unique. My older brother, Chris, has Costello Syndrome. The below responses were from Chris himself, and our mother. We also have a sister that had Costello Syndrome and passed away at age 2 in 1988. She was a twin, with the other twin not being born with Costello Syndrome or any genetic mutations. I have included some pictures of her to show the full picture of our family's experience with Costello Syndrome.

Age: 45
Millville, UT, USA

In 5 Words:
- Cool
- Jokester
- Inquisitive
- Thoughtful
- Spunky

HOBBIES:
Making keychains with beads, playing with our nephew, collecting Pokemon cards, playing video games, watching movies

Medications:
- Omeprazole

Medical Consultants:
- Primary Care Physician
- Cardiologist
- Sleep Specialist
- Ear-Nose-Throat Specialist

How Others Can Include Me Better:
More in-person visits

Most Challenging Neurocognitive Issue:
Chris doesn't experience significant neurocognitive concerns now. As a child, his speech was delayed, but he eventually caught up. Throughout life, he has been particularly sensitive to touch or people in his personal space, possibly as a defense mechanism, but he doesn't like people to be too close to him.

Most Challenging Cardio Issue:
Most of his life, Chris hasn't presented with any cardio issues. Recently he has had heart irregularity/murmur/tachycardia, which seems to affect his sleep quality.

Most Challenging GI/Feeding/Swallowing/Speech Issue:
Chris has an overactive gag/choking reflex while eating, and experiences regular acid reflux. He makes loud and sometimes alarming sounds as he tries to eat.

Most Challenging Gross Motor/Rehab Issue:
Chris' activity has decreased in recent years, leading to decreased muscle strength and overall motor skills, i.e. pushing himself in his wheelchair, not able to sit up in his wheelchair all day, ability to sit straight up.

Most Challenging Sleep Issue:
Chris wakes up frequently in the night, and when he his asleep he has periods of breathing hard and fast, then breathing alarmingly slow and quietly.

Most Unique Challenge:
A declining disposition as Chris ages. As he gets older, Chris' overall disposition has become crankier and less tolerant. He's quick to anger, more demanding, and less agreeable.

Medical Success Story:
Eating was really difficult for Chris and he didn't eat solid foods til he was 2 years old. Now he eats well and likes lots of different kinds of foods.

Strengths Gained by Previous Failure:
Chris was losing the ability to use his right hand, so via orthopedic surgery, a surgeon transferred one of his tendons from the front of his wrist to the back of his hand, removed 7 small bones, and fused his wrist. Since then and with physical and occupational therapy, he has developed excellent use of both of his hands, and can perform many tasks ambidextrously.

What new issues have cropped up in adulthood?
Declining vision, cardio concerns, GI concerns, unusual creases in his skull, stamina.

How has having your RASopathy helped you navigate life?
Unique person things look different than his perspective, he breaks through barriers and is friends with a lot of different people.

How has having your RASopathy negatively affected your life?
Chris' life is just different. He's not able to participate in activities or have relationships like the average person could.

Top Things that Affect Quality of Life on a Daily Basis:
1. Getting shots
2. Doctor appointments

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
Access to therapists and other providers that understand his unique case is difficult.

How Has Having Costello Syndrome Changed Your/Your Family's Life for the Better?
Chris is a unique, valued, and loved member of our family. In some ways, he keeps us young with his love of video games, movies, comics, etc. Caring for him has taught us to be more sensitive and aware of other people that are dealing with disabilities and medical concerns.

How has having your child negatively impacted your life and your other family members?
His challenges have stretched our abilities as family members and caregivers more than we ever would have thought. Caring for him and his needs has affected the overall story of our family life, but not necessarily negatively.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for eating and diet because that has been an issue his whole life.

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Costello Syndrome – G13C
FORD VARNEY

Age: 16
Blountville, TN, USA

IN 5 WORDS:
- Funny
- Caring
- Loving
- Talented
- Smart

HOBBIES:
Archery, drums, video games, weather












How Others Can Include Me Better:
Invite me to social outings

Most Challenging Neurocognitive Issue:
ADHD

Most Challenging Cardio Issue:
Potential POTS Postural Orthostatic Tachycardia Syndrome)

Most Challenging GI/Feeding/Swallowing/Speech Issue:
Cognition - reduced executive functioning skills

Most Challenging Gross Motor/Rehab Issue:
N/A

Most Challenging Sleep Issue:
N/A

Most Unique Challenge:
Reduced depth perception and seeing 3D due to strabismus.

Medical Success Story:
Failure to Thrive when little and almost needed a feeding tube, but then started to thrive on soy milk. Also my hand cord surgery helped regain balance/walking

Strengths Gained by Previous Failure:
I'm understanding information better. I've learned what to do and what not to do.

What new issues have cropped up in adulthood?
N/A

How has having your RASopathy helped you navigate life?
It's helped me realize how mild my syndrome is and how lucky I am.

How has having your RASopathy negatively affected your life?
Not being able to walk on my heels and having all my other surgeries.

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. ADHD
2. Autism
3. Anxiety

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
Difficulty with ADHD/meds

How has having a RASopathy changed your/your family's life for the better?
N/A

How has having a RASopathy negatively impacted your life and your other family members?
N/A

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for ADHD/Anxiety because I have the most issues with that.

Medications:
- Sertraline
- Adderall

Medical Consultants:
- Family Physician
- Cardiologist
- Orthopedist

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Neurofibromatosis type 1 (NF1) - p.Tyr489Cys

CARTER BELL

Age: 21
Vacaville, CA, USA

IN 5 WORDS:
- Friendly
- Genuine
- Hard working in my own way
- Loyal
- Very Passionate

HOBBIES:
Dog walking, Pizza-making, Handcrafting artisan rings

Medical Success Story:
From the age of 12 months to 11 years I would travel with a bucket or bowl because I never knew when I would throw up. Finding and ruling down the gluten allergy – because of NF, a food allergy wasn't the first thing they drew into. [The prescription] that didn't work was [for] slow motility. Gastroenterology: during a recent gastric emptying study my gastric half-emptying time was 79 minutes which was a huge improvement from 2010 when my gastric half-emptying time was 272 minutes

How Others Can Include Me Better:
eye contact, directly talking to me and making sure I understand what's happening in the conversation or that I understand the request being asked of me

Most Challenging Neurocognitive Issue:
Executive Function

Most Challenging Cardio Issue:
I don't really have any Cardio issues. I use to have heart palpations when I was little – I still have to do yearly 24 hour heart monitor

Most Challenging GI/Feeding/Swallowing/Speech Issue:
When I was younger 12mo to 11 years, I would throw up for no reason. I would travel w/ a sand bucket or a bowl to the air port, school, drs appointments. For a long time the doctors didn't know what was causing it so they had me go to speech therapy to see if that would help. Ended up being intolerant to gluten. Minimal issues now.

Most Challenging Gross Motor/Rehab Issue:
Since I was a year old. I had therapy for my low and gross motor delays. I have always been slower than my peers. However, I have been able to accomplish more than some of my teachers or doctors thought I would. Prior to surgeries – really prior to my 11th surgery I had little issue it wasn't till my 11th surgery when I lost full function of my right hand. Its slowly coming back but I still have a ways to go.

Most Challenging Sleep Issue:
When I was younger I would have night after night that I could not go to sleep. After several years we finally found a doctor that figured it was a reaction I had to a generic medication, guanfacine, I was on. Name brand I was ok. Now at the age of 21 I do have some nights that I have a hard time falling asleep but it's not as bad.

Most Unique Challenge:
The time it has taken me to recover from my last three surgeries, including some nerve damage, hand droop.

Strengths Gained by Previous Failure:
losing my job due to my executive function challenges. I am learning to go towards things I am strong in and a place that values me for who I am. Learning to concentrate on my strengths and things I really enjoy – pizza making, ring making, dog walking and the social interaction with people

What do you wish the researchers to know about having a RASopathy?
Transition from child to adult I have a hard time finding care. The understanding of what I should follow up on as an adult and how often these follow ups should happen. Bumps, understanding pain and the different type of pain, – my last three surgeries pain management during and after joint pain, inflammation – NERVE pain. As a young adult my medical issues are not always taken seriously

What new issues have cropped up in adulthood?
Difficulty of finding a job, increase of skin tumors, having to adult when I am still emotionally younger than my peers. Developmental delays that come with NF maturity is slower for me and some adults have a hard time dealing with me.

How has having a RASopathy helped navigate life?
I'm thinking answers could be, [me] are more determined, stronger, able to understand others' issues, being positive, gregarious etc.

Fearless about talking about NF, introducing myself to others with NF, being around strangers all my life – my scars is fearful of how friendly I am to strangers, no fear of needles, how I helped another person [getting a] lab draw when I was 5 years old is something I will always remember. Sadly, going to the doctors, surgery, is just part of my life. What would I do if I didn't have a doctor's appointment or surgery every 6 months. – the continued unknown – and what to follow up and how often to follow up, disadvantage to not drive on my own.

How has having a RASopathy negatively impacted your life?
I am 21 without a driver's license. It limits where I can look for work. Continued surgeries, therapy, radiation and follow up doctor visits makes me less employable.

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. Radial nerve damage that affects how I use my right hand
2. Foot and leg pain
3. Going to sleep
4. Also medical professionals' shut down or lack of knowledge, especially therapists who don't understand how to treat me.

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
1) Foot issues
2) Prep for surgery nerve pain vs after surgery
3) Good PT / OT prior to surgery to prophylactically prepare for surgery so I can be stronger in recovery

I would like to see treatment available for ___ because ___.
I would like to see treatment for the little bumps that are starting to grow because I see how adults are treated because of their bumps. The public is not kind. It would be nice to not have bumps.

Medical Consultants:
- Primary Care Doctor
- Radiology Oncologist
- Neuro Oncologist
- Neurologist
- Neurosurgeon
- Dermatologist
- Thoracic Surgeon
- Developmental Pediatrician
- Ear Nose Throat Specialist
- Plastic Surgeon
- Gastroenterologist
- Physical Therapist
- Occupational Therapist
- Speech Therapist
- Nephrologist
- Integrative Medicine
- Cardiologist
- Optometrist/Ophthalmologist
- Neuro-ophthalmologist

Medications
No prescriptions, just supplements
- Omega 3
- Pro biotic
- Glutamine
- Digestzyme
- Vitamin D
- Transfer Factor

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Neurofibromatosis type 1
ELANA LOFTSPRING

Age: 25
Houston, TX, USA

Profession:
Corporate Communications

IN 5 WORDS:
- I am a unique woman

HOBBIES:
Travel, puzzles, cooking

How Others Can Include Me Better:
Appreciate my differences and accept me how I am.













How has having your RASopathy helped you navigate life?
I have been able to be part of a community that accepts and appreciates me how I am. I have learned how to advocate for myself, too. Because of my struggles, my successes are sweeter.

How has having your RASopathy negatively affected your life?
It has made me feel different, often in a negative way, so I sometimes feel lonely. I also had to work harder, academically.

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. My anxiety about how my NF may progress
2. My social isolation
3. My wish to be accepted in all aspects of my life

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus On More:
Social challenges

Most Challenging Neurocognitive Issue:
My rigidity

Most Challenging Cardio Issue:
N/A

Most Challenging GI/Feeding/Swallowing/Speech Issue:
N/A

Most Challenging Gross Motor/Rehab Issue:
N/A

Most Challenging Sleep Issue:
Don't always sleep through the night

Most Unique Challenge:
I have trouble making friends and fitting in socially. I also struggle with anxiety and depression.

Medical Success Story:
I had a brain tumor removed right when I turned 12.

Strengths Gained by Previous Failure:
I am resilient despite my medical and emotional challenges.

As an adult, what do you wish the researchers to know about having Noonan syndrome?
The struggles continue, though they may look differently than they did when I was a child. Sometimes they are not evident at all to outsiders, and that presents its own challenges.

What new issues have cropped up in adulthood?
I have recently discovered that I have a dilated pulmonary artery. I am not sure how am seeing more and more neurofibromas. I am also having more tests (like a neuroimagram earlier than recommended for most).

How Has Having Noonan Syndrome Changed Your/Your Family's Life for the Better?
N/A

How has having your child negatively impacted your life and your other family members?
N/A

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for NF because I don't want people to suffer and believe everyone is entitled to a positive quality of life.

Medications:
- Trazodone (for sleep)

Medical Consultants:
- An NF Specialist once a year besides other "regular" doctors

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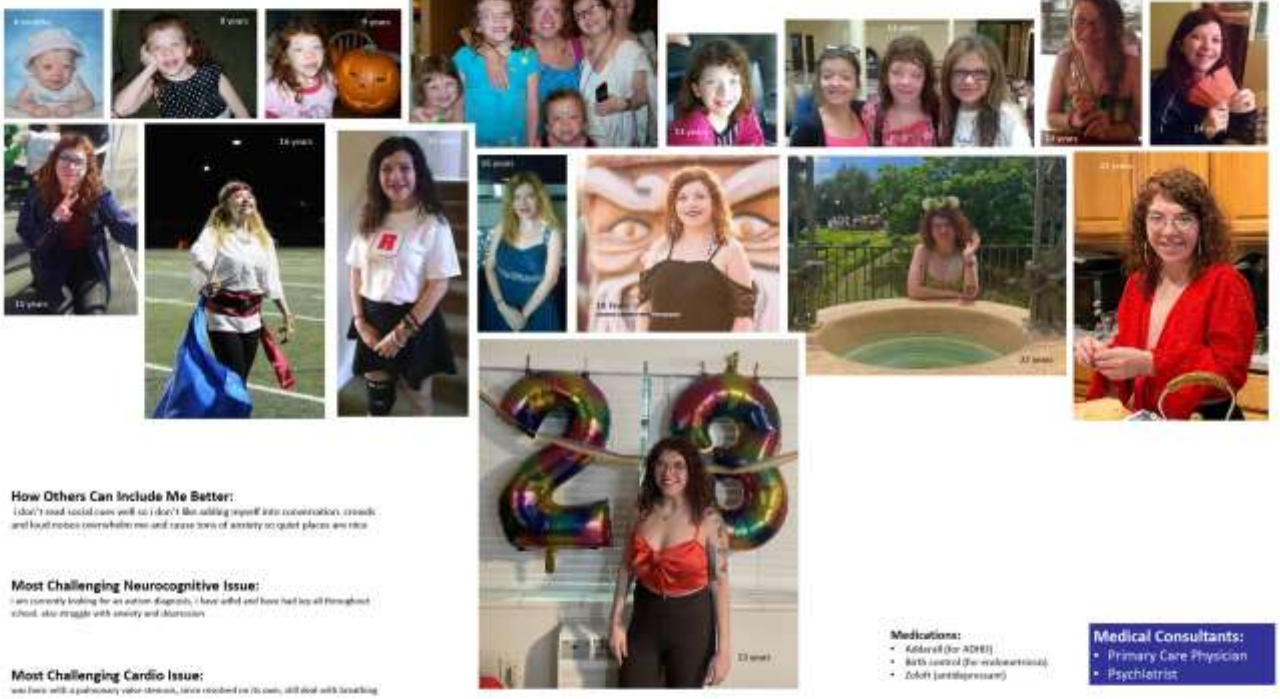
Noonan Syndrome – PTPN11
GRACE MAYR

Age: 23
Littleton, CO, USA

Profession:
Nail Technician

IN 5 WORDS:
- Strong
- Caring
- Funny
- Advocate
- Lover

HOBBIES:
Weightlifting, listening to Taylor Swift, meditating



How Others Can Include Me Better:
I don't read social cues well so I don't like adding myself into conversation, crowds and loud noises overwhelm me and cause tons of anxiety so quiet places are nice

Most Challenging Neurocognitive Issue:
I am currently looking for an autism diagnosis, I have adhd and have had iep all throughout school, also struggle with anxiety and depression

Most Challenging Cardio Issue:
was born with a pulmonary valve stenosis, since resolved on its own, still deal with breathing issues

Most Challenging GI/Feeding/Swallowing/Speech Issue:
constipation as a child, failure to thrive, doctors wanted me on a feeding tube as a baby but I ended up just vomiting it, severe reflux but has gotten better over time, speech therapist from age 18 months to 6 years

Most Challenging Gross Motor/Rehab Issue:
my walking and crawling was delayed as a baby, physical therapy when I was a baby to school age, did OT in elementary school, not great coordination but has gotten better with age

Most Challenging Sleep Issue:
growing up I would get chronic leg pain every night which caused me to wake up constantly throughout the night, starting growth hormone at age 10 helped with chronic pain so it stopped

Most Unique Challenge:
endometriosis since 2018, I've had one surgery so far and am still dealing with it every single day

Medical Success Story:
pulmonary valve stenosis resolved on its own, starting growth hormone from age 10-14 helped with my chronic pain, almost has gone away completely but still affects me sometimes

Strengths Gained by Previous Failure:
because of my social struggles I've developed a ton of empathy towards others and relate to people so much as I can, also because of my learning disabilities, I have taught myself different ways to manage money, understand credit and budget

What do you wish the researchers to know about having Noonan syndrome?
I wish the researchers understood the individual differences in how Noonan Syndrome expresses itself with each of us, just all of us are affected the same way

What new issues have cropped up in adulthood?
endometriosis is a new one for me, it affects me every day it's a large struggle on top of chronic pain it definitely makes it worse

How has having your RASopathy helped you navigate life?
I got diagnosed with Noonans when I was 3 and my parents have been very open and candid about my syndrome and how it's effected my life, because I've known from a young age it's really helped me become more of an advocate for myself and others and has helped me understand what about me is different because most of it isn't physical and you can't see it

How has having your RASopathy negatively affected your life?
growing up was always a struggle, being different but also being able to mask myself and behave "properly" didn't really help me, kids were mean growing up because of the way I looked or acted sometimes, it got better when I went into high school and found a good group of friends but having a rare disorder that people can't physically see is hard for people to understand at times

Medications:
- Adderall (for ADHD)
- Birth control (for endometriosis)
- Zoloft (antidepressant)

Medical Consultants:
- Primary Care Physician
- Psychiatrist

Top Things that Affect Quality of Life on a Daily Basis:
1. Chronic pain – still affects me weekly with random pain and constant soreness, I'm good about resting when it flares up so it doesn't mess with my work but it's hard to work through
2. Endometriosis is definitely the thing that affects me most daily it's pretty constant and can be severe sometimes I can't move or walk
3. Bending over also also hurts and that's what my entire job is
4. Anxiety also affects my quality of life, makes it hard for me to get out there and make friends

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
chronic pain is definitely the biggest thing day to day there's no real causes for it only things that tend to flare up the pain

How Has Having Noonan Syndrome Changed Your/Your Family's Life for the Better? (Answered by my mom, Kelly Mayr)
this opened [our] eyes to the special needs community. We have made lifelong friends and learn so much because of that. Because of these connections, we were on to adopt another child with a different disability. If we weren't already connected to the special needs community, I don't know if we would've done that.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for chronic pain because it's so hard to plan about your everyday life and have to mask the fact you are in pain, no one should have to live in pain all the time.

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Noonan Syndrome – PTPN11
MATTHEW BALTES

Age: 39
Troy, OH, USA

Profession:
5th Grade Science Teacher

IN 5 WORDS:
- Patient
- Self-improving
- Determined
- Introverted
- Empathetic

HOBBIES:
Watching sports, reading, going to museums, being with the family

How Others Can Include Me Better:
I am an introvert and lack self-confidence in new situations. It sometimes just takes someone to include me, but once people get to know me and I feel comfortable I will start to open up.

Strengths Gained by Previous Failure:
I feel that my difficulties, especially with feeding, when I was younger helped me to continue to keep trying and to not give up. It has helped me to be determined and I feel that it has helped me to not give up on any student that I teach. It was challenging to get to the point where I would try new foods and eat enough to thrive. Many other things have been hard such as learning to drive, going away to college, or living on my own after college. I am so thankful that I am able to have a family and that I am able to provide for all of their necessities of life. It is such a rewarding feeling.

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
I would say that being very self-conscious and having anxiety are two things that I wish weren't as challenging when I was growing up. I still have anxiety, but it isn't as severe as it was.

How Has Having Noonan Syndrome Changed Your/Your Family's Life for the Better?
My son has brought so much joy to our family. He makes us smile and every obstacle that he overcomes is so much more rewarding. We are so very proud of all his accomplishments. He is able to read at an advanced level and can count. He loves to make us smile and laugh. He is determined to try his best. He loves to learn new things and wants to learn about anything related to science or the world around him. He is very good at remembering facts.

Most Challenging Neurocognitive Issue:
I have had a few cases of syncope. I can get dizzy if I get up too fast. Sometimes, I can feel dizzy if I look up too fast as well. It only happens some of the time.

Most Challenging Cardio Issue:
It has always been challenging for me to run for long distances and to keep up with others. My dad is a very hard worker and it has always been hard for me to keep up with him.

Most Challenging GI/Feeding/Swallowing/Speech Issue:
I still have a gag reflex to certain smells and I have a challenging time at the dentist or doctor when they need to look inside my mouth.

Most Challenging Gross Motor/Rehab Issue:
My most challenging gross motor issue is jumping rope. This includes jumping with both feet at the same time and the stamina to keep going. I also find it challenging to walk down stairs without looking at where my feet are going.

Most Challenging Sleep Issue:
I sometimes have trouble staying asleep. I can usually get to sleep pretty easily, but I will wake up at least a few times during the night.

Most Unique Challenge:
Blowing up a balloon is one thing that I have tried over and over again.

Medical Success Story:
I had a g-tube from age 1 ½ to age 18. I just never ate enough during the day. I would be on a night time feed and get about half of my calories at night during my elementary and middle school years. The smells of many foods would cause me to gag. I didn't like crunchy foods or foods with strong smells. When I was a Senior in high school I was able to have the g-tube officially removed because I was eating enough.

As an adult, what do you wish the researchers to know about having Noonan syndrome?
I was really self-conscious about the way I looked and having a g-tube. I also felt self-conscious about being short. I was able to get growth hormone which helped me to grow taller than what I would have been.

What new issues have cropped up in adulthood?
I have recently discovered that I have a dilated pulmonary artery. I am not sure how long it has been a problem. I also found out in the last few years that I am allergic to dust and mold.

I also had to have surgery in both eyes in September. The angles of my eyes were closing and this could have created some serious eye issues.

How has having your RASopathy helped you navigate life?
I really feel that having Noonan Syndrome has allowed me to have more empathy toward others and their situations. There are many issues that people face everyday that are out of their control. There are many things that I can't control, but I can control how I respond to those events. My parents did a good job of teaching me to be thankful and that my situation could also be worse. It has taught me to be thankful. I am glad that life isn't always easy or I think I would take a lot of things for granted.

How has having your RASopathy negatively affected your life?
I do think that having Noonan Syndrome has caused me to have a lot of anxiety. I am not as confident as I would like to be. I can be hard on myself at times and I would like things to be easier than they are, but I do feel that the challenges overall have made me a more compassionate person.

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. Anxiety
2. Allergies
3. Loose stamina

How has having your child negatively impacted your life and your other family members?
My son, Jonathan, also has Noonan Syndrome. I used to feel guilty a lot that he had Noonan syndrome, especially knowing that I was the reason that he has Noonan Syndrome. I know he has a lot of difficulties and challenges that he faces and will face in the future. But, I am also thankful that he has some challenges, because I am hopeful that it will help him to be a better person just as I feel that having Noonan Syndrome has helped me to be a better person. I appreciate all of the sacrifices that my wife has made. She is a stay-at-home mom in order to help give Jonathan the care he needs. Jonathan has needed a lot of intensive care to get him to be the person that he is today. He gets all of his food through his g-tube. He gets two feeds during the day and a long feed throughout the entire night. I feel very blessed to be a dad to such a wonderful little guy.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for Noonan syndrome because there are many people with Noonan Syndrome that have severe feelings of issues, and heart issues. I don't want anyone to have to suffer. Life is so much more fun when I see others reaching their potential and when they are filled with joy.

Medications:
- Zyrtec
- Azelastine nasal spray
- Zoloft
- Wellbutrin
- Multi-vitamin
- Flonase

Medical Consultants:
- Cardiologist
- Neurologist as needed
- Allergist
- Family Doctor
- Optometrist
- Geneticist

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Noonan Syndrome – PTPN11 c. 1510A>G (p. Met504Val)

JONATHAN BALTES

Reported by Melissa Baltes, Mother

Age: 6
Troy, OH, USA

IN 5 WORDS:
- Intelligent
- Fast
- Great at Climbing
- Curious
- Reader

HOBBIES:
Reading anything non-fiction and/or Science-related, learning and sharing facts with others, drawing, bird watching, making nature collections, playing outside, going to zoos and museums, playing games on the tablet, watching TV

Medications:
- Milk of Magnesia
- Periactin (cyproheptadine)
- Vitamin D3
- Probiotic
- Flovent inhaler for respiratory illness
- Tranexamic acid and other hematologic meds for surgeries

How Others Can Include Jonathan Better:
Invite me to play because I may be too shy to join in on my own.

Most Challenging Neurocognitive Issue:
Distractibility and attention difficulties

Most Challenging Cardio Issue:
None day-to-day, but I do not like getting my occasional echoes. They tickle me.

Most Challenging GI/Feeding/Swallowing/Speech Issue:
Totally relying on getting food through my g-tube because I am extremely sensory sensitive when it comes to food.

Most Challenging Gross Motor/Rehab Issue:
Navigating playgrounds or group exercise activities

Most Challenging Sleep Issue:
Mild obstructive sleep apnea

Most Unique Challenge:
Swinging on a swing set

Medical Success Story:
I have accomplished so much through my 3 years of special needs preschool! I am so much more independent, can express my needs and emotions well, have made huge academic gains, and am better at communicating and interacting with grown-ups and kids!

Strengths Gained by Previous Failure:
I am so much more persistent and confident now that I have worked so hard to get where I am!

How Has Having Noonan Syndrome Helped Navigate Life:
I am resolute to do things on my own and am a great cheerleader when I see others struggling with a task.

How Has Having Noonan Syndrome Changed Your/Your Family's Life?
SO MANY DOCTOR AND THERAPY APPOINTMENTS

Top 3 Things that Affect Quality of Life on a Daily Basis:
1. G-tube reliance
2. Sensory processing difficulties
3. Struggling to maintain attention when it is important

Major Day-to-Day Issues You wish Doctors/Therapists Would Focus More On:
As a baby and up to preschool age, I vomited so often when I was fed orally and through the feeding tube and could only tolerate a very small volume of food at one time. I would love if clinicians and researchers would be able to pinpoint the cause of the many GI difficulties in children with RASopathies so that better medications or treatments can be developed to help us.

How Has Having Noonan Syndrome Changed Your/Your Family's Life for the Better?
Jonathan is our miracle kiddo! Parenting him has taught us a lot that we otherwise may not have learned. He makes us laugh often, is so full of knowledge, and just loves life and wants to be the best kid he can be. We are in awe of the big kid he is becoming!

How has having your child changed your family's life for the better?
Jonathan is our miracle kiddo! Parenting him has taught us a lot that we otherwise may not have learned. He makes us laugh often, is so full of knowledge, and just loves life and wants to be the best kid he can be. We are in awe of the big kid he is becoming!

How has having your child negatively impacted your life and your other family members?
Managing travel and appointments, medical equipment, insurance and social services and programs, IEP meetings, and the daily medical and behavioral ups and downs of symptoms and treatments have been demanding and emotionally taxing.

I would like to see treatment available for ___ because ___.
I would like to see a treatment available for frequent vomiting because it was one of the most worrisome symptoms to manage when Jonathan was a baby.

Medical Consultants:
- Gastroenterologist
- Hematologist
- Cardiologist
- Developmental and behavioral pediatrician
- Orthopedist
- Neurologist
- Neurosurgeon
- Geneticist (RASopathy Clinic)
- Pulmonologist
- Endocrinologist
- Ear-Nose-Throat
- Audiologist
- (used to see Urologist)

PARTICIPANT BIOGRAPHIES

Gregor Andelfinger, MD, PhD (CHAIR; MODERATOR; SPEAKER)

Gregor Andelfinger is Professor of Pediatrics at Université de Montréal, where he also holds the Banque Nationale Research Excellence Chair in Cardiovascular Genetics. He is a pediatric cardiologist at CHU Sainte Justine, with interest in the genetic causes of valve disease and rare diseases. In recent work, he has focused on therapies for rare diseases, in particular in patients with RASopathies using MEK inhibition. The overarching goal of his research program is to define novel diagnostic and therapeutic avenues in pediatric cardiac patients through the use of genetics.

Dr. Andelfinger's work has been recognized by all major funding agencies, including the CIHR, FRQS, Heart and Stroke Foundation of Canada, FRSQ, Canadian Foundation for Innovation, Fondation Leducq and others. He is regularly involved in patient advocacy and serves as a board member for several journals and advocacy groups. gregor.andelfinger.med@ssss.gouv.qc.ca

April Anschutz (NOONAN SYNDROME ADVOCATE)

April Anschutz (she/her) was born in 1969, shortly after the syndrome with which she lives, became a diagnosable disease. She was two months early, weighed under 4lbs, had a heart murmur, collapsed lung, webbed neck, inferior pectus excavatum, a bleeding disorder and malformed palate. April went undiagnosed for a few years, but dealt with feeding, and sleeping problems as well as slow physical development, until her parents created their own feeding system, during her second year.

As a youth and teen she suffered from multiple throat and ear infections, dental issues causing multiple dental surgeries and had problems with keeping up physically with her peers. At around 8 years old, April became part of a study on Noonan Syndrome through John Sealy Hospital in Galveston, TX. She would have bi-annual EKGs, bloodwork, physical exams, intellectual and hormonal testing as well as treatment, and early puberty consultation. Her passion and voice for self-advocacy began when she demanded a female doctor during puberty thus ending the interminable intern observations and examinations.

As an adult, April's health has been demanding and eye-opening. At 31, April began 20+ years of increasing health issues; including two heart surgeries, a pacemaker, ablations, fractures, heart failure, breathing issues and most recently osteoporosis and vocal dysphonia. Due to these obstacles, she has a greater commitment to self-advocacy and a deeper involvement in the Noonan and RASopathy communities.

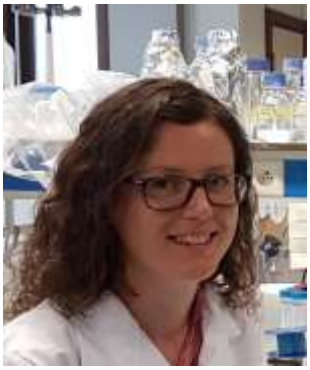
With her new role as part of the Communications team for RASnet, she has been involved with their Giving Tuesday Campaign & has taken the lead in a new initiative to connect international family support groups. She helps adults with NS via the Adults With Noonan Syndrome FB group, shares her experiences & gives support to parents of those with RASopathies & provides education to her doctors and various therapists, on NS, to raise awareness. april.anschutz@gmail.com

Anton Bennett, PhD (CHAIR; MODERATOR)

Dory's McConnell Duberg Professor of Pharmacology and Professor of Comparative Medicine; Interim Chair, Department of Pharmacology; Director, Yale Center for Molecular and Systems Metabolism; Director, Minority Affairs Yale BBS Graduate Program

Dr. Anton Bennett graduated with an undergraduate degree in Biochemistry from Sir John Moore's University in Liverpool, U.K. in 1988. He moved from the U.K. to the U.S. shortly after to work with Dr. Gary M. Williams at the American Health Foundation and he matriculated with a Ph.D. from the Department of Pathology at New York Medical College in 1993. For his Ph.D. graduate work Dr. Bennett studied how non-genotoxic carcinogens caused liver cancer. Following his Ph.D., he joined the laboratory of Dr. Benjamin Neel at the Beth Israel Hospital and Harvard Medical School in Boston in 1993 for his post-doctoral fellowship. In the lab of Dr. Neel, Dr. Bennett first began work on a new family of enzymes known as protein tyrosine phosphatases. He continued working on protein tyrosine phosphatases when he went to work with Dr. Nicholas Tonks at Cold Spring Harbor Laboratory, New York in 1996. Dr. Bennett joined the faculty at Yale University School of Medicine in the Department of Pharmacology as an Assistant Professor in 1998. Dr. Bennett is currently a tenured professor in the Department of Pharmacology and has a joint professorship in the Department of Comparative Medicine. He is the Director of the Yale Center for Molecular and Systems Metabolism. Dr. Bennett is actively involved in promoting underrepresented groups in the biological sciences and is the Director of Minority Affairs for the Ph.D. Program in the Biological and Biomedical Sciences. He is also the training grant director for the graduate program in Pharmacology in his department. Dr. Bennett has continued his research in the area of protein tyrosine phosphatases which is the focus of his laboratory. Dr. Bennett's research provides insight into the signaling pathways regulated by protein tyrosine phosphorylation, which serves as a fundamental mechanism for the control of virtually all biological processes. When the regulation of phosphate group removal by protein tyrosine phosphatases on certain substrates is disrupted, this can cause human disease. As such, protein tyrosine phosphatases have been directly linked to a variety of human diseases such as cancer, diabetes, neurological and cardiovascular diseases. Dr. Bennett's lab investigates how protein tyrosine phosphatases are involved in various human diseases and whether, once identified, if these enzymes can be targeted for therapeutic purposes. Currently, Dr. Bennett's lab is focusing on the links between protein tyrosine phosphatases in metabolic diseases and a rare genetic disorder called Noonan syndrome. anton.bennett@yale.edu

Sarah Borrie, PhD (SPEAKER, EARLY STAGE INVESTIGATOR)



Sarah Borrie (she/her) obtained her PhD in neuroscience at the Medical University of Innsbruck, Austria. She carried out postdoctoral research at the Centre for Human Genetics at KU Leuven, Belgium, with Prof Eric Legius and Prof Hilde Brems where she focused on modeling and pharmacologically targeting behavioral aspects of RASopathy disorders. She is currently a senior scientist in the laboratory of Prof Bart De Strooper at KU Leuven. sarahborrie@kuleuven.be

Benjamin Briggs, MD (SPEAKER)

My academic career started at the University of Maine where I studied chemistry. I then went to the University of Vermont for medical school and was part of the Health Professions Scholarship Program through the United States Navy. Since graduating medical school I have served with the Navy attending Pediatric Residency at the Naval Medical Center San Diego. After serving as a General Pediatrician for 3 years I was selected for full time outservice fellowship in Pediatric Hematology and Oncology at the University of California San Diego.

I first became interested in understanding bleeding disorders in Noonan syndrome in my third year of medical school while on pediatric clerkship. I was admitting a one year old female pre-operatively for pulmonary valve stenosis repair and during the admission her mother came to me with a stack of printed abstracts which supported her concern that her daughter, who had Noonan Syndrome, was at risk of having bleeding complications from the upcoming surgery. I had never heard of Noonan syndrome before let alone any association with bleeding disorders. I read the abstracts and found the associated papers, which confirmed the mother's concern. I brought this to the team during rounds and we initiated a bleeding workup identifying a deficiency in Factor XI allowing for enactment of a perioperative hemostatic management plan.

Based on my reading of these manuscripts I found that there were no comprehensive reviews outlining what was currently known about the association between NS and bleeding disorders, so I set myself to this purpose. After publishing this work I was approached by the Noonan Syndrome Foundation who invited me to come speak at their biennial conference. It was here while meeting a community of patients with Noonan syndrome and their families that I found a continued unmet need and have continued to spend my career working to better understand bleeding disorders in Noonan syndrome. It was this goal that led me to choose sub-specialization in Pediatric Hematology and Oncology.

During fellowship I joined the Rady Children's Institute of Genomic medicine, which specializes in rapid whole genome sequencing, and was able to participate in multiple scholarly works in addition to the study of NS. Based on my prior research and work with the Noonan Syndrome Foundation I had hypothesized that the association between Noonan syndrome and bleeding disorders was under recognized and therefore under evaluated. Using a retrospective review, we identified 101 patients with NS, 70 of whom required surgery for a total of 164 procedures. Nine patients (9/70; 12.8%) had bleeding complications, occurring in those without comprehensive testing or perioperative intervention and undergoing major or dental surgery. Based on these findings, the risk of a bleeding complication for patients with Noonan syndrome who did not have comprehensive testing or perioperative intervention was 6.2% (95% CI 2.3%-10.1%), indicating the number needed to treat or screen would be 16 to prevent 1 bleeding complication (95% CI 9.9-43.9). The majority of patients had either no or incomplete evaluation (59 of 101; 58.4%).

The finding of this work launched a prospective cohort study in which we enrolled twenty participants 12 of whom completed clinical and laboratory evaluation with five meeting the definition for bleeding phenotype. Four of the five participants with a bleeding phenotype had platelet aggregation defects and at least one additional coagulation defect. Thromboelastography was performed in nine participants, four with bleeding phenotype and five without, and results were normal in all cases. BBriggs@rchsd.org

Emma Burkitt-Wright, MBChB, PhD, MRCP (PANELIST)

Emma Burkitt Wright (she/her) has been a consultant clinical geneticist in Manchester Centre for Genomic Medicine (MCGM) since 2015. She offers a specialist interest clinic for patients with Costello, CFC and Noonan syndromes, being involved with patient support networks for people with these conditions and is the Research and Development lead for Manchester's NHS England nationally commissioned highly specialised service for complex neurofibromatosis type I.
She graduated in medicine (MBChB with Honours and intercalated MPhil in Clinical Psychology) from the University of Liverpool in 2002 and started higher specialist training in clinical genetics in MCGM in 2006, as the first NIHR academic clinical fellow in clinical genetics in the UK. Clinical training included clinics with Professor Bronwyn Kerr (focussing on Costello, CFC and Noonan syndromes), Dr Sue Huson and Professor Gareth Evans (focussing on NF1). Her research has included 5 months with Professor Mariano Barbacid's group at the Spanish National Cancer Centre, helping to characterise the first B-Raf mouse model of cardio-facio-cutaneous syndrome (CFC) (Urosevic et al, *PNAS*, 2011). Her PhD (awarded 2014) with Manchester Biomedical Research Centre and Wellcome Trust Research Training Fellowships (2009-2013), focussed on de novo germline disorders of the Ras-MAPK pathway, in particular CFC syndrome, and she has an ongoing observational study of patients with these conditions. She is co-ordinating the revision of European consensus management guidance for people with Noonan syndrome spectrum conditions, and as training programme director for Clinical Genetics in North West England, she is trying to ensure that the next generation of UK clinical geneticists are enthused and informed about Ras-MAPK pathway disorders. Emma.Burkitt-Wright@mft.nhs.uk

Pau Castel, PhD (MODERATOR; SPEAKER)

Dr. Pau Castel (he/his) is an Assistant Professor at the Department of Biochemistry and Molecular Pharmacology at the New York University School of Medicine. Dr. Castel performed his graduate work at Memorial Sloan Kettering Cancer Center under the supervision of Dr. José Baselga and undertook postdoctoral studies at the University of California San Francisco in the laboratory of Dr. Frank McCormick. His research is aimed at understanding the molecular mechanisms underlying oncoprotein transformation in cancer and congenital disorders, including RASopathies and the neurofibromatoses. His laboratory employs biochemical, signal transduction, and mouse genetics to study oncoproteins of the Ras-MAPK and PI3K pathways with the goal of developing rational-based therapies for these disorders. Pau.Castel@nyulangone.org

Ion Cirstea, Dr. rer. nat. (SPEAKER)

Institute of Comparative Molecular Endocrinology (CME), Ulm University (DE); Principal investigator - Dysregulated cellular signaling and biological processes in RASopathies. Ion Cristian Cirstea is biochemist and cell biologist who focuses on regulation on RAS signaling. He works on the identification of the molecular and cellular bases of dysregulated biological processes associated with RASopathy pathophenotype, as well as on the identification of novel regulators of RAS function. ion.cirstea@uni-ulm.de

Fieke Draaisma, MD (SPEAKER, EARLY STAGE INVESTIGATOR)

Fieke Draaisma (she/her) is a young enthusiastic health care professional who is currently working at the neonatal intensive care unit of the Radboud University Center in Nijmegen, the Netherlands. Here she gains experience with a diverse patient population, among which patients with congenital hereditary defects. In the beginning of 2023 she got involved in the research in patients with Noonan syndrome and Noonan syndrome related disorders. Many of them experience pain, although the cause of this pain is unknown. Recently, she published her first case series on this subject and there is more yet to come! Besides her work as a clinician Fieke is committed to diversity, inclusion and equality. In her role within the diversity and inclusion board of the Dutch Association of Pediatrics she advocates for making the Dutch health care system more diverse and inclusive for both caregiver and patient. In her free time Fieke enjoys being outside: walking, running or riding her bike. fieke.draaisma@radboudumc.nl

Michelle Ellis (MODERATOR, NOONAN SYNDROME ADVOCATE)

Michelle Ellis is an adult with NS who first heard of NS when she was diagnosed in Belgium at the age of 17. She was actively supporting The Noonan Syndrome Support Group, assisting with their family conferences, working with the researchers and setting up the UK chapter, Noonan UK. She has worked with the Genetic Alliance UK, and is a founding member of the RASopathies Network UK. After merging with RASopathies Network USA, Michelle has been an enthusiastic advocate advisor, including helping with planning our symposia, & in addition, of late, strategic communications & fundraising. Michelle has presented in the USA, the UK, and the Netherlands. Her message to parents, people with NS, doctors and researchers continues to be "Although NS can and does present challenges, if you are determined and positive, there is very little that you can't do. It is part of who we are but it shouldn't define us." Michelle firmly believes Knowledge IS Power. mellis@rasopathiesnet.org

Vanessa Fear, PhD (SPEAKER)

Telethon Kids Institute, Centre for Child Health Research, The University of Western Australia. I am the current position as Head, Translational Genetics, with over 15 years of expertise in molecular biology and genetic engineering (including CRISPR), as well as a depth of research expertise in cell biology, virology, and immunology. My current research is focused on CRISPR gene editing for rare disease patient genetic variants with development of disease models which include differentiation to neural, cardiac, kidney, bone, and lung tissue. Vanessa.Fear@telethonkids.org.au

Elisabetta Flex, PhD (SPEAKER)

Staff-scientist, Group leader of the Functional Genomics Unit, Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy; Member, Editorial Board, Frontiers in Genetics (section "Genetic Disorders"); Member, Italian Society of Human Genetics (SIGU).

In the last decade, my scientific activity has been directed to understanding the disease mechanisms underlying human genetic disorders affecting development and growth, and molecular processes contributing to hematological malignancies. In particular, my

research has contributed to the identification of novel disease-genes implicated in RASopathies (*i.e., NRAS, RRAS, RRAS2, MAPK1*), as well as to the understanding the molecular and cellular mechanisms underlying these disorders, with particular attention to LEOPARD and Noonan syndromes. My work also contributed to the identification and functional characterization of disease genes involved in severe unrecognized rare disorders characterized by multiple malformations, early-onset neurodegeneration, defects of neurodevelopment, and premature aging (*i.e., ATP6V1B2, KCNH1, TBCD, TBCE, HIST1H1E, VPS4A, KIF5B*). Actually, my research activity is aimed at defining the metabolic profile of Costello and cardiofaciocutaneous syndromes (CFC), two developmental disorders clinically related to Noonan syndrome, and to understanding the mechanisms underlying several issues characterizing these conditions as poor growth, muscle-skeletal anomalies and reduced bone mineral density.

I have extensive expertise in functional genomics and for my research activity I use a broad variety of experimental approaches utilizing both patients' derived cell lines and transduced/transfected cellular models. elisabetta.flex@iss.it

Megan Frone, MS, CGC (SPEAKER)

Megan Frone, MS, CGC, (she/her/hers) is a board-certified genetic counselor with the Clinical Genetics Branch of the National Cancer Institute in the Division of Cancer Epidemiology and Genetics. She received her Bachelor of Science in Cell & Molecular Biology from SUNY Binghamton University in 2008 and her Masters in Genetic Counseling from Virginia Commonwealth University in 2010 where she also graduated the Virginia Leadership Education in Neurodevelopmental Disabilities (Va-LEND) program. Prior to joining the NIH, Megan worked as an Adult and Pediatric Cancer Genetics Counselor at UT Southwestern Medical Center in Dallas, TX, and in the Inborn Errors of Metabolism and Pediatric Genetics Clinics at Childrens Health, Dallas. At the NIH, Megan serves as a Genetic Counselor for RASopathies Natural History study as well as the Li Fraumeni Syndrome Study. Megan has specialty interest and expertise in variant annotation and classification which is the primary focus of her research within DCEG. She also serves as the Coordinator of the ClinGen TP53 Variant Curation Expert panel. megan.frone@nih.gov

Bruce D. Gelb, MD

(SPEAKER; NS & NSML FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Bruce D. Gelb, M.D. (he, him, his) is Dean for Child Health Research and Director and Gogel Family Professor of the Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai. He is Professor of Pediatrics and Genetics and Genomic Sciences. He oversees an extensive program in gene discovery for congenital heart disease as well as in pediatric precision medicine. He is Director of the Mindich Child Health and Development Institute, which he helped found in 2009. He is the President Elect for the American Society of Human Genetics, the former President of the American Pediatric Society and an elected member of the American Society for Clinical Investigation and the National Academy of Medicine. bruce.gelb@mssm.edu

Tamar Green, MD

(SPEAKER, EARLY STAGE INVESTIGATOR, NS & NSML FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Dr. Green, an MD graduate from Ben Gouin University, is a child psychiatrist trained at Tel Aviv University and has completed her postdoctoral studies in neuroscience at Stanford University. She currently serves as an Assistant Professor at Stanford's Department of Psychiatry and Behavioral Sciences and leads the Brain Imaging, Development, and Genetics (BRIDGE) Lab.

Funded primarily by NIH grants and acknowledged through prestigious awards such as the Francis S. Collins Scholar and the Stephen Bechtel Endowed Faculty Scholarship, Dr. Green's work is centered around neurodevelopmental disorders. Her area of interest lies in Rasopathies, syndromes caused by mutations in the Ras/MAPK genes, including conditions such as Noonan syndrome and Neurofibromatosis 1.

In a "genetic first" approach to neuropsychiatry, Dr. Green and her team are exploring how these genetic mutations influence cognitive and social functions such as attention, memory, and social skills. By utilizing advanced brain imaging technologies, they aim to uncover the brain-related changes brought about by these genetic disorders. This in-depth research seeks to forge a link between genetic alterations and their implications in neuropsychiatry. tgreen2@stanford.edu

Karen Gripp, MD (MODERATOR, COSTELLO SYNDROME FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Karen W. Gripp, MD (she/her/hers) is the Chief of the Division of Medical Genetics at the Nemours Childrens' Hospital in Wilmington, DE. She is a Professor of Pediatrics at the S. Kimmel Medical College at T. Jefferson University. She is board certified in pediatrics and clinical and clinical molecular diagnostic genetics. Dr. Gripp serves as medical director for the Genetic Testing Stewardship Program and the Molecular Diagnostic Laboratory at Nemours. Her areas of clinical expertise include dysmorphology and RASopathies. Costello syndrome is the focus of her research and she is closely involved with the Costello syndrome family support network as the co-director of the professional advisory board. Her professional activities include participation in the ClinGen expert panels on RASopathies and on inherited cancer predisposition, and organization of the "D.W. Smith Workshop on Malformation and Morphogenesis". Dr. Gripp is the VP Clinical Genetics for the American College of Medical Genetics and Genomics. Karen.Gripp@nemours.org

Sattar Khoshkhoo, MD (SPEAKER, EARLY STAGE INVESTIGATOR)

Sattar (he/him/his) is an Instructor in the epilepsy division and the director of the epilepsy genetics clinic at Brigham and Women's Hospital. He completed his medical training at UCSF where he studied the cellular mechanisms of focal epilepsies as an HHMI-CURE fellow. Sattar then moved to Boston for neurology residency at Mass General Brigham and his epilepsy training at Brigham and Women's Hospital and Boston Children's Hospital. During residency he joined the laboratory of Chris Walsh where he shifted his research focus to the genetic underpinnings of focal epilepsies, which he continues to work on today. Sattar's research has been recognized through several awards including the American Epilepsy Society Young Investigator Award and he was selected as an Emerging Scholar by the American Neurologic Association. skhoshkhoo@bwh.harvard.edu

Mark W. Kieran, MD, PhD (PANELIST)

Dr. Kieran is currently the VP of Clinical Development at Day One Biopharmaceutics, a company focused on the development of targeted drugs for children. He received a PhD in Immunology from the University of Alberta, Canada in 1993 and his MD in 1986 from the University of Calgary. After a post-doctoral fellowship in the Department of Molecular Biology at the Pasteur Institute in Paris, France where he cloned the regulatory molecule NFkB, he completed a pediatric residency at McGill University in Montreal and a pediatric oncology fellowship at Boston Children's Hospital. Dr. Kieran became Director of Pediatric Neuro-Oncology at the Dana-Farber Cancer Institute in 1998 focused on targeted, gene, immune modulatory and antiangiogenic therapies for pediatric brain tumor patients and other rare cardiac and premature aging diseases. Dr Kieran moved to Bristol-Myers Squibb in 2018 where he was the Senior Director of Pediatric Oncology until July 2021. mark.kieran@dayonebio.com

Karolin Kleemann, PhD Candidate

(SPEAKER, EARLY STAGE INVESTIGATOR)

Karolin Kleemann was born and raised in a small Village near Dortmund in Germany. In 2013 she started studying molecular biology at the University of Applied Sciences in Recklinghausen and moved to cologne to do her bachelor thesis in the field of lung cancer research with a focus on epigenetics in cells with KRAS mutation at the University Hospital Cologne at the institute of translational molecular pathology in the group of Prof. Margarete Odenthal. In 2016 she started studying molecular biomedicine at the University of Muenster. During her studies she spent one semester in the molecular aging and chronobiology lab of Prof. Anita Jagota at the Central University of Hyderabad, India. Afterwards, she finished her master thesis which was focussing on the efficacy of plant extracts as anthelmintic drug in the lab of Prof. Eva Liebau at the institute of animal physiology in Muenster. After finishing her studies, she did an internship in the Max-Planck Institute for experimental medicine in Goettingen before starting her PhD in 2019 at the University Medical Center Goettingen in the Clinic for Cardiothoracic Surgery directed by Prof. Ingo Kutschka. Under supervision of Dr. George Kensah, she is working on cardiac *in vitro* disease modelling of RASopathies using 3D myocardial tissue engineering. The main focus of her work lays on $RIT1^{F82L/+}$-associated Noonan syndrome in order to understand the underlying pathophysiological mechanisms on the one hand and doing drug testing on the other hand. This work was awarded in 2021 with the "Hans-Georg-Borst"-price from the German Society for Thoracic and Cardiovascular Surgery and also received the Early Stage Investigator Award from our RASopathy Network Meeting this year. karolin.kleemann@web.de

Bonnie Klein-Tasman, PhD

(SPEAKER; NF1 FAMILIES' POST-SYMPOSIUM SESSION)

Bonnie Klein-Tasman, Ph.D. (she/her/hers) is a Professor in the Department of Psychology and Associate Dean in the Graduate School and the Office of Research at the University of Wisconsin-Milwaukee. She is the director of the UWM Child Neurodevelopment Research Lab. Together with graduate students in Clinical Psychology she conducts research about the psychological functioning of children with genetically-based neurodevelopmental conditions including NF1. Within her NF1 research program, she uses developmental neuropsychological and cognitive-behavioral therapy approaches to study: 1) cognitive, social, attention, adaptive, and academic functioning and development beginning in the preschool years with an eye to identification of the measures most likely to be appropriate for use with children with NF1; 2) neural underpinnings of attention in NF1; and 3) telehealth group intervention to support social functioning development in teens with NF1. Her research has been funded

by NF Midwest, NF Northeast, NF MidAtlantic, NF Northeast, and the Children's Tumor Foundation (CTF). She serves on the CTF Clinical Care Advisory Board and on the Neurocognitive Committee of the REiNS initiative. bklein@uwm.edu

Maria Kontaridis, PhD (SPEAKER)

Dr. Maria Irene Kontaridis (she/her/hers) is the Executive Director, Gordon K. Moe Professor and Chair of Biomedical Research and Translational Medicine, and the Director of Research at the Masonic Medical Research Institute (MMRI) in Utica, NY. She also holds a part-time faculty appointment as an Associate Professor of Medicine at Harvard Medical School (HMS) and Beth Israel Deaconess Medical Center (BIDMC), Department of Medicine/Division of Cardiology in Boston, MA. Dr. Kontaridis received her undergraduate degrees (B.A. and B.S.) from the University of Florida in Classics and Chemistry, and subsequently obtained her master's degrees in pharmacology and biomedical and Biological Sciences from Yale University in 1999 and 2001, respectively. In 2002, she was awarded a Ph.D. from Yale University. In 2015, she was named Director of Basic Cardiovascular Research at BIDMC and in 2016 was promoted to Associate Professor of Medicine at HMS. In 2018, Dr. Kontaridis became the Director of Research at the MMRI in Utica, NY, and in 2020 was promoted to Executive Director.

Dr. Kontaridis' independent research program focuses on the fundamental mechanisms underlying congenital heart disease and end-stage heart failure, as well as the processes that lead to abnormal development, aberrant signaling and disease onset of lupus, gastrointestinal disease, autism, and cancer. A myriad of tools and techniques are utilized in the lab, including iPS cells, in vivo mouse model systems, and molecular biology techniques. Her work has been awarded grants from multiple foundations, the Department of Defense, and the National Institutes of Health, as well as from industry and pharmaceutical companies. Dr. Kontaridis is also actively involved in the medical and research communities and has established herself in several significant leadership roles both locally and nationally, including with the American Heart Association and the International Society of Heart Research. mkontaridis@mmri.edu

Bruce R. Korf, MD, PhD (NF1 FAMILIES' POST-SYMPOSIUM SESSION)

Dr. Korf (he/him/his) is Wayne H. and Sara Crews Finley Endowed Chair in Medical Genetics, Distinguished Professor of Genetics, and Associate Dean for Genomic Medicine at the UAB Heersink School of Medicine. He is a medical geneticist, pediatrician, and child neurologist, certified by the American Board of Medical Genetics (clinical genetics, clinical cytogenetics, clinical molecular genetics), American Board of Pediatrics, and American Board of Psychiatry and Neurology (child neurology). Dr. Korf is past president of the Association of Professors of Human and Medical Genetics, The American College of Medical Genetics and Genomics, and the ACMG Foundation for Genetic and Genomic Medicine. He has served on the Boards of Scientific Counselors of the National Cancer Institute and the National Human Genome Research Institute at the NIH. His major research interests are integration of genomics into medical practice and the natural history, genetics, and treatment of neurofibromatosis. He serves as principal investigator of the Department of Defense funded Neurofibromatosis Clinical Trials Consortium. He is co-author of *Human Genetics and Genomics* (medical student textbook, now in fourth edition) and *Emery and Rimoin's Principles and Practice of Medical Genetics* (now in 7th edition), and is editor-in-chief of the *American Journal of Human Genetics.* bkorf@uabmc.edu

Paul Kruszka, MD, MPH (PANELIST)

Paul Kruszka, MD, is Chief Medical Officer of GeneDx, with responsibility for leading genomic research in rare diseases and promoting access to genomic medicine.

Paul is a board-certified clinical geneticist who uses genomic and precision medicine to enhance the delivery of healthcare to individuals with rare diseases. Paul's career is motivated by the idea that genetic technology can be used to have a beneficial impact on people's lives and that there are still many challenges to implementing genomic medicine.

Prior to working at GeneDx, Paul spent a decade at the National Institutes of Health conducting genomic research and taking care of individuals with rare genetic diseases. He is credited with the clinical and molecular delineation of multiple novel genetic conditions.

After attending medical school at the University of Michigan, Paul completed a family medicine residency at the University of Virginia. He also completed a clinical genetics residency at the National Human Genome Research Institute at the National Institutes of Health. pkruszka@genedx.com

Chiara Leoni, MD, PhD (SPEAKER)

Chiara Leoni is a pediatrician graduated at the Catholic University of the Sacred Heart in Rome, IT. From the beginning of her training in pediatrics she has directed her clinical and scientific interest towards taking care of children with "special care needs" due to genetic conditions. She holds a Fellowship in Genetics at the Division of Medical Genetics, University of Utah, Salt Lake City, UT-USA and a PhD in Medical Genetics at the Medical Genetics Unit of the Catholic University of the Sacred Heart of Rome, IT.

Thanks to the education and training in pediatrics and clinical genetics followed in Italy and abroad, she developed a great expertise in the diagnostic work up and multidisciplinary management of patients affected by rare syndromic diseases. The hard work characterizing recent years at Policlinico Gemelli, allowed her to set up a Board for Rare Diseases for the multidisciplinary discussion of most challenging cases, to organize a research group for drafting scientific papers focused on RASopathies and to participate in profit and non-profit clinical trials, as well as to apply to national and international competitive grants. Starting from clinical evidence of distinctive issues in particular RASopathies, she has also opened collaborations with basic researchers aiming to understand the pathogenic mechanisms of specific organ disorders and to find objective outcomes to be measured and monitored in future clinical trial. In recent years, she focused the interest on personalized medicine for Rare Diseases gaining extensive experience on the use of targeted therapies in clinical trials, off label and compassionate use programs. She is author and co-author of various scientific publications in international peer reviewed journals and is a reviewer for different scientific medical journals with IF. chiara.leoni@policlinicogemelli.it

Clifford Liu, MD/PhD Candidate

(SPEAKER, EARLY STAGE INVESTIGATOR)

Clifford Liu is a 7th year MD/PhD candidate at Icahn School of Medicine at Mount Sinai and is a recipient of the American Heart Association & Children's Heart Foundation's Predoctoral Fellowship. Prior to joining Mount Sinai, he attended UC San Diego, where he received a Bachelor's degree in both Biochemistry and Sociocultural Anthropology. At UC San Diego, he also received a Master's degree in Biology, where he studied nicotinic acetylcholine receptor regulation. Currently, he is finishing up his doctoral work in the lab of Dr. Bruce Gelb, where he utilizes

iPSCs to model valve disease in Noonan syndrome and to investigate the mechanisms of its pathogenesis. After completing his MD/PhD training, Clifford hopes to pursue a research track residency in cardiology. clifford.liu@icahn.mssm.edu

Pilar Magoulas, MS, CGC

(MODERATOR;
NS AND NSML FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Pilar Magoulas (she/her) is a certified genetic counselor and Associate Professor in the Department of Molecular and Human Genetics at Texas Children's Hospital and Baylor College of Medicine. She received a Master of Science degree in Genetic Counseling from Northwestern University in 2003. She currently works as a pediatric genetic counselor at Texas Children's Hospital where she serves as the Manager of the Genetics clinic and Chief of the Division of Genetic Counseling. Pilar serves on the Board of directors for CFC International, support group for individuals with Cardio-facio-cutaneous syndrome, on the Scientific Advisory Council for the National Foundation for Ectodermal Dysplasias, and on Scientific Advisory Board for RASopathies Network USA. She has planned and hosted a Houston Noonan Syndrome Conference and has been active in the Rasopathy communities for the past 20 years. plmagoul@texaschildrens.org

Nadia Merchant, MD (SPEAKER, EARLY STAGE INVESTIGATOR)

Nadia Merchant, M.D., (she/her) is a pediatric endocrinologist and geneticist at Children's National Hospital. Dr. Merchant's clinical interests include bone health, skeletal dysplasias, growth, and the intersection of genetics and endocrinology. She is involved in multiple multidisciplinary clinics as the endocrinologist: The Bone Health Program with Orthopaedics; the Muscular Dystrophy Clinic; the White Matter Clinic specifically for X-linked adrenoleukodystrophy; the 22q clinic. She is passionate about maximizing a patient's potential. nmerchant@childrensnational.org

Christopher Moertel, MD

(SPEAKER; NF1 FAMILIES' POST-SYMPOSIUM SESSION)

Dr. Christopher Moertel is the Kenneth and Betty Jayne Dahlberg Professor of Pediatric Neuro-oncology in the University of Minnesota School of Medicine. As clinical director of the pediatric brain tumor program at the University of Minnesota, he leads both the pediatric brain tumor and comprehensive neurofibromatosis clinics. He has active research collaborations with scientists in the cancer genomics and brain tumor immunotherapy laboratories in addition to fellow physician investigators in epidemiology, oncology, orthopedics and neurosurgery. His current research focus is on the development of directed therapeutics for plexiform neurofibroma, cutaneous neurofibroma and malignant peripheral nerve sheath tumor in patients with neurofibromatosis, type 1 (NF1). He is currently co-PI of the CTF Synodos grant exploring new therapies for MPNST. Prior to coming to the University of Minnesota in 2007, he was medical director of the Theodora Lange Pediatric Oncology Clinic at Children's Hospital, St. Paul and was founder of the Neurocutaneous Clinic Without Walls. Dr. Moertel is a graduate of St. Olaf College and received his MD from the University of Minnesota. He completed a pediatric residency at Texas Children's Hospital, Baylor College of Medicine and was a fellow in pediatric hematology and oncology at Mayo Clinic. moert001@umn.edu

Rene Pierpont, PhD, LP

(CHAIR; MODERATOR; SPEAKER;
CFC SYNDROME FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Dr. Rene Pierpont is an Assistant Professor and pediatric neuropsychologist in the Department of Pediatrics at the University of Minnesota. In her clinical work, Dr. Pierpont conducts neuropsychological evaluations and consultations with children with complex medical and neurodevelopmental conditions. Her research program evaluates the impact of neurological disease and clinical treatment on brain structure and function in children with rare genetic conditions. Much of her research focuses on the RASopathies. This work explores neurocognitive and behavioral phenotypes and treatments, and their relationship with specific variants in the RAS/MAP kinase pathway. Dr. Pierpont is presently a K23 scholar funded by the National Institute for Neurological Disorder and Stroke. In addition to her research and clinical work, Dr. Pierpont is passionate about partnering with patient communities to develop better resources, guidelines, and avenues of care for children with genetic conditions.
pier0053@umn.edu

Carlos Prada, MD (PANELIST)

Dr. Carlos Prada is honored to be the division Head of genetics, genomics, and metabolism at the Ann & Robert H. Lurie Children's Hospital of Chicago. Dr. Prada has been principal investigator for numerous clinical trials including gene therapy for lysosomal storage diseases and many other novel therapeutics for neurofibromatosis, RASopathies, and metabolic diseases. Dr. Prada was awarded a multicenter R61 grant from NINDS/NIH to perform whole-body imaging combined with biomarker validation in children with neurofibromatosis. He also has received funding from the Department of Defense for treatment of neurofibromatosis motor behaviors.

Dr. Prada leads a multidisciplinary team for management of RASopathies at Lurie Children's Hospital of Chicago. He also developed the RASopathy program at Cincinnati Children's prior to moving to Chicago. He is also the director for the NORD Rare Disease Center of Excellence at Lurie Children's Hospital of Chicago and Northwestern University. He is also developing novel approaches to improve access to genetics care to match the demands of expertise for Chicagoland.

Dr. Prada is internationally regarded as an outstanding clinician, researcher, and mentor. He received his medical degree at the Universidad Industrial de Santander in Colombia. He completed his residency in Pediatrics and Medical Genetics and fellowship in Clinical Biochemical Genetics at Cincinnati Children's Hospital Medical Center. He also completed a postdoctoral fellowship in cancer genetics research at the University of California, San Diego.

He serves as the director of the Center for Genomics and Metabolism in Colombia. With this and other global partnerships, Dr. Prada will extend opportunities at Lurie Children's to recruit clinicians and researchers and welcome children with genetic disorders from around the world.

The goal of Dr. Prada is to build a highly impactful division and propel scientific discovery to have a long-term impact on our current and future patients, as well as future trainees in a new genetics fellowship program.
cprada@luriechildrens.org

Katherine A. Rauen, MD, PhD

(MODERATOR; CFC SYNDROME FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Dr. Katherine (Kate) Rauen is Professor Emeritus in the Department of Pediatrics, Division of Genomic Medicine at UC Davis. She received a MS in Human Physiology and a PhD in Genetics from UC Davis doing research on gene dosage compensation and genetic evolution. She obtained her MD at UC Irvine where she also did research in cancer genetics. Dr. Rauen did her residency training in Pediatrics and fellowship in Medical Genetics at UC San Francisco.

Dr. Rauen is internationally known for her pioneering work in the early application of microarray technology in clinical genetics and as a leader and major contributor to the understanding of RASopathies, genetics syndromes of the Ras/MAPK pathway. Her research program involves the clinical and basic science study of cancer syndromes with effort to identify underlying genetic abnormalities affecting common developmental and cancer pathways. Dr. Rauen led the research team, including the CFC International Family Support Group that discovered the genetic cause of cardiofaciocutaneous syndrome.

Dr. Rauen is committed to academic medicine, medical education, and advancing best practices for patients with RASopathies. She has successfully obtained both intramural and extramural funding for her research activities and has published extensively on in Costello syndrome, CFC syndrome and the RASopathies with her most current work focusing on skeletal myogenesis and the mechanism of hypotonia and myopathy in the RASopathies.

She is the innovator of the world-renowned NF/Ras Pathway Clinic for RASopathies which she initiated in 2007 and this clinic has now been emulated around the globe. She serves on the medical advisory board of CFC International, is a Co-Director for the Costello Syndrome Family Network Professional Advisory Board and serves on the advisory boards for RASopathies Network USA and Global Genes.

Dr. Rauen has received many honors and awards including the prestigious Presidential Early Career Award for Scientists and Engineers (PECASE) for her work for CFC and Costello syndrome. This Award is the highest honor bestowed by the United States Government on science and engineering professionals in the early stages of their independent research careers. This Presidential Award is awarded for innovative and far-reaching developments in science and technology, in an effort to increase awareness of careers in science and engineering, give recognition to the scientific missions of participating agencies, enhance connections between fundamental research and national goals, and highlight the importance of science and technology for the nation's future. rauen@ucdavis.edu

Renée Roelofs, PhD (SPEAKER, EARLY STAGE INVESTIGATOR)

Renée Roelofs is a health care psychologist. She combines clinical care for patients with rare genetic disorders (neuropsychological assessment and treatment) with scientific research. NSSDs are her area of expertise. She also participates in the RadboudUMC Expert Centre for Rare Developmental Disorders (ERN/Ithaca). reneeroelofs@vigogroep.nl

Rodrigue Rossignol, PhD (SPEAKER)

Dr. Rodrigue ROSSIGNOL (Ph.D) is an INSERM Research Director in Bordeaux (France). He is co-director of the 'Rare Diseases, Genetics and Metabolism' laboratory at the University of Bordeaux (www.mrgm.fr). Dr. Rossignol published >100 articles on energy metabolism and 4 patents. Our team investigates the molecular mechanisms involved in bioenergetic regulation in various models and diseases. We study the implication of mitochondria in rare diseases as RASopathies and we evaluate the efficacy and toxicity of drug modulators active on mitochondrial biology (www.cellomet.com) rodrigue.rossignol@u-bordeaux.fr

Lisa Schoyer, MFA

(PRESIDENT, RASOPATHIES NETWORK;
PRINCIPAL INVESTIGATOR AND CO-ORGANIZER)

Lisa Schoyer is the mom of Quin Johnson, who had Costello syndrome (G12S) and died in 2002 at 6-1/5 years old, of embryonal rhabdomyosarcoma (eRMS) related to the syndrome. She is founder and President of the RASopathies Network USA. Lisa is also a trustee of the International Costello Syndrome Support Group (ICSSG), as well as past President and past Secretary for the American Costello Syndrome Family Network (CSFN). Though trained as a professor of studio art, after Quin died, she was hired by the County of Los Angeles first as Chief of Family Support at the Department of Public Health's program for children with special healthcare needs (2003-2009), and, since then, for the County's Department of Mental Health in the Family and Community Partnerships unit - where she works to develop and sustain Subject Matter Mavens on providing mental health interventions for individuals with co-occurring developmental disabilities. lschoyer@rasopathiesnet.org

Christine Sevilla (SPEAKER, RASOPATHY ADVOCATE)

Christine Sevilla (she/her/hers) is the mother and dedicated advocate and supporter of Gigi Sevilla who is a young woman living a full and active life with a RASopathy, CFC Syndrome. Christine is an artist and nature and wildlife enthusiast. She is an experienced interior designer and painter. She has affection for photography, fashion, story telling, music, dancing, and the culinary arts. She enjoys travel and spending time with friends and family. Christine is a partner in a small business, HGR Construction Services in the Chicago suburbs and works alongside her husband of 26 years, Joel Sevilla. Christine is an experienced public speaker and loves sharing her knowledge of parenting a child with a disability. One of Christine's favorite mottos is: "Parenthood is about raising and celebrating the child you have, not the child you thought you'd have. It's about understanding your child is exactly the person they were supposed to be. And if you are lucky, they will be the teacher who turns you into the person you're supposed to be." christine.sevilla.1@gmail.com

Gigi Sevilla (SPEAKER, RASOPATHY ADVOCATE)

Gigi Sevilla (she/her/hers) is 25 years old and living her best life with CFC Syndrome. Gigi is a beloved family member and friend to many, and an active community member. Gigi works at Maxine Elmhurst, a women's clothing and accessory boutique. Gigi is a model and has been featured in social media campaigns from clothing and beauty products to healthcare and disability finance management. Her image is on corporate signage and on the cover of a magazine publication, and has had her life's work featured in news media stories. Gigi is the 2018 Illinois Miss Amazing Queen with her platform being wildlife conservation. Miss Amazing is a national pageant for girls and women with disabilities. Gigi had a primary role in a documentary produced by New Zealand's Attitude Pictures following her experience and journey as Miss Amazing as she competed for the national title. The documentary was aired on YouTube and on global media programming and went on to win an Asian Academy Award for Best Direction of a Documentary. Gigi has been public speaking in front of audiences since 2016. Gigi uses a speech communication device to augment her expressive language, a customized app on an iPad. Gigi has volunteered since she was a teenager and is a Zoo Docent at the world renown Chicago Zoological Society aka Brookfield Zoo. She teaches and guides zoo visitors about wildlife and the importance of conservation. In 2016 Gigi was the keynote speaker at Chicago Zoological Society's annual fundraising gala attended by 800 esteemed guests where she successfully assisted the zoo in securing substantial record-breaking event contributions during and after the event. Gigi is a social change, climate change, women's rights, and disability activist. Gigi has lobbied legislators to advocate for important issues including speaking at a press conference at her State Capitol, is an active constituent, and votes in elections. Gigi is an artist, dancer, lover, jokester, adventurist, party girl, ally to the LGBTQ+ community, horse rider, swimmer, and traveler. Gigi is a fighter, and a thriver. Gigi is delighted to have an opportunity to share her story with the RASopathy community.

Suma Shankar, MD, PhD, FRCS, MRCOphth

(COSTELLO SYNDROME FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Dr. Suma Shankar MD, PhD, FRCS, MRCOphth is a Professor in the Departments of Pediatrics and Ophthalmology and is Chief of Genomic Medicine at University of California Davis. She serves as the Director of Precision Genomic Program and Ocular Genomics clinic at UC Davis and holds the Albert Rowe Endowed Chair of Genetics II. She is board certified in Medical Genetics from the American College of Medical Genetics & Genomics and in Ophthalmology from the United Kingdom. She has published extensively on rare syndromes including RASopathies, ophthalmic genetic disorders, lysosomal storage disorders, and neurodevelopmental disorders. Her special area of interest is ophthalmic manifestations in RASopathies. spshankar@ucdavis.edu

Ryan Sheedy (SPEAKER)

Ryan Sheedy is a dad, rare disease caregiver and founder. He lives in Bentonville, AR with his wife and 3 sons. In 2018, after 15+ years in business development and fundraising, he "retired" early to become a stay at home dad/caregiver for his twin sons.

One of his sons, Reynolds, was diagnosed with Costello syndrome in 2018. Since birth, Ryan has been Reynolds' primary caregiver (100+ days in the NICU, countless surgeries and managing a 25+ person care team). He and his son's rare journey and the countless families they have met along the way inspired him to create mejo.

mejo (short for 'me journal') is a web app that provides parents and caregivers with a better way to simplify, organize and share their child's most important medical and care information. Simple and easy to use, mejo helps caregivers save time and gain peace of mind by organizing their loved one's information into easily digestible views that can be securely shared in a click.

Adored by users, loved by providers and endorsed by numerous rare disease organizations, mejo is built for caregivers by caregivers to save them time, money and bring their families joy! He's on a mission to start putting "*me*" back in medicine. ryan@mymejo.com

David Stevenson, MD

(COSTELLO SYNDROME FAMILIES' POST-SYMPOSIUM SUMMARY SESSION)

Professor of Pediatrics, Division of Medical Genetics, Service Chief, Stanford University. Dr. Stevenson's research has focused on the effects of Ras dysregulation on bone homeostasis previously funded by the NIH, Doris Duke Charitable Foundation, Thrasher Research Fund, and Department of Defense. He is currently a Professor at Stanford University where he directs the clinical medical genetics service and is the program director for the Medical Genetics Residency Program. He currently serves on the Board of Directors for the American College of Medical Genetics and Genomics. He is actively involved on medical advisory boards for both Costello and CFC syndrome and is the director of a RASopathy clinic at Stanford Children's Health. dasteven@stanford.edu

Elliot Stieglitz, MD (SPEAKER)

My research focuses on improving outcomes for children with leukemia, particularly those with juvenile myelomonocytic leukemia (JMML), an aggressive hematologic malignancy of infancy caused by mutations in the Ras/MAPK pathway. Clinically, I am study chair for ADVL1512, a phase II clinical trial sponsored by the Children's Oncology Group (COG) that tested trametinib, an oral MEK inhibitor in children with relapsed JMML, that has met its primary objective with a 50% objective response rate. I am also study chair of TACL2020-004 which will risk stratify newly diagnosed JMML patients based on the mutational burden and methylations status and move trametinib into the front-line setting. This trial is funded by an R37 award from the NCI. elliot.stieglitz@ucsf.edu

Beth Stronach, PhD

(BOARD MEMBER, RASOPATHIES NETWORK; CO-ORGANIZER)

Beth Stronach has been an academic research scientist for over a dozen years. After receiving a PhD in Biology from the University of Utah in 1997 and pursuing postdoctoral work in Genetics at Harvard Medical School, she moved to Pittsburgh in 2002. Since then, she has been a faculty member at the University of Pittsburgh, first in the Dept. of Biological Sciences, then in the Microbiology and Molecular Genetics department at the School of Medicine. Her research focused on understanding how cells organize into complex tissues during organism development. Ironically, the subject of Dr. Stronach's research was a signaling pathway closely related to the RAS pathway, so it was quite a shock to learn of her son Sam's diagnosis of Noonan syndrome (PTPN11) in 2007. Yet, his diagnosis validated for her the importance of basic research science to understand the molecular underpinnings of health and disease. She is currently a Scientist Administrator in the Office of Research for Health Sciences at the University of Pittsburgh and Secretary for RASopathiesNet. bstronach@rasopathiesnet.org

Daochun Sun, PhD (SPEAKER, EARLY STAGE INVESTIGATOR)

Dr. Sun earned his PhD in the School of Medicine at Wayne State University. His doctoral research focused on studying the mechanisms of Neurofibromatosis Type 1 (NF1)-associated Malignant Peripheral Nerve Sheath Tumors (MPNST). Following his PhD, he pursued postdoctoral training in the Developmental Biology Department at the University of Texas, Southwestern Medical Center, and the Cancer Biology and Genetics program at Memorial Sloan Kettering Cancer Center. During his postdoctoral training, Dr. Sun's research primarily centered around tumor heterogeneity and the tumor microenvironment. His work placed particular emphasis on identifying tumor cell-of-origin and tumor associated immune cells. In the case of NF1-associated plexiform neurofibromas and MPNST, he discovered a stem-like cell population that plays crucial roles in tumor formation, relapse, and metastasis. These significant findings hold the potential to offer new strategies for preventing tumor transformation, inhibiting tumor progression, overcoming chemoresistance, and managing metastasis. Dr. Sun's research contributes to a deeper understanding of these diseases and may ultimately lead to improved treatment approaches. dsun@mcw.edu

Dagmar K. Tiemens, MSc, MEd, PhD Candidate

(SPEAKER, EARLY STAGE INVESTIGATOR; PARENT ADVOCATE)

Radboud university medical center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Department of Pediatrics, Nijmegen, The Netherlands; Dutch Noonan Syndrome Foundation, Nijkerk, The Netherlands (Member of the Board in 2019-2020). Dagmar Tiemens, an accomplished graduate of Leiden University in medical biology, specializing in anatomy and cellular biology, is currently pursuing a PhD at Radboudumc. With 15 years of firsthand experience caring for her Rasopathy-affected child, she skillfully combines her extensive professional expertise and practical insights. This unique blend empowers her to offer a distinct perspective in exploring the (pathological) effects linked to RAS/MAPK/ERK pathway hyperactivation and its associated targets. Dagmar.Tiemens@radboudumc.nl

Forest White, PhD (PANELIST)

Forest White is a Professor in the Department of Biological Engineering at the Massachusetts Institute of Technology (MIT). After receiving his Ph.D. from Florida State University in 1997 and completing a post-doc at the University of Virginia from 1997-1999, he joined MDS Proteomics as a Senior Research Scientist and developed phosphoproteomics capabilities for the company. In July 2003 he joined the Department of Biological Engineering at MIT. Research in the White lab is focused on quantification of protein phosphorylation-mediated signaling networks and MHC peptide presentation in normal and pathophysiological cell biology. Specific applications include novel drug target discovery in glioblastoma, melanoma, and triple negative breast cancer, as well as analysis of mechanisms underlying therapeutic resistance and metastasis. In addition to his appointment in the Department of Biological Engineering, Forest is a member of the Koch Institute for Integrative Cancer Research. fwhite@mit.edu

Ellen Wingbermühle, PhD (SPEAKER)

Ellen Wingbermühle is a clinical neuropsychologist. Her activities include research, diagnostics and clinical management of Noonan syndrome spectrum disorders, as well as other rare genetic disorders. She participates in the RadboudUMC Expert Centre for Rare Developmental Disorders (ERN/Ithaca), and she is also a member of the specialist advisory board of the Dutch Noonan Syndrome Foundation. p.wingbermuehle@donders.ru.nl

Cordula Wolf, MD (SPEAKER)

Dr. Wolf obtained her medical and doctoral degree at the Ludwig-Maximilians University in Munich, Germany. After a decade of extensive clinical and scientific training in pediatrics, pediatric cardiology, and molecular genetics at Boston Children´s Hospital and the Seidman laboratory, Harvard University Boston, USA, from 2003 until 2012, she relocated back to Germany. She now works as pediatric cardiologist and physician-scientist at the German Heart Center in Munich. She founded the Center for Rare Congenital Heart Diseases at the German Heart Center of the Technical University in Munich, with a specific interest in childhood onset cardiomyopathies, sudden cardiac death, and Rasopathies. Dr. Wolf is the sub-representative of the Munich Consortium for Rare Heart Diseases, a full member of the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart). She is scientific principal investigator in several basic research and clinical projects focusing on congenital heart diseases and rare childhood disorders. wolf@dhm.mhn.de

Martin Zenker, MD (KEYNOTE SPEAKER)

Martin Zenker, MD is Professor of Human Genetics and director of the Institute of Human Genetics at the University Hospital of Magdeburg, Germany. He is board certified in pediatrics, neonatology, and human genetics. His area of clinical expertise and research is regarding human developmental disorders with a particular focus on RASopathies. He has been involved in the discovery of several genes underlying Noonan syndrome and is particularly interested in studying genotype phenotype correlations for RASopathies. He is coordinator of a German national research network for RASopathies (German Network for RASopathy Research, GeNeRARe) and member of the European network NSEuroNet. Dr. Zenker is closely involved with the German Noonan and CFC syndrome family support groups and a member of the ClinGen expert panel on RASopathies. He is a co-organizer of the European Meetings on Rare Disorders of the RAS-MAPK Pathway. martin.zenker@med.ovgu.de

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RASOPATHIES NETWORK

connect • collaborate • accelerate

Thank You to Our Partnering Organizations

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Noonan Syndrome Association

Noonan UK

NOONAN SYNDROME FOUNDATION


HAPPY TRAILS
-uh- TRIALS!*
See you in 2025!
*attributed to Gregor