

Why I go

By Jennifer Bishop

"Why go to a CFC conference?" I am often asked.

The reasons to stay home are clear enough: time, money and energy are especially finite for the parent of a child with a rare condition...plus I'm basically shy. Wouldn't it be more fun NOT to dwell on the realities of his irreversible condition? Having attended past conferences, could I have anything "useful" left to learn?

Still, I am surprised by the original question, and sad to think the answer is not universally understood.

You never step into the same stream twice, as the saying goes, and this is certainly true of a CFC conference. Although there are familiar faces-- families and doctors who return every two years-- the experience is always new and bracing. It calls me to reach both inside and outside of myself, and each time, I am glad I did.

The 2009 conference, the largest ever, brought together families and doctors from all over the world; and it recognized the consolidation of four rare syndromes into one category - the "Ras-opathies"- which now forms the



Nathaniel, Jennifer and Theo

largest existing genetic disorder.

There is power in numbers, as the ebullient Dr. Rauen points out in her inspiring

presentation. And with numbers like ours, and pre-existing research on this pathway also known as the cancer pathway, possibilities exist for clinical drug treatment trials - which

might impact future CFC children and open a new way for medicine to treat genetic disorders. All it takes is enough people getting together and sharing information.

I have seen measurable progress on the scientific front throughout the duration of just 3 conferences. From collecting and banking blood, to discovering the genes, to the discussion of treatment trials...this energy is generated by both the doctors and CFC International, under the guidance of Brenda Conger, and with the contributions of many families. The importance of furthering research and helping future children born with CFC is self-evident, and exciting. Going to the conferences, and submitting medical information on our children, is a way to be part of something larger than myself.

But that's probably not the real reason I go. Yes, as Nathaniel's mom, I go to learn and participate. But as a photographer, I also go to see. And what I see brings me back deeper into my own experience as Nathaniel's mom.

Why I go continued on page 6.

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CFC International

183 Brown Road

Vestal, NY 13850 USA

(607) 772-9666 (Evenings and weekends)

E-mail: bconger@cfcysndrome.org

Web page: <http://www.cfcysndrome.org>

We offer information, support, newsletters, an address directory, brochure and Parent's Guide. Our mission is to assist those whose lives are touched by CFC Syndrome and to improve lives through family support, research and education. The group is self-funded. Contributions are gratefully accepted and will help the next family to receive information about CFC Syndrome.

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Message from the President

Our Fifth International Family Conference and Medical Clinic program in Berkeley, California drew 176 participants from eight countries making August's gathering the largest and one of the most successful ever. Twenty-two new families joined twenty-two veteran family attendees representing the United States, Mexico, Canada, Australia, Belgium, Ireland, England and Germany. This remarkable ten-year anniversary event cost CFC International \$23,000 from our fundraising sources. We are thankful to all of you who have helped us host our conference and medical clinic program. During these tough economic times, each and every penny is so appreciated. We thank all of you for supporting our mission and bringing researchers and families together again.

In addition to our CFC families, the Noonan, Costello and Neurofibromatosis syndrome organizations were also on site at the same hotel. Saturday evening topped off a very fast paced Scientific Symposium with all the syndrome groups of the RAS MAPK pathway joining forces for an evening social so the researchers could meet the families.

It still takes my breath away when I think back to ten years ago when our group was just getting up and running. Never in my wildest dreams could I imagine the advances that would be made in such a short time. Although we have come so very far, we are just heading into new waters to look at potential treatments for affected individuals along this very famous and extensively studied pathway. I can only dream of a better day for all children, adults and their families living with these syndromes. As I watch our own 16-year-old son and compare him to the high school special needs students I work with at Binghamton High School, I see the impact of the MEK2 gene on his body. He shuffles along due to the low muscle tone. He tires so very easily and at times I wonder how he will keep up with his work-study job and the other activities in life. What is so different with this pathway of disorders is that the gene mutation is in every cell of the body and keeps affecting different areas as the person ages. Life is never dull and we never quite know what to expect! It is very hard to not worry about the future for our son and all the other affected individuals. We are humbled by the dedication of the researchers in this field and their dedication to our small population of children. We could never have progressed this far without them.

I am hopeful for the future. Just reading genetics reports that state that the affected child was tested for CFC within the first few months of life brings tears to my eyes and joy into my heart! So many veteran parents searched for years and years for answers to their child's rare condition. Unlocking the CFC syndrome mystery is not only helping our children, but in time can also assist with other medical conditions found on the RAS MAPK pathway. I am proud to say we are all part of making history as we open the door for treatments in the upcoming years.

Brenda Conger

E-mail: bconger@cfcysndrome.org

Donations

Thank you!

CFC International is grateful to its supporters for their generosity. We extend our deepest thanks to the contributors listed below for their kind donations.

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DEDICATED TO



Harley Crawford

March 5, 2005 - September 29, 2009

Tiny Angel rest your wings
sit with me for a while.
How I long to hold your hand,
And see your tender smile.
Tiny Angel, look at me,
I want this image clear....
That I will forget your precious face
Is my biggest fear.

Tiny Angel can you tell me,
Why you have gone away?
You weren't here for very long
Why is it, you couldn't stay?
Tiny Angel shook her head,
"These things I do not know
But I do know that you love me,
And that I love you so".

-Author Unknown

Swimming, Riding and Running for CFC in the Big Apple

On Sunday July 26th, 2009, Nola Rose Iacobelli's Uncle Danny competed in the New York City Triathlon to raise funds for CFC.

When Danny Hojnowski decided to compete for the first time in a triathlon we knew that this was a big deal and wanted it to really mean something, and that's when we both knew that he would do this to raise money for CFC. Anyone who meets our adorable niece knows that her big smile is all it takes to melt your heart, the decision was made. So Danny began training for over three months nearly everyday either biking, running, or swimming so he could compete at his best.

The day of the triathlon was a grey and muggy NYC summer day, but the air was filled with excitement for the race! It began with a mile long swim in the Hudson River, not the prettiest body of water in NY state. Then it was onto a 25 mile bike ride up the West Side Highway and into the Bronx, I don't think anyone knew how many hills were up there. My mother in-law and I were there to cheer on Danny through the first part of the bike race, truly amazed at the amount of determination in all of the athletes. The last leg was a 6.2 mile run with a slow up-hill start from the water, and then a big loop through Central Park. While we were cheering on the runners, the Paratriathlon Group came through and an older woman who happened upon the race said, "It really gives you hope in the human spirit", and I thought to myself she couldn't be more right. Seeing so many triumph over adversity to compete at this level, not to mention the commitment of all the athletes was truly awe inspiring. Danny finished the race in 3 hours and 48 minutes, a very respectable time, but the biggest victory of that day was the money that he was able to raise for CFC International which was a grand total of \$2,606.



Danny Hojnowski running the New York Triathlon

7th Annual "Toast the Angels" raises \$7,132 Despite Bleak Economy

Despite a terrible time for the local and national economy, the 7th annual "Toast the Angels" held on April 4th had a very nice turn out with 120 guests. The silent auction was not as abundant as the year prior but everyone still had a good time bidding. As usual, chef Russell and his wife Melissa came up with a delicious 6 course meal fit for a king! The wine paring was top notch from Dick Reno who owns Chateau LaFayette



Clifford Conger

Reneau on Senaca Lake in New York State. The Conger family would like to thank everyone for their annual support at this tasty event and especially Dan and Karen Gates who won the bid on a catered party by Chef Russell. Clifford is still talking about driving your girls all over the property in your golf cart during this party! Mark your calendars for April 17, 2010 when we host the next "Toast the Angels" at the Kalurah Shrine Center in Endicott, NY.

Valley Bash raises over \$7,000 to benefit CFC International

Each year the Getts Family pulls together their community to host a fun filled day to help worthy causes. This year CFC International was honored to be chosen as their cause. On Sunday August 2, 2009, 180 guests attended the annual Valley Bash at the Colonial Tavern in Oxford, Connecticut. Although the day started out with a huge downpour, the skies did clear and everyone had a fantastic time. The day also included a two mile Hike for Hope. Burns Construction, Triple Stitch, Southern Connecticut Gas, Pure Platinum and the Colonial Tavern sponsored the Valley Bash. The fun filled day kicked off at 2:00 PM with food and beverages, games, swimming, live music by Gunslinger Squirrel, and comedy hypnotist HypnoLorenzo. Proceeds from the event were donated to CFC International. Erik Lydiksen, dad to Luke, supported CFC International by selling tickets and rounding up guests to attend. We thank Erik and the Getts family for their support and their donation of over \$7,000 to CFC International.



CFC International Joins NDRI Biorepository

The CFC International Board of Directors is pleased to announce their newly established partnership with the National Disease Research Interchange (NDRI) tissue and biorepository. The NDRI is a non-profit organization founded in 1980 in the US to provide approved biomedical researchers with access to human tissue. “The way to study human disease is to study human tissue,” states Lee Ducat, founder and president of NDRI and founder of JDRF (the Juvenile Diabetes Research Foundation). “Before NDRI existed, scientists could not get human tissue easily or in any continuous way for their studies. In those days, most human tissue was trashed or incinerated.

NDRI announced in 2008 that the National Institutes of Health (NIH) awarded a \$7.6 million grant to NDRI to enable the human tissue science organization to expand its core mission to collect, process, and distribute donated human tissue to hundreds of leading research facilities throughout the US, for the next five years. Since 1980, NDRI has served a vital need providing some 5,000 scientists with more than 300,000 human biomaterials, leading to more than 2,500 papers published in scholarly journals on diseases from diabetes to cancer to HIV and rare diseases. Today NDRI is the leading national organization that connects donated human tissue with the research scientists who need it to develop new therapies and cures for human diseases. NDRI serves almost every disease imaginable.

Some 20,000 tissues pass through NDRI each year to about 500 scientists, at about 250 of the finest university-based research centers. The role that NDRI plays in science today has grown tremendously with the number of tissues, derivatives and initiatives they provide, including their “Stem Cell Initiative”, providing vital stem cell material from discarded birth tissues. NDRI is able to provide thousands of cancer tumor samples each year helping support some of the most important cancer studies in the country. NDRI has special projects in type 1 and type 2 diabetes and supports eye disease research in retinopathy, glaucoma, macular degeneration, retinitis pigmentosa, and other eye diseases. NDRI administers a large collection of uniquely valuable families within a genetics registry. This program provides DNA, cell lines

and medical history data to scientists for the genetics of thyroid disease, type 1 diabetes and autoimmune diseases.

Funded in part by the National Institutes of Health (NIH), NDRI provides biomaterials to more than 200 of the nation’s most prominent academic-based research centers including the Harvard Medical School, the Massachusetts Institute of Technology, Mt. Sinai School of Medicine, Stanford University, and Thomas Jefferson University, among others. NDRI also provides tissues to government agencies and grantees including the NIH, the U.S. Food & Drug Administration, the U.S. Department of Agriculture, The Centers for Disease Control, and to some of the nation’s top Pharma, Biotech R&D programs.

This NIH support over the next five years will enable the growth and development of the NDRI “National Rare Disease Human Tissue Resource.” NDRI has built a parallel, “National Rare Disease Resource” serving literally hundreds of rare disease scientists. This program has collected thousands of donated rare disease tissues from donors throughout the country. The NDRI “Online Catalog of Biospecimens” holds over 3,300 rare disease tissues, which can be accessed easily and instantly by scientists studying some 120 rare diseases. In addition, most of these rare diseases do not have animal models useful for research purposes, so the human tissues are vitally needed by scientists for their studies. There are 15 Voluntary Health Organizations joined in the “NDRI Rare Disease Alliance,” helping to support and grow research among the various rare diseases. CFC International is pleased to join the other Voluntary Health Organizations to help provide researchers and families with even more research to help promote treatment for this rare syndrome.

A glimpse is not a vision. But to a man on a mountain road at night, a glimpse of the next three feet of road may matter more than a vision of the horizon.

Why I go (Continued)

Picture this scene from a clinic exam: a beautiful, young baby with a killer smile is propped up on a round table, encircled by its proud and worried parents and several doctors from all over the world. As the doctors scrutinize this baby with interest both kind and serious, the room is silent, as if the combined weight of thoughts and feelings surrounding this tiny child is more than the glass-walled room can bear. There is no room for sound, and nothing enough that can be said.

What would you like to ask us, the doctors finally offer. Then the mother's plaintive question: Although the gene test came back positive, could there be a mistake? Could it be a different syndrome?

These parents have good reason to wonder and seek answers, but the question brings me back to my own early doubts. I hoped the same thing when my baby was small. CFC is a club nobody chooses to belong to. And the conference, bringing together so many ages, stages, and expressions of CFC, puts a lot out there for the new parents to take in. I wondered once, too, was my baby, seemingly full of unexpressed potential - a mystery as all babies should rightfully be - struggling to grow, only to face so many medical and developmental challenges?

I can only imagine what the doctors might be feeling. They have taken time out of busy schedules to travel, and meet and talk with these families, not only in clinic but at meals, in the hallways and elevators. CFC is so rare and scattered worldwide, the conference is a singular opportunity to see many affected children at once. Yet, often there are no answers to offer the parents. Each child is different, and stands to teach something new to everyone - doctors and parents alike. The young parents are probably relieved to hear this, remembering that their baby is still really only their baby. A syndrome does not claim the individual, even though the shared traits are observed.

Although these doctors have dedicated their lives to studying this disorder, they do not live with it the way families do. There is a tacit trust between doctor and patient here. Both choose to be here in the same room, to learn from each other. But they inhabit different realms within the room. And maybe the only thing shared equally by both parties is respect for the mystery - the understanding that neither knows what might be learned by such a meeting.

Picture another clinic exam: this one makes history. All the specialists are meeting in one room with the oldest living person with (confirmed) CFC. I am moved by the gathering of these people in this time and place. And even more, by the dignity of these older parents. They laugh easily and share the

details of their daughter's medical history as she explores the room. She is playful with the doctors, trying to pick up their clipboards and coffee cups. Her parents have one eye on her always. I have seen them guiding her down the hallways of the hotel; it takes both of them to bodily direct her to keep her on track.

As she and the doctors exchange curious smiles, there is a deep sense of awe for the rare and special person everyone in the room knows she is. And I feel the gulf between doctor and patient is filled with respect for human strength of all kinds - the abilities of intelligence, knowledge and medicine, and the resilience of love that can upstage suffering.

That is part of what I see.

Everywhere at this conference, I see small, unforgettable moments, some of which I can catch with my camera. Cliffy holding his dad's hand. Jamie's fascination with the light from the projector. Jack's infectious smile. Emily wolfing down scrambled eggs at breakfast, with help from her dad, who also happens to keep old footballs and sporting equipment in his car in case anyone wants to play (my son Theo did). Amara, whose face lights up at the sound of her dad's voice. Jessie who hugs the bigger girls. Avery wriggling his body around in new joyful ways. Mothers and fathers from other countries sharing photos of a child who could not attend- because they are too medically fragile to travel, or in the hospital. Each of the 44 families present has their own story worth hearing and seeing, which my camera catches just a glimpse of.

When I put the camera down, I recognize the same deer-in-headlights look on photographer Rick Guidotti's face, that I must have...because we are witnessing in every family a level of unconditional love, the sheer wattage of which could light up the hotel without any help from Pacific Gas & Electric. And the energy of these families reminds me to find my own spirit inside.

That's the kind of power in numbers I go for.

For All You Do

*Thank you so much for all you do;
You're truly a delight;
When my life overwhelms and does me in,
You make everything all right.*

By Karl and Joanna Fuchs

From Belgium to Berkeley

The flight was a nice experience, I have never flown so far. It was a tiring 10 hour flight but worth doing it. When I arrived I lay down on the hotel bed and before I knew I was asleep and slept for 4 hours. My mother and I made the trip together as my brother Mattias became sick and had to be hospitalized. My dad stayed home to look after him.

When I went with my mother to the welcome reception I noticed that there were more people than I expected. There we met Paul and Deidre from Dublin Ireland, who also could speak Dutch. Because of that we have spoken a lot with them about all kind of things. The next day we also met the Holland family. They invited me to come along to downtown Berkeley, we drove around the city and were looking for Jamba Juice but it was closed so we went to Yogurtland. This, Walgreens and Starbucks are shops we don't have in Belgium so it was again a new experience. The next day we went with a bunch of teenagers to the movie. Unfortunately it wasn't my kind of movie, it was more for girls. But still I enjoyed myself. On Wednesday we did some sightseeing in downtown San Francisco. It was beautiful and it was fantastic to visit places which I've only seen on TV or in the movies.

With my mother I also attended the workshops and the presentations. The professors did their best to explain everything and to keep it understandable, even for me with my basic medical knowledge. Because it was in English, it was sometimes hard to understand what exactly was being said. I understood just enough to know what they were saying. This all was very tiring, that's why I had most of the time a bit of a head-ache. But overall it was very interesting and educational and in particular, my knowledge about CFC increased a lot.



Kevin Bos and his mother from Belgium

staying in Poland with the scouting (~pathfinders). It was good that we phoned everyday to the hospital to get information about how Mattias was doing.

That Mattias wasn't there felt weird. We planned to be there with the whole family instead of only me and my mother. I missed him very much, also because I hadn't seen him for two weeks before I went to SF. I was

At the end of the week my mother went back to Belgium and at the same time my father arrived. This gave me the impression that the staff working at the hotel must think that they were divorced. My father and I left the next day to go on a trip with an RV around mid CA for a week. We visited Yosemite Park, Mono Lake, a Ghost town called Bodie, the Big Trees and the Gold Rush Area around Coloma. The trip was a very big experience and it was a lot of fun. Unfortunately my father couldn't meet the Holland family, who were so kind to invite us to their home in Sacramento, as the rafting took longer than expected. But you never know, maybe at a next conference or at another opportunity.

I had such a great time during the conference so I hope to attend another one in the future, but this time with the whole family.

Kevin Bos, age 15
Belgium

Incidence, Severity and Prognosis of Cardiac Disease in CFC Syndrome

Dr. Mary Ella Pierpont attended the 2009 CFC International Conference to discuss her research study on the incidence, severity, and prognosis of cardiac disease in CFC syndrome. Dr. Pierpont is a geneticist and a pediatric cardiologist at Children's Hospital and Clinics of Minnesota, and was also present at the 2007 CFC conference in Orlando, FL. She has determined that the knowledge regarding cardiac disease in CFC syndrome is widely unknown, and is an area that needs definite improvement.

Dr. Pierpont's study will involve looking at CFC patient's medical records, particularly their cardiology records and genetic test results in order to evaluate the incidence, severity, and prognosis of cardiac disease in these patients as well as evaluate whether mutations in the 4 genes causing CFC syndrome contribute equally to the incidence and severity of the cardiac disease.

The questions Dr. Pierpont hopes to answer with her study will have great impact for families and children with CFC syndrome. The study is expected to provide information to physicians caring for individuals with CFC as to long-term expectations and important areas to consider in their care.

Dr. Pierpont had a booth set up at the conference where she was available to discuss the study with families, answer any questions, and obtain consent from those families wishing to participate in her study.

Photo Gallery



Michael, Lauren, & Jennifer Wallace from Texas



Kinley & Shelly Greenhaw from Oklahoma



Jesus & Patricio Acosta from Mexico



Ted Tobby from Hawaii gives a loving kiss to his daughter Amara



Avery Thomas from Arizona dancing in Kiddie Corp playroom



Emily & Ernie Santa Cruz from California take a rest



Judy, Jessie, & Rocky Bartolo from Australia



Eddie, Eleanor, Robert, & Matthew Crowe from Ireland



Roseanna, Lacey, & Keith Allen from Colorado



Armaan Rangnekar from CT visiting with Kasi Hawkins-Rivers from Michigan



Jennifer, Darin and Nola Rose Icobelli from St. James, New York



2000 conference with the "three darlings", Emily, Jack, & Meg



Michael & Stan Pavilonis from Illinois



Rachael Holland, California and Sarah Lindgren, Wisconsin



Emily, Patricia, & Jessica Hannan from England



Emily, Jack & Meg meet up again in 2009



Participants at the 5th International CFC Family Conference in Berkeley, California

Genetic Syndromes of the Ras/MAPK Pathway: From Bedside to Bench and Back, August 1-2 in Berkeley, CA

Review by: Kyle Stowell

The Ras/MAPK pathway conference was held at a hotel at the Berkeley Marina on August 1st and 2nd. It consisted of presentations from researchers and medical doctors who have interest in the Ras/MAPK pathway due to its link to cancer and 6 genetic syndromes – CFC, Noonan, Costello, Neurofibromatosis Type I, LEOPARD, and Legius. These are a few of my observations. This conference was very technical in nature. I have attempted to simplify the language and make it easier for a non-technical person to understand. This is not an easy task.

The Ras/MAPK pathway is a message signaling pathway that is used by the body to pass a message from outside the cell to the cell nucleus. The types of messages that are relayed through this pathway include cell differentiation (become a liver cell, a muscle cell, a neuron, a skin cell, etc.), apoptosis (cell death), and cell division. This pathway is complex, making it difficult to describe. A simple

explanation would be that it uses a series of proteins to pass messages in the same way a bucket brigade works. The proteins are formed from the pattern that DNA provides. The proteins involved in the bucket brigade come from different genes. When one of these genes has a mutation, it causes problems and determines which syndrome applies – the CFC-causing genes are B-Raf, MEK1 and MEK2. A new term being used by many of the researchers to refer to the collection of syndromes on the pathway is RASopathies

Keep in mind that there is a lot of overlap of symptoms between the syndromes. This is to be expected because the genes for the different syndromes are on the same pathway. At the same time, symptoms can vary greatly even among those with the same mutation on the same gene. A very interesting note that came out of the CFC conference presentations was presented by Dr. Grace Yoon, a neurogeneticist from Toronto. She showed the cognitive function of three different individuals with the same mutation (Q257R) on the B-Raf gene. One had a mild mental disability, one was severely affected, and a third had a profound mental disability. Each person has about 30,000 genes, all expressed a little different and all affecting how our other genes are expressed. This is what makes each of us unique in the world.

Several of the researchers who presented spoke about the drugs that have been developed to treat cancers that are caused by mutations on the pathway. 70% of all melanoma skin cancers are caused by mutations on the B-Raf gene,



Participants at the Genetic Syndromes of the Ras/MAPK Pathway Scientific Symposium



with a high majority of the mutations being the “V600E” mutation (this describes the gene location where the mutation occurs). If a skin cell develops a B-Raf mutation, the Ras/MAPK pathway becomes activated independent of the signals it receives from the body. It continually divides due to the activation, causing cancer. There is a drug called Sorafenib that was developed by Nexavar and Bayer that targets the V600E mutation. The drug is a molecule that was designed to bind with the molecular structure of B-Raf so that the message being passed by the above-mentioned “bucket brigade” is stopped. This shuts down the pathway, thereby preventing cancer growth. This drug worked very well in a test-tube, but not so well in clinical trials. It is thought that the pathway has feedback loops that overcome the blocking of the message to keep the pathway activated. Kidney and liver cancer patients apparently have very few treatment options, so it has been approved to treat those two cancers.

Another researcher spoke about a class of drugs called MEK inhibitors. These drugs work in the same way as B-Raf inhibitors (blocking the bucket brigade by creating a molecule that binds with the molecular structure of the target protein), except that they target the MEK gene. Right now there are about 10 companies working on MEK inhibitors. Some of them have shown great promise in treating cancers caused by pathway mutations. One drawback that is being found is that tumors start to grow again if the patient stops taking the drug.

How might these classes of drugs help our kids? In the test tube, most of the mutations our kids have cause the pathway to become activated. So if the message can be blocked, the pathway is not activated and some of the symptoms in our kids might go away. The only way to determine if the drugs will be effective is through clinical trials. These take time and money. They also require willing patients. CFC Syndrome has a very small cohort of patients. If all of the Rasopathy groups stick together, researchers will have access to a larger group of participants who are hopefully willing to participate in clinical trials.

There was quite a bit of interest in modeling various pathway mutations in mice and zebrafish. One researcher tried introducing the V600E cancer causing mutation in knock-in mice, but the embryos constantly died, suggesting that “sustained activation of the [pathway] is incompatible with survival.” There was quite a bit of work done on CFC mutations in zebrafish. Researchers introduced B-Raf and MEK mutations in zebrafish and observed their development. Their development was significantly altered. In the next step, they used “chemical inhibitors” of the pathway when the zebrafish embryos were developing, and found that their development was near-normal. Their conclusion was that “treatment with a MEK inhibitor can restore the normal early development of the embryo, without the additional, unwanted developmental effects of the drug.”

One more fascinating bit of research was observed with Neurofibromatosis Type I knock-in mice. These mice had learning disabilities and attention deficits that were due to the NF1 genetic mutation. To quote from the abstract: “Recently, we discovered that statins, at concentrations ineffective in controls, can reverse their spatial learning and attention impairments. Strikingly, recently completed pilot clinical trials...uncovered suggestive evidence that statins may also be able to reverse cognitive deficits in children with NF1.” This is an exciting discovery with potential to help our kids’ cognitive difficulties. It was noted that statin drugs given at an early age can negatively affect myelination. Myelin is a material that forms a layer, the Myelin sheath, around the parts of our nerves and is essential for the proper functioning of the nervous system, especially coordination. So more research is needed before we put our kids on statin drugs.

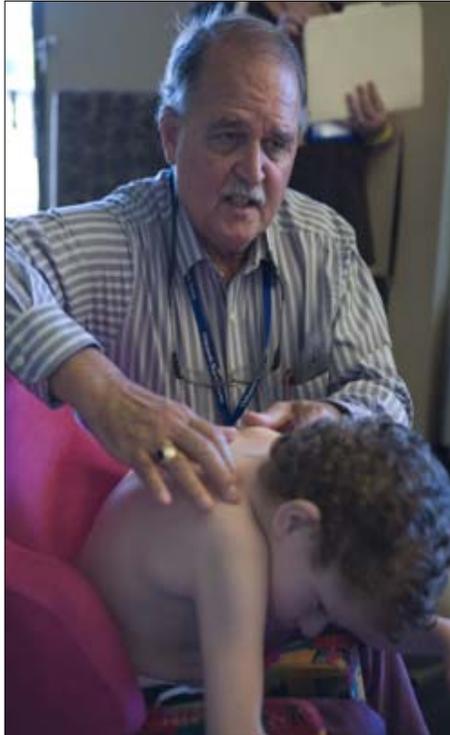
It was personally exciting for me to see so much research into the Ras/MAPK pathway, specifically relating to the Rasopathies. I believe it will result in treatments that will help our kids, although it will probably take 3-5 years. I think it is imperative for the syndrome groups to work together in some form so that researchers have enough participants for their studies and so more funding dollars will be directed our way. Many thanks to Dr. Rauen and her group for organizing this scientific meeting of the minds.

Bone in CFC syndrome

Dr. Reinker and Dr. Stevenson attended the 5th CFC International Conference in Berkeley, California. Dr. Reinker is an orthopedic surgeon and Dr. Stevenson is a pediatrician and medical geneticist. Both physicians are currently studying the orthopedic manifestations of cardiofaciocutaneous (CFC) syndrome. Although CFC syndrome is a rare disorder, the overlapping clinical features of the various other related syndromes of the Ras-MAPK pathway (e.g. neurofibromatosis type 1 (NF1), Noonan syndrome, Costello syndrome) help provide insight into potential clinical problems and the causes in CFC syndrome. It appears that orthopedic abnormalities are seen in all of these related conditions. However, a detailed clinical description of the orthopedic findings in CFC syndrome is lacking and there is little data on the effects of the various genes known to cause CFC syndrome on the cells that build and break down bone.

Dr. Reinker and Dr. Stevenson conducted research during the conference in order to obtain more information on the clinical orthopedic features, natural history of the musculoskeletal features, and cellular function of bone cells. During the conference individuals and their families who

were interested in participating in the various research projects were examined and enrolled in the respective research studies. A medical history and examination to document musculoskeletal features were obtained. Dr. Stevenson also collected biologic samples for future



Dr. Kent Reinker, The University of Texas, conducting orthopaedic exams

examination. Urine was obtained in order to look at biologic markers of bone resorption to see if the bones are being broken down more quickly than individuals without CFC syndrome. Blood samples were also obtained in order to collect specific bone cells called “osteoclasts”, which are the cells that break down and remodel bone, in order to see if these cells are hyperactive.

Dr. Stevenson and his group are continuing to investigate the effects of the genes that cause CFC syndrome on bone

remodeling. Families who are interested in orthopaedic research and did not have a chance to enroll in Dr. Stevenson’s study can contact him and his research coordinators at 1-877-942-6600.

Dr. Reinker was able to interview and/or examine 42 individuals with MAPK disorders. The data from these interviews has been placed on a computerized database and are going to be analyzed in more detail some time during the next 3-4 months. We expect that the results can be made ready for publication during the next year, and that this data will help a lot to further define the disorders. Detailed conclusions will have to await detailed analysis. Some preliminary conclusions are obvious already, however.

First, Noonan syndrome, CFC, and Costello syndrome have quite different orthopaedic manifestations.

Second, many of the orthopaedic problems seen in these disorders are unusual in patients who do not have MAPK disorders. In some instances, the pathophysiology leading to the problems are not very clear. For example, the chronic pain seen in many adult patients with Noonan syndrome is not well explained at present. The calluses seen on the feet

of many CFC patients are striking, unique and not very well explained.

Third, there is some inkling of a difference in orthopaedic manifestations depending upon the gene abnormality that is associated with the problem. This needs to be evaluated more carefully in our analysis of the data. We may not have enough patients in each category to make definitive conclusions, but we may at least be better able to frame more interesting and pertinent questions for future study.

Dr. Reinker has received clinical information from several participants since the meeting, and this information has been added to the database. The resultant database is the largest collection of orthopaedic data on these disorders to date. When analyzed properly, it is sure to give valuable information that can be shared with practitioners and patients in the near future.

National DNA Day at Binghamton High School

Mr. Pourby and Mr. Larnerd’s Biology classes celebrated the April 24 National DNA Day along with the assistance of Mrs. Conger and the National Human Genome Research Institute (NHGRI).

Established by Congress seven years ago, National DNA Day commemorates the successful completion of the Human Genome Project in 2003 and the discovery of DNA’s double helix by Watson and Crick in 1953. Of course, National DNA Day is much more than a time to honor historical achievements. It’s a day filled with opportunities for students, teachers and the public to learn how the exciting field of



Mrs. Conger

genome research will soon touch all of our lives.

Each year the NHGRI supports a diverse number of activities to foster interaction

between genome researchers and the public. For instance, NHGRI researchers, called DNA Day

Ambassadors, have visited dozens of high schools throughout the nation during April to give presentations and field questions from students.

Binghamton High School was fortunate to have their own “in house” expert on hand to present in the classes. In addition to her jobs on the School Based Intervention Team, Work-Study and Transition coordinator, Brenda is also the Executive Director of CFC International.

As a Binghamton High School DNA Ambassador, Mrs. Conger presented a short video on CFC syndrome and then fielded questions from the students. She also utilized a webcast from the NHGRI site titled, “The Genome Era: What It Means to You”. Mr. Larned’s class followed up with a trip to Roberson’s DNA lab for hands on activities.

Brenda hopes that personalizing the future of health care options and careers in the research field will spark interest in students at Binghamton High School who will help shape the future of research to make life better for all of us.

The “Rasopathies” Enter a New Era

By: Dr. Katherine Rauen, UCSF Helen Diller Family Comprehensive Cancer Center

History was made during the 5th CFC International Family Conference held in August 2009 in Berkeley, CA and it was nice seeing so many families be part of it. For the first time, 6 different advocacy groups of the Ras Pathway Syndromes came together. These advocacy gatherings were anchored by the NIH-sponsored scientific symposium “Genetic Syndromes of the Ras/MAPK Pathway: From Bedside to Bench and Back” [<http://cancer.ucsf.edu/raspathway2009/index.php>]. This scientific symposium not only included international experts on Ras syndromes, but also included scientists in cancer research and drug development who are the leading experts in the Ras pathway. By bringing such a broad group of researchers together to focus on the “RASopathies”, we were able to spark interest in the scientific community and forge many new collaborations.

With the presence of CFC International and the support from the families, YOU made the scientific symposium the success that it was. Nearly 200 participants came together including leading researchers, clinicians and families from around the world. Studying this recently identified group of “RASopathies” together, of which CFC is one, broke new ground; it allowed us to embark directly toward strategies for possible clinical trials. We know we still have a long way to

go and we recognize the many steps it will take to get there, but in my view, I felt as though the research symposium moved us in the right direction. By coming all together, with the scientific symposium along side the Family Conference, I felt the study of CFC was propelled into a new stratosphere.

Families with CFC Syndrome have joined the Ras Family of Syndromes. You have become part of a larger community— although you have your own identity and special uniqueness, sometimes it really does take a village to move forward. As a larger group, you have clout; and by putting all the RASopathies together —this may well



Dr. Katherine Rauen

represent one of the largest syndromes groups known. Learning about other syndromes in this family of syndromes will help us learn more about CFC syndrome, and the treatments and best practices identified for one syndrome may help another. But most importantly, this historic weekend exponentially

expanded your clinical base and your research base ---- there are now so many more doctors and researchers that know about CFC syndrome. This is just the beginning of new chapter.

The NeuroCardioFacio Cutaneous Syndromes: Overview and update on phenotypes and genes

The term “neurocardiofaciocutaneous syndromes” (NCFCS) designates a family of genetic conditions including: Noonan syndrome (NS), LEOPARD (Lentiginos, ECG conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness) syndrome (LS),

Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFCS), Neurofibromatosis 1 (NF1) and the recently described neurofibromatosis like syndrome (NFLS), also known as Legius syndrome.



Dr. Giovanni Neri from Rome, Italy

These developmental disorders share several clinical manifestations such as typical facial appearance, cardiovascular defects, growth failure, ectodermal, musculoskeletal, genitourinary and gastrointestinal anomalies, as well as different degrees of developmental delay. Given these similarities, any attempt at diagnosis on purely clinical grounds can be very challenging, especially among NS, LS, CS and CFCS.

SHARED CLINICAL MANIFESTATIONS

The facial phenotype has a tendency to become more distinct over the years. During the newborn period and in early infancy it is difficult to make a distinctive diagnosis based on facial gestalt. The facial features observed in most cases of NCFCS are a relative macrocephaly with high forehead, hypertelorism with epicanthic folds, ptosis and downslanting palpebral fissures. The nose is usually short, with a depressed root, anteverted nostrils and a bulbous tip. The ears can be low-set and posteriorly angulated.

Among the cardiac defects, those most frequently observed are pulmonic stenosis and hypertrophic cardiomyopathy. Atrial and/or ventricular septal defects are less frequent findings.

The involvement of the skin and the hair can be significant. The hair is typically curly, sparse or absent;

eyebrows and eyelashes can be sparse or absent as well. The skin can be affected with a particular disorder called ulerythema ophryogenes, characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Café-au-lait spots, the hallmark of NF1 and NFLS, can also be seen in NS, LS, CS and CFCS.

The neonatal period is often complicated by moderate to severe feeding difficulties, sometimes requiring placement of a nasogastric cannula or a G-tube, and usually resulting in failure to thrive. The feeding issues may be related to the muscular hypotonia, an almost constant feature, and to immaturity of the esophageal function, resulting in gastro-esophageal reflux and vomiting.

A growth and pubertal delay is almost invariably present, and the affected subjects generally end up with a short stature. In males, cryptorchidism is common and it may require surgical correction.

Other typical features observed in patients affected with NCFCS are:

- chest deformities
 - pectus carinatum (in which the sternum protrudes and the chest is pushed out)
 - pectus excavatum (in which the sternum is depressed and the chest is hollow)
- joint hyperextensibility
- joint contractures
- spine deformities
 - scoliosis (in which the spine abnormally rotates and curves from side to side)
 - kyphosis (an exaggerated curvature of the spine that gives the back a rounded appearance)
- short and webbed neck.

Looking at all the overlapping features, some important questions arise: why do NS, LS, CS, CFCS, NF1, NFLS all look alike? What is their common denominator?

THE RAS/MAPK PATHWAY

The answer to the above question is to be found in the fact that mutations underlying the NCFCS affect genes operating in the same RAS/MAPK signalling pathway, which is crucial for cell proliferation, differentiation, survival and death. These genes are listed in the Table. Mutations usually result in increase of their expression, accelerating the activity of the pathway beyond normal limits.

NCFC SYNDROMES AND UNDERLYING GENES

| CONDITION | GENE |
|----------------------|---------------------------------------|
| Noonan syndrome | PTPN11, RAF1, SOS1, KRAS, NRAS, SHOC2 |
| LEOPARD syndrome | PTPN11, RAF1, BRAF |
| Costello syndrome | HRAS |
| CFC syndrome | BRAF, MEK1/2, KRAS |
| Neurofibromatosis 1 | NF1 |
| Legius syndrome/NFLS | SPRED1 |

Despite all the similarities, every syndrome has some peculiar traits.

NS is characterized by the possible occurrence of juvenile myelo-monocytic leukaemia and bleeding disorders. In addition, most affected individuals have a normal intellectual development.

Distinctive of CS are a facial appearance that reminds of what is seen in a storage disorder, the ulnar deviation of wrists and fingers, the presence of papillomata and, above all, a high frequency of solid tumours (rhabdomyosarcoma and neuroblastoma in young children and transitional cell carcinoma of the bladder in adolescents and young adults).

CFCS has typically a more severe skin and hair involvement, and virtually all affected subjects appear to be intellectually delayed.

Over the last decade, our knowledge of NCFCS has greatly improved, both clinically and molecularly, thanks also to the efforts and commitment of the family support groups. Yet, much remains to be done. Mutations in the genes known to date do not account for all cases of NCFCS, suggesting that other genes are still awaiting to be discovered. More importantly, it is time to start thinking about possible cures. Interestingly, most genes of the RAS/MAPK pathway are oncogenes, whose somatic mutations can cause cancer. For instance, BRAF mutations in skin cells can cause melanoma, a relatively common cancer. Studies are already underway to identify drugs capable of blocking the excessive activity of mutant BRAF, and of other mutant genes as well. Recent studies highlight the therapeutic potential of drugs capable of inhibiting MEK activity. Other therapeutic perspectives are given by drugs blocking the tyrosine-kinase activity (imatinib and sorafenib) and the farnesylfarnesylation (lonafarnib) of the RAS genes, both essential for the signal transduction along the pathway. Similar drugs may turn out to be applicable to the treatment of NCFCS.

Giorgia Mancano and Giovanni Neri
 Institute of Medical Genetics
 Catholic University School of Medicine
 Rome, Italy
 E-mail: gigia308@gmail.com gneri@rm.unicatt.it

GLOSSARY

- hypertelorism: an abnormally increased distance between the eyes.
- epicanthic fold: a vertical skin fold over the nasal corner of the eye.
- ptosis: drooping of the upper eyelid.
- pulmonic stenosis: heart malformation in which outflow of blood from the right ventricle of the heart is obstructed at the level of the pulmonic valve.
- hypertrophic cardiomyopathy: increased thickness of the heart walls.
- septal defect: a hole in the septum dividing the left and right sides of the heart.
- café-au-lait spots: pigmented birthmarks. The name café-au-lait is French for "coffee with milk" and refers to their light-brown colour.
- G-tube: a tube surgically placed directly into the stomach, through the abdominal wall, in order to facilitate feeding.
- hypotonia: low muscle tone, often involving reduced muscle strength.
- gastro-esophageal reflux: backflow of gastric juice (gastric acid) into the esophagus due to transient or permanent changes in the barrier between the esophagus and the stomach.
- cryptorchidism: condition in which one or both testes fail to move from the abdomen, where they develop before birth, into the scrotum.
- papillomata: benign tumours of the squamous epithelium, commonly known as warts.
- rhabdomyosarcoma: a malignant tumour that originates in the soft tissues of the body such as muscle, tendons, and connective tissue.
- neuroblastoma: malignant neoplasm characterized by immature nerve cells (neuroblasts).



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