UCSF RASopathies Research Program Newsletter

January 2014

Greetings, from the Researchers!

Lauren Weiss, PhD

Ophir Klein, MD, PhD

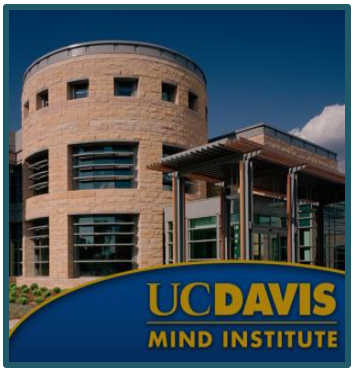
Katherine Rauen, MD, PhD

Erik Ullian, PhD

Jean Nakamura, MD

On behalf of the UCSF Community, we wish you health and happiness for the upcoming year! We would like to take this opportunity to update you on all that we are doing at UCSF to improve our understanding and treatment of the RASopathies.

NF/Ras Pathway Genetics Clinic to be established at the UC Davis Medical Center/ MIND Institute in Sacramento, CA



The NF/Ras Pathway Clinic was originally launched in 2007 at UCSF under the direction of Dr. Kate Rauen. This new and innovative pathway-based clinic was built around the needs of patients. The novel features of the clinic include: 1) a pathway-based approach; 2) comprehensive case management and multidisciplinary referrals; 3) a network of more than 60 specialists; 4) facilitated transition from pediatric to adult care in all specialties; 5) prenatal and obstetric care; 6) guidance from an external patient advocacy advisory board and 7) guidance from an internal scientific advisory board.

After over 18 years at UCSF, Dr. Rauen has transferred to UC Davis Medical Center / MIND Institute in Sacramento, California and is establishing a new and additional NF/Ras Pathway Clinic. Like the clinic at UCSF, the new clinic at UC Davis will have the same features to better serve its patients and provide best medical practices for NF and other RASopathies.

With the transfer of Dr. Rauen, Dr. Joseph Shieh will assume the clinical direction of the UCSF NF/Ras Pathway Clinic working with Dr. Rauen, and one larger NF/Ras Pathway Clinic will be formed. This intercampus network of the sister UC Medical Centers will better serve the NF and RASopathy community in Northern California.

For UCSF NF/Ras Clinic scheduling, please contact:
Ms. Janelle Arquiza at 415-514-0838.

The new "NF/Ras Clinic" is due to launch in early Spring 2014 at the UC Davis MIND Institute. For those patients that are interested in obtaining an appointment, please contact:
Ms. Julaila Musgrove
Phone number: 916-703-0308
julaila.musgrove@ucdmc.ucdavis.edu
www.MINDinstitute.org

RASopathies Recognized by the White House

Dr. Rauen was named one of 102 scientists to receive the 2013 Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the U.S. government on science and engineering professionals in the early stages of their research careers.
www.ucdmc.ucdavis.edu/publish/news/newsroom/8567

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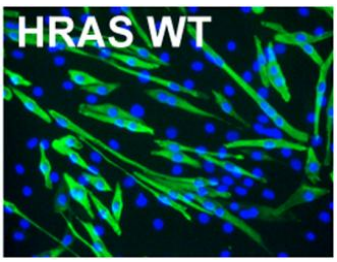
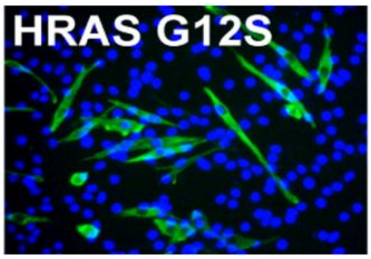
Research Updates

Rauen Lab: Skeletal Muscle in CS and CFC

Dr. Katherine Rauen and her team at UC Davis study how the genetic alterations that cause Costello and CFC syndromes affect the function and signaling of the Ras/MAPK pathway in cells. This is important in understanding how development may be altered and how cancer may arise. Recently, Dr. Rauen's lab has identified a specific skeletal muscle abnormality in CS and CFC individuals which affects muscle strength and stamina, and is now studying the effects of the gene mutations on skeletal muscle development. Recent studies have demonstrated that the skeletal muscle in the CS and CFC mouse models are also affected. The information gained in these studies will be used to pursue and help design clinical trials for individuals with RASopathies.





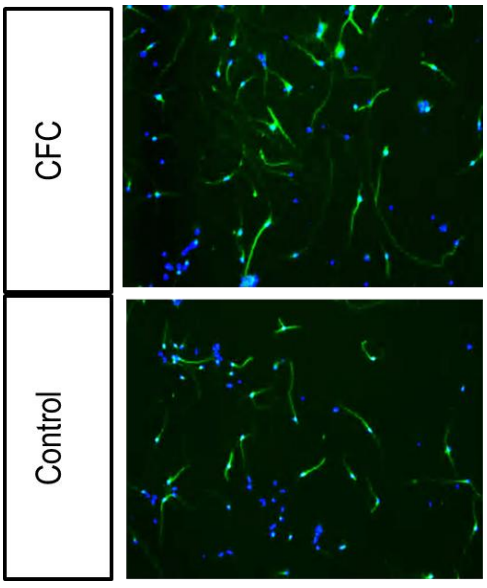
Skeletal muscle cells grown in culture show that cells with normal HRAS are able to differentiate into normal multi-nucleated skeletal muscle, whereas muscle cells with an activated mutant Ras G12S (right) do not differentiate normally.

Weiss Lab: Autism in the RASopathies

Thanks to those who completed parent questionnaires, the Weiss lab analyzed data from 231 individuals with NF1, CS, NS, or CFC, and their unaffected siblings. They found that individuals with a RASopathy were significantly more likely than their siblings to have social and communicative traits associated with autism. Both the severity of autistic traits and the proportion of individuals who screened positive for them varied within each RASopathy, with the greatest proportion seen in CFC subjects (54%), followed by CS (26%), NS (21%), and NF1 (11%).

Weiss Lab: Skin Cells to Stem Cells

From the skin samples donated, we were able to revert the cells to stem cells. These, in turn, were successfully transformed into neurons in our lab. We are eager to compare CFC neurons to control neurons.



Left: Image of CFC neurons (top) compared to a control subject (bottom).

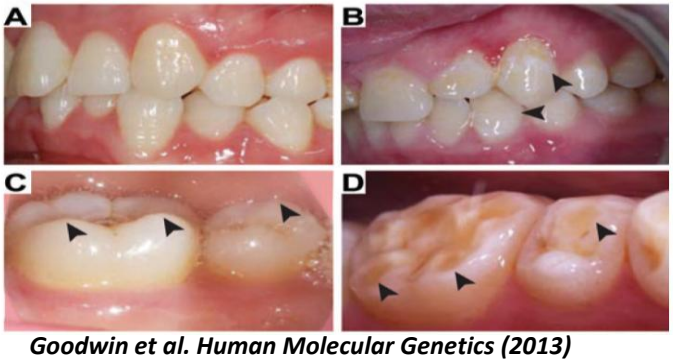
Right: Image showing how thin enamel affects the teeth of individuals with Costello syndrome (right) compared to an individual with normal enamel (left). Goodwin et al. Human Molecular Genetics (2013)

Nakamura Lab: Tumor Development in NF1

We study how tumors develop in the NF1 syndrome, in order to better treat and one day prevent them. Our research employs a comprehensive array of genetic, biochemical and functional approaches to discover the biological processes affected by the NF1 gene and thereby design appropriate molecular strategies to block tumor development. We developed novel experimental models to identify molecules that work in conjunction with NF1 mutations to cause tumors. In collaboration with clinical groups at UCSF and other major medical centers, we are using our research findings to perform state-of-the-art genetic analysis of tumors from individuals with NF1.

Klein Lab: Dental Development in CS and CFC

Data from our dental examinations of individuals with CS and CFC have given insight into the unique craniofacial and dental characteristics of these syndromes. These data have been published and will provide clinicians with information to aid in treating individuals with CS and CFC. Additionally, an interesting finding is that individuals with CS have thin enamel (the hard outer layer of the teeth), and we further studied a mouse model of CS to learn how Ras affects the behavior of the cells in the tooth.



Goodwin et al. Human Molecular Genetics (2013)

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Publications & Presentations

Weiss Lab

Autism in the RASopathies. Journal of Medical Genetics. 2014; 51(1):10-20. Adviento BA, Corbin IL, Widjaja F, Desachy G, Enrique N, Rosser T, Risi S, Marco EJ, Hendren RL, Bearden CE, Rauen KA, Weiss LA.

SFARI Blogs:
http://sfari.org/news-and-opinion/news/2013/cancer-pathway-connects-autism-to-set-of-rare-disorders

http://sfari.org/news-and-opinion/blog/2013/hidden-symptoms

Ullian Lab

Accelerated astrogliogenesis and modulated extracellular signaling of RASopathic human astrocytes. Presented at: Gordon Research Conference: Glial Biology: Functional Interactions among Glia & Neurons ; Cell Symposia: Using stem cells in modeling and treating diseases; Society for Neuroscience Meeting . 2013. Krencik R, Hokanson K, Narayan AR, Rooney GE, Weiss LA, Rauen KA, Ullian EM.

Klein Lab

Craniofacial and Dental Development in Costello Syndrome (CS). *American Journal of Medical Genetics*, In Press. A.F. Goodwin, S. Oberoi, M. Landan, C. Charles, J. Groth, C. Fairley, K.A. Rauen, O.D. Klein.

Abnormal Ras signaling in Costello syndrome (CS) negatively regulates enamel formation. *Human Molecular Genetics*. October 2013. A.F. Goodwin, W.E. Tidyman, A.H. Jheon, A. Sharir, X. Zheng, C. Charles, J.A. Fagin, M. McMahon, T.G. Diekwisch, B. Ganss, K.A. Rauen, O.D. Klein.

Craniofacial and Dental Development in Cardio-facio-cutaneous Syndrome: The Importance of Ras Signaling Homeostasis. *Clinical Genetics*, June 2013. A.F. Goodwin, S. Oberoi, M. Landan, C. Charles, J. Groth, A. Martinez, C. Fairley, L.A. Weiss, W.E. Tidyman, O.D. Klein, K.A. Rauen.

Rauen Lab

KA Rauen. **The RASopathies**. *Annual Review of Genomics and Human Genetics*. 2013; 14:355-69.

Deletion of MAP2K2/MEK2: A novel mechanism for a RASopathy? *Clinical Genetics.* 2013 Feb 4. doi: 10.1111/cge.12116. [Epub ahead of print]. Nowaczyk MJM, BA Thompson, S Zeesman, U Moog, PA Sanchez-Lara, PL Magoulas, RE Falk, J Hoover Fong, DAS Batista, SM Amudhavalli, SM White, GE Graham, KA Rauen. 2013**.**

Constitutional Ras Pathway Dysregulation: Juvenile Myelomonocytic Leukemia in a 16 year old with Noonan syndrome. *Journal Pediatric Hematology and Oncology.* 2012 . Oct;34(7):569-72. Ortiz MV, S Skoda-Smith, KA Rauen, RW Allan, WB Slayton..

Peripheral Muscle Weakness in RASopathies: Handgrip Strength in Costello, Cardio-facio-cutaneous, Noonan and Neurofibromatosis Type 1 Syndromes. Muscle and Nerve. Sep;46(3):394-9. 2012. Stevenson, DA, S Allen, WE Tidyman, JC Carey, DH Viskochil, A Stevens, H Hanson, X Sheng, BA Thompson, M Okumura, K Reinker, B Johnson, KA Rauen.

Germline loss-of-function mutations in LZTR1 cause an inherited disorder of multiple schwannomas in SMARCB1-negative patients. *Nature Genetics*. 2013 Dec 22. doi: 10.1038/ng.2855. [Epub ahead of print]. Piotrowski A, J Xie, AB Poplawski, YF Liu, A Gomes, P Madanecki, C Fu, MR Crowley, D Crossman, L Armstrong, D Babovic-Vuksanovic, A Bergner, JO Blakeley, AL Bloomingthal, M Daniels, H Feit, K Gardner, S Hurst, C Kobelka, R Nagy, KA Rauen, J Slopis, P Suwannarat, J Westman, BR. Korf, LM Messiaen.

Fetal autopsy findings of cardiofaciocutaneous syndrome with a unique BRAF mutation. *Pediatric and Developmental Pathology*. 2013 Dec 4. [Epub ahead of print]. Terry J, KA Rauen, MJM Nowaczyk

CFC International
Cardio-Facio-Cutaneous Syndrome
Caring, Facilitating & Connecting

Costello Syndrome Family Network

NOONAN SYNDROME FOUNDATION

2013 RASopathy Family Conference, Orlando, FL

Special Thanks to the RASopathy support groups who organized the 2013 CFC, Costello syndrome, and Noonan syndrome International Family Conference in Orlando, FL this past July! And thank you also to all the families who participated in our research program by giving saliva samples, filling out questionnaires, and brightening our day!

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A Parent's Experience with NF1

Marian Keeler's son was diagnosed with Neurofibromatosis type 1 (NF1) in 2010 by Dr. Kate Rauen at UCSF's NF/Ras Pathyway Clinic. NF1 is caused by mutations in the NF1 gene of the Ras/MAPK pathway. It is characterized by multiple cafè au lait spots, freckling at the armpits or groin, Lisch nodules (bumps on the eyes), and benign skin tumors called neurofibromas.

Although Ms. Keeler noticed cafè au lait spots on her son when he was only three months old, there were not enough for a diagnosis. Throughout her son's childhood, Ms. Keeler visited doctor after doctor searching for an explanation for her son's challenges with sensory and motor skills, executive functioning, and social/attentional abilities. Every professional seemed to offer a new "provisional" diagnosis, but nothing seemed to explain all of his symptoms. When they finally received an NF1 diagnosis, her son was 17 years old. Ms. Keeler says, "It was like a light bulb went off because the diagnosis explained everything. It was devastating, but it was better to know for sure." She searched the internet to find out more about NF1, but she would discourage other parents from doing the same. Reading about some of the more serious potential symptoms and trying to separate the facts from fiction only increased her stress level.

One of the most difficult things for Ms. Keeler was telling her son about his diagnosis. He was angry at first because he did not want to be different from his peers, but he has come to acknowledge his diagnosis without allowing it to label him. Support from friends and family has been a great source of comfort to both Ms. Keeler and her son. She says, "After my son's diagnosis, my friend gave me the best advice. She said 'He's the same person he was yesterday. He's not defined by this disease.'"

Ms. Keeler believes NF1 research is important and is enthusiastic about supporting the discovery of a treatment or cure. She wants her son and others to be able to benefit from the innovative, robust research that characterizes UCSF. Ms. Keeler made a generous donation to the RAS clinic because of the personal connection the clinicians made with her and her son. After some misinformation and bad experiences with doctors in the past, she is very happy to donate to an institution that took such excellent care of its patients and makes the effort to connect personally with families.

Dr. Rauen and her team at the NF/Ras Pathway clinic thank Ms. Keeler immensely for her generous donation to the UCSF NF/Ras Pathway Clinic and wish her son success as he starts his fourth semester of college this upcoming spring.

Donations

Donations to the NF/Ras Pathway Clinic and RASopathies Research Programs are greatly appreciated. They allow us to continue running the clinic and to conduct important research in the field.

Instructions on making a donation:
Go to https://makeagift.ucsf.edu/children
Click "Choose a destination"
Select "Other" and type in the text box the following: B2937 Genetics – Kate Rauen.

We are happy to answer any questions you may have about making donations to UCSF. Please contact Brigid Adviento at (415)476-6988.

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Upcoming Event

UC San Francisco
Genentech-Byers Auditorium
600 16th Street • San Francisco

NF1 Symposium

& Ask the Expert Session

Saturday, February 8, 2014
10:00am to 3:30pm

Join us for a day of informative presentations by renowned physicians and specialist specializing in NF care for adults and children. Enjoy the opportunity to participate in a research project. Invite your family, friends, medical and educational professionals.

Potential Topics: Peripheral Nerve Tumors, Brain Tumors and NF1, GI Disorders, Hematologic Disorders, Impact on School Performance, Surgery for Cutaneous Neurofibromas, Genetic Counseling, Pain Management

3 easy ways to RSVP by February 1: (Seating is limited)

1. online by visiting www.NFCalifornia.org
2. By emailing events@NFCalifornia.org
3. Call NFC office 707-469-0467

NEUROFIBROMATOSIS NF CALIFORNIA

UCSF Benioff Children's Hospital

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Enrolling Research Study

The RasCal Study –

RASopathy Associated Traits

California

Dr. Weiss and Dr. Rauen are enrolling families in their federally funded study. They are looking for families with someone affected by NF1, Costello syndrome, cardio-facio-cutaneous syndrome, or Noonan syndrome. The affected person, both biological parents and a healthy sibling can participate. Participating families will complete several brief questionnaires over the mail or phone. Saliva samples will also be collected. This can be done at home and returned via mail. Participation in this research study is very important because it can help identify variation that puts people at higher risk for different features of RASopathies. This research may also help us understand related traits in the general population, so it may ultimately benefit not only families affected by RASopathies, but also those affected by common disorders like autism and cancer.

If you would like to learn more about this study, please visit http://anp.ucsf.edu/research/studies/rascal or contact the study coordinator Brigid Adviento at (415) 476-6988 or brigid.adviento@ucsf.edu

Brigid Adviento, Study Coordinator

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