CFC International
Cardio-Facio-Cutaneous Syndrome

The CFC Chronicle

Caring, Facilitating & Connecting

Volume X Number II *May 2008*

CFC Research Progresses Rapidly Since 2006 Gene Discoveries

Ophthalmic and Hearing Manifestations in Individuals with CFC

Investigators:
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Dr. Terri Young, Duke University Eye Center, Durham, NC
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Cardio-facio-cutaneous (CFC) syndrome is a rare, congenital, multiple anomaly disorder in which affected individuals have characteristic head shape and facial feature changes, cardiac defects, skin and hair differences, failure to thrive, developmental delay, and lower muscle tone. The mode of inheritance for this condition is sporadic, with males and females equally affected. CFC has similarities with other syndromes, such as Noonan and Costello syndrome. Ocular abnormalities of structure and function are also commonly described, as well as recurrent ear infections and possible hearing impairment.

The causative genes have recently been identified for CFC by Dr. Rauen and others such that this syndrome, along with the Noonan and Costello syndromes, can now be distinguished on the basis of genetic testing. Knowing the causative genes for CFC now allows us to re-evaluate the clinical characteristics of this rare syndrome. The ocular findings in CFC patients (prior to the gene discovery) have been studied and published in two reports of small and medium-sized groups of individuals with CFC by Dr.Young. The ophthalmic associations reported include a high incidence of ptosis (eyelid droop), depth perception issues, strabismus (eye misalignment), nystagmus (rhythmic, involuntary movement of the eyes), refractive errors (need for spectacle correction), reduced visual acuity, and optic nerve abnormalities. Currently, there has been no study that has correlated ocular findings in a large number of CFC patients with mutations in one of the four known genes causing CFC syndrome. No descriptive clinical or coordinated study has been performed regarding otologic issues in patients with CFC.

We would like to build upon our knowledge of CFC syndrome and further delineate the ophthalmic and hearing manifestations in individuals with CFC. The identification of four different genes (BRAF, MAP2K1, MAP2K2 and KRAS) causing CFC syndrome provides an opportunity to study the clinical manifestations in detail. This will allow for more accurate matching of genetic testing results with clinical presentation (genotype/phenotype correlations), and greatly facilitate physicians who care for patients with CFC in providing informed anticipatory guidance about visual and hearing prognosis.

We would be most grateful to have the opportunity to partner with parents of and individuals with CFC to develop and pursue this project. It entails completion of a questionnaire, obtaining ophthalmic and otologic medical records, and consenting to allow us to merge that information with the known genetic data for the individual with CFC. We are hopeful that you will be willing to participate.

CFC Research Continued on page 10.

In this Edition:

CFC International

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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.

CFC International and any associated parties will not be held responsible for any actions readers take based on their interpretation of published or disseminated materials. Please review medical treatments and decisions with your own physician.

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Message from the President

2008 is off to a fantastic start with many research projects in the works. I can't thank our CFC families enough for the large envelopes that keep arriving with more and more clinical data on the children. We have called or sent many of you requests for more medical reports so more confirmed CFC children can be enrolled in these projects. Our organization has wonderful parents who have followed up to help fuel these research projects! Without your help there can be no further research on CFC Syndrome. Please keep rounding up your specialist reports and we will keep our two interns busy working on these valuable research projects.

We are in the initial stages of conference planning for the summer of 2009. This upcoming conference will be a once in a lifetime event with the Costello Syndrome Family Network and the Noonan Syndrome Family Support Group all in one central hotel location with their own separate conferences occurring around the hopeful NIH Sponsored Scientific meeting on all three related syndromes! This is definitely THE conference to plan to attend as scientists merge research and treatment ideas into the next stage of planning. All upcoming conference plans will be posted on the CFC list serve and eventually our website once we have a firmed up date and hotel.

As a final note, I would like to thank so many of you for your messages, calls and cards while Cliff was recovering from his burn accident. He is doing very well and the doctors at the burn clinic in Syracuse, NY feel his skin is healing nicely. His one foot is still swollen but that is something he may have to live with. He still checks in regularly with his family doctor to have his blood monitored. He is back to his usual kidding self and loves to tell people he no longer has to shave his legs since there is no hair left. He ordered his support stockings in black just to be different. I must say that my two Conger boys (Cliff and Clifford) are surely survivors! The boys were back to skiing together in March.

Brenda Conger
E-mail: bconger@cfcsyndrome.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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Executive Director Honored at Luncheon

Bloomsburg University President David Soltz, Brenda Conger, and Eugene Walker, Alumni Association Board of Directors

CFC International Executive Director Brenda Conger was honored at the Bloomsburg University of Pennsylvania Alumni Awards Luncheon on April 12th, 2008. The Alumni Board of Directors awarded Mrs. Conger the Distinguished Service Award for her ten years of advocacy work with CFC International. Brenda is a 1978 graduate of Bloomsburg University with a teaching degree in Special Education. She has been employed with the Binghamton City School District for the past 30 years as a special education teacher.

I believe in angels,
The kind that heaven sends,
I am surrounded by angels,
But I call them friends.

- Aizabel Parinas -

OHIO CFC Chili Bowl

The Doyle family from Ohio hosted their 5th CFC Chili Bowl on Saturday, February 23, 2008, at the Medina Eagles. Attendance was estimated at about 250 people. The banquet room was donated by the Medina Eagles and Giant Eagle was a sponsor again this year donating most of the extra food and beverages. John and Cindy Boosinger and Maryann Bolton from SimplexGrinnell brought the hot dogs and helped man the food tables. Jim Shields covered the evening's beer tab and Pete Effinger supplied enough cheese to feed everyone and then some. The Doyle family covered the rest of the incidental expenses so the total amount from sponsors, donations, admission, chili entries, big screen TV raffle, raffle prizes, and silent auction items went directly to CFC International. We exceeded all previous years' totals and raised $14,000!

The official Chili Bowl voting process

The chili competition was as hot as ever. 25 cooks entered for a chance to win the Chili Bowl's top spot. For the second year in a row, taking 1st and the third year placing, Lisa Kellogg won with her infamous traditional Texas style chili. Lisa will add her second Chili Bowl trophy and first place ribbon to her kitchen wall, the apron to her collection and she graciously donated back her $100 in gold coins. First timer Stacy Bonitz took the 2nd place ribbon and chili bowl apron with her white chicken chili. There was a tie for 3rd place between Mike Campbell and our couple team of Megan Ryland and Josh Ryan who all received a ribbon and apron. Congratulations to all of this year's winners!


Unfortunately Jack was sick and took a rest with his Aunt Mary Kay

We appreciate everyone who donated raffle prizes and silent auction items. We had a great selection this year. A special thanks goes to Sam and Michelle Meuler and Mandy Elick who really went all out to get donations for the silent auction. The 42" LCD TV raffle was big hit again this year. Betty Pacholski was the lucky winner.

Jack really looks forward to the Chili Bowl each year. He woke up on Saturday morning saying, "Today is the big day, happy Chili Bowl!" Unfortunately Jack had a migraine on Saturday. Judy and Jack went home shortly after the drawings. He is feeling much better now and we are trying a new medication to control his headaches. He was very disappointed that he didn't get to pass out his artwork. Every year he prepares drawings, paintings and car book collages to hand out to the guests.

Next year's event is planned for Saturday, February 21.

Judy Doyle

Resignation of Chuck Kline, CFC Board of Directors

I have recently made the decision to step down from the CFC International Board of Directors. The decision was not an easy one to make, but at this time it was most certainly the right decision for me. I have to share, though, that the last 2.5 years I have spent on the board have been some of the most rewarding of my life, certainly my life as it concerns CFC! Watching, and playing a part in our organization grow into a true advocate for our, and our children's, cause(s) has been phenomenal! We, CFC International, are at a point where the medical community not only value our contributions but also seek them in understanding CFC and that is remarkable! We have the gene(s) discovery, which is directly attributed to the BioBank --> whose success is directly attributed to you, the CFC family members! We have a family support network that is unparalleled in the worlds of non-profit organizations. The camaraderie that is displayed on a daily basis is breath-taking. The support system that is in place for those of us in need gives me goose bumps when I think of what goes into making it a success. These success stories are made possible and available due to the unyielding effort of the officers and Board of Directors of CFC International. Thank you!

As a now "retired" member of the board, I can, without a doubt, say that the board is always looking to expand, to further the cause(s), to get better. It will cost you time, sweat and yes, some tears, but the rewards by far outweigh the costs. For me, the absolute biggest reward I got came every 2 years at the conferences -- getting re-acquainted with old friends, making new friends and just watching the interactions of our family. I will look forward to these events starting at the closing remarks of the current conference.

To the current Board of Directors and Officers, I wish to thank you for allowing me to share in the growth and successes of CFC International over the last 2+ years. It truly has changed my life! I will look forward to raising a toast to the success of CFC International at upcoming conferences!

Chuck Kline
Hubby to Dana
Daddy to Zach, Logan, Camden (CFC, 9) and Raegan

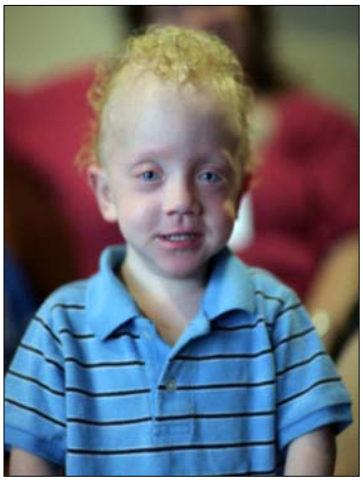
Still Seeking the Elusive Diagnosis

For two months I have known that I was going to write this article for the CFC International newsletter. Normally, writing comes easy to me and the words simply end up on paper in an organized, easy to read fashion. However, in this case, the story I am supposed to be telling seems to be jumbled in my head and has no rhyme or reason to it. I have pondered this article for what seems like an eternity. How can something as simple as writing a story about the life of a four year old be so difficult? Sure, we all know that any child who belongs to the CFC International group has a very long history but how hard can it be to tell the story of a 4 year old?

That's it! That's where my mental block keeps coming from. CFC International, the amazing group that gives much needed support to individuals and their families who are affected by Cardiofaciocutaneous Syndrome is an organization that our family has been a part of for almost a year now. The part that causes the lack of clarity for me is that my youngest son, Andrew, according to his lab results, does not have CFC Syndrome! Now, someone who is not well versed in this syndrome, which I dare to say would be over 99.9% of the general population, would wonder why Andrew would then belong to this group. This is where the lack of clarity begins. How did Andrew end up being a part of this unbelievable family? Does he fit? Is being a member of the CFC family as simple as a positive or negative blood test? Like Andrew's story, like my mind trying to tell Andrew's story, and of course like Andrew himself, nothing about Cardiofaciocutaneous Syndrome is simple. In fact, as I am typing this I am getting a bit annoyed by the squiggly little red line that my spell check program keeps adding underneath the lengthy name "Cardiofaciocutaneous Syndrome". Before I type any more I need to add the syndrome to my spell check dictionary or this whole article is going to be a bunch of squiggly lines. Ok, I just added it. Now, if only it were that easy to teach the world about this syndrome as it was for me to instruct my spell check program that cardiofaciocutaneous is, indeed, an actual word.

Now, back to Andrew and CFC. I have been asked many times when I first began to realize that Andrew had CFC. Okay, there goes that whole mental fog thing again. You see, if it confuses me a bit to write that Andrew has CFC Syndrome then I'm sure anyone reading this is even more confused than I. So, let's cut to the chase, and for the sake of this article, and my sanity, say that Andrew definitely has CFC Syndrome. It will make this whole story much easier to convey. I just need to remind myself at the end to tell you a few things about his diagnosis-or lack there of.

Oprah often talks about "aha moments". They are moments in ones life when all of the sudden something that has been perplexing to you suddenly seems to make sense. It's like a light bulb was turned on in your head and you finally get it, whatever that "it" is. Well, my "aha moment" with Andrew came this past summer when our family was in Orlando for the CFC conference. We were attending the conference to learn more about CFC and to have the wonderful team of medical experts who would be in attendance examine Andrew to make sure they thought he should indeed be tested for CFC and/or the very closely related Noonan Syndrome. We were at our hotel and decided to take the kids swimming at the pool. As we entered the seating area by the pool, Judy Doyle, a member of the CFC International Board of Directors, took one look at Andrew and very sweetly walked up to us and said "You must be here for the CFC Conference". We had nothing to identify us as being members of the CFC group. It was clear to me that she spotted Andrew from a mile away and zeroed in on this child who, in her well trained CFC Mom eyes, was another CFC child like her son, Jack.


Andrew Sadilek

This was not the only encounter like this that afternoon and in fact, my "aha moment" did not slap me across the face until a third family spoke to my husband Dave, Andrew, and myself as we were getting in an elevator. This time it was a family from Mexico who has a daughter with CFC. Although the father's English was somewhat broken, I could clearly understand the words "You must

be here for the CFC Conference". For a brief second I even looked to see if we had some type of CFC icon somewhere on us. No we did not. Our CFC icon was Andrew, the cute little blonde curly haired boy getting on the elevator with us.

After this third run in with the CFC law, I looked at my husband Dave and said "He's got it". And, for the first time since Andrew's birth, I sensed that Dave finally believed that Andrew did have a syndrome that could be diagnosed. We would finally be able to find an answer and put a name to this mystery that has hung over Andrew's head since the day of his birth.

The second day of the conference we were able to meet with a group of doctors who specialize in CFC and Noonan. Finally, this was what I had wanted for 3 ½ years, to have a group of experts all in one room to discuss Andrew's case. I wanted doctors to study his features, touch his skin, look at his hair, examine his flat feet, talk about his short stature, have him open his mouth so they could see his grooved palette, and pick my brain for every little idiosyncrasy that makes Andrew the little person that he has become. I remember when Andrew was 5 months old I had asked my pulmonologist's nurse if Andrew's pulmonologist, gastroenterologist, and I could all meet to discuss whether Andrew should have a g-tube inserted. She kindly told me that, though it may be possible, nothing like that had never been done before. I realized then that if this nurse, who was one of Andrew's biggest fans, couldn't get two doctors to meet at the same time to discuss Andrew that I had a slim chance of ever getting more than one doctor in a room at one time to discuss Andrew's case. So when CFC International was offering clinic exams with the best doctors in the world who are familiar with his syndrome, it was a chance in a lifetime. I was going to have Andrew in one of those clinic spots if I had to tie myself to the exam room door until they looked at Andrew. Fortunately, Brenda Conger simply told me to get my paper work to her within a couple of days and he would have a clinic spot. I sent it to her the very next day and if next day air service would not have been an option with UPS, I would have gotten in my car and drove straight from my home in Michigan to Brenda's in New York State with stopping only for gas and an occasional potty break.

Now, if you have never met the doctors and genetic counselors who give so much time researching and helping children with CFC/Noonan, you may imagine a group of stuffy, boring, arrogant doctors who would make you feel uncomfortable. Well, I felt like I was in a room full of family and friends. I was amazed at how these world renowned CFC/Noonan Syndrome doctors and counselors (Dr. Kate Rauen, Dr. Mary Ella Pierpont, Dr. Amy Roberts, Dr. Grace Yoon, and genetic counselor, Pilar Magoulas) acted like I knew more than they did about these syndromes. They were so genuinely intrigued with Andrew and the rest of the CFC group. I realized during clinic that they were at this conference to learn as much from the CFC group as we were there to learn from them. The doctor's examined Andrew and carefully reviewed his medical records. They were most intrigued with how Andrew's facial features had changed over time. As an infant, Andrew didn't really have the typical CFC look. However, at about the age of two years, his CFC features became more prominent. I remember looking at Andrew's pictures on our plane ride to Florida thinking that very thought and wasn't surprised when one of the doctors mentioned the same thing.

The Sadilek Family

The doctors were all in consensus that Andrew had either CFC or Noonan Syndrome. However, they felt that, based on Andrew's developmental milestones, that Andrew should be tested for Noonan Syndrome first and if the tests were negative then we should proceed to CFC gene mutations. They felt that because Noonan kids typically reach developmental milestones sooner than CFC kids that Andrew fit more with the Noonan group. This was not a surprise to me since I had the same thought in the back of my mind for months. But I still had some doubts as Andrew clearly looks more like a CFC child than a Noonan child.

So, this is where Andrew's story gets real fuzzy in my mind. As I mentioned earlier, we did end up having Andrew tested for both CFC (BRAF, MEK1, MEK2) and Noonan (PTPN11, SOS1 and KRAS) Syndromes. The results came back negative for both syndromes. It took over a month to get Andrew's test results back and I knew that the longer it took the less likely we were to have a positive result. Therefore, I really wasn't taken off guard when my sweet little boy's nurse told me that the tests were negative.

So how did I feel about the negative test result? Well, it was six months ago when we got the results and I still, to this day, have conflicting emotions about it all. Of course no one wants to find out that their child has a very rare genetic syndrome. But when your child has been through what Andrew has and stands out in a hotel filled with thousands of people as a CFC child, it's very surreal. On one hand I want to be able to say that he was a child who was born with a litany of problems that he is outgrowing and there is nothing at all wrong with his genetic makeup. Given his very rough start to life, it's nothing short of a miracle how well he is doing today. On the other hand, I can't ignore his past. I can't ignore the fact that his list of medical problems is so long that sometimes I can't even remember all of the things he had to endure. As his mother, I can't just pretend that he never had any health concerns. The biggest reason I can't ignore this is that it's hard to turn my head from the fact that he looks like more of a brother to many of the boys and girls at the CFC Conference than to his own brother and sister. I can't look at Andrew and not notice his sparse curly hair, his rough skin, his droopy eyelids, the adorable goofy toenails, his tiny size, and the braces on his feet. While I find his features to be absolutely adorable I also know that they are a constellation of variables that shout "syndrome" whenever a trained eye spots Andrew. I also don't want to forget all that he has been through. If I do, I fear that I will lose my gratitude for the many problems he has outgrown. I still appreciate every bite of food he takes, every step he makes, smile he takes, and every word he speaks. His doctor's said he may never walk, talk, smile, or eat. He now does all of those things with ease.

I thank God every day for the miracle he has given us in Andrew. Last December, Andrew had a doctor's appointment scheduled for December 21, the Friday before Christmas. This appointment was with his pulmonologist and Andrew has outgrown his lung issues so I seriously considered canceling the appointment given that Christmas was just a few days away. Something in my heart told me not to cancel. In fact, I had this odd feeling that Andrew really needed to make it to this appointment but I didn't know why. That reason became clear once his doctor walked into the room. She was at least an hour behind schedule and looked quite frazzled. She hurriedly walked into the room, took one look at Andrew and tiny tears began to well up in her eyes. She smiled and very softly said to me "He is a miracle". That was all that needed to be said. That particular moment in that doctor's office will be one that I will never forget.

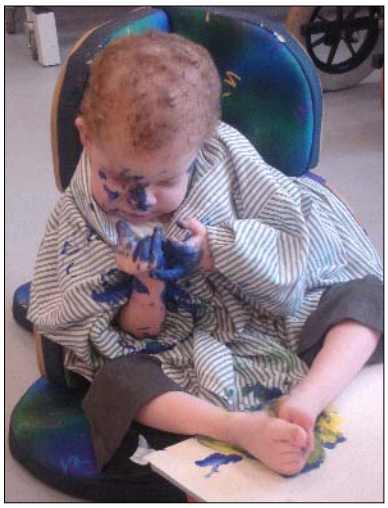
So, back to that diagnosis. As I stated, Andrew never did have a positive blood test for either CFC or Noonan Syndrome. In my heart I know he has one or the other, or perhaps some other closely related syndrome that may not have even been discovered yet. Sure, my family and friends sometimes think I'm looking for something that is not there but I am Andrew's mom and I know in my heart that Andrew is special for so many reasons. His list of symptoms look like they came right from the Cardiofaciocutaneous Syndrome website…short stature, sparse curly hair, droopy eyelids, keratosis pilaris, flat feet, grooved palette, delayed teeth eruption, severe hypotonia, laryngomalacia, GERD, tube feedings, failure to thrive, milk allergy, poor sleep, achy legs at night, large belly, global developmental delays, absent eyebrows, high forehead, dysmorphic toenails and I'm sure there are more that I can't even remember.

What I find amazing is that Andrew has outgrown almost every medical problem except for a handful. In fact, there is one aspect to Andrew that makes me chuckle every morning when I comb his hair and put mousse into his wild mane to tame it a bit. You see, at the age of four, Andrew does have the sparse curly hair that is so prevalent with CFC kids. What I find amusing is that his entire head of hair is not curly. The sides and back are not tight with curls, only the top. Why do I find this amusing? I'm amused because even Andrew's hair seems to be confused about whether he has Cardiofaciocutaneous Syndrome. Go figure!

I do have one last comment about Andrew's remarkable progress. I truly believe that Andrew was given to my husband Dave and me as our third and final child for a reason. Andrew came into this world with a big brother and sister, Jacob and Tyler. Jacob was six and Tyler was five when Andrew was born. They had to learn at a very young age to put their own needs on hold at times so that Dave and I could take care of Andrew. It brings tears to my eyes to think back on all of the times I watched Jacob encourage Andrew to walk and to play basketball with him. Tyler has always been a little mother-hen with him, taking care of his every need. More than any doctor, nurse, therapist, or even his own parents, Andrew's success can be attributed to the love and determination of his siblings. Jacob and Tyler are now 11 and 9 years old and continue to act like Andrew's parents but have also eased their way into your typical brother/sister relationship with him. In an odd way that perhaps only a parent of an ill child could understand, I find joy in hearing the older two children teasing Andrew like most siblings tease each other. It just means that Andrew has become tough enough to take it—and to dish it out.

Julie Sadilek, Chesaning, Michigan

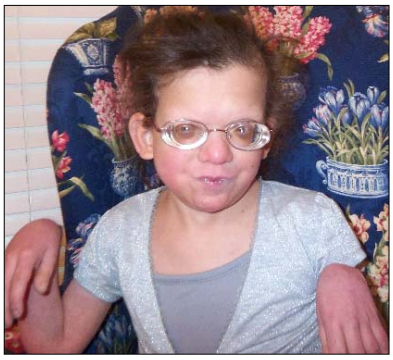
Photo Gallery



Maddy Mitchell enjoying art at school

Marcus Weston playing the piano

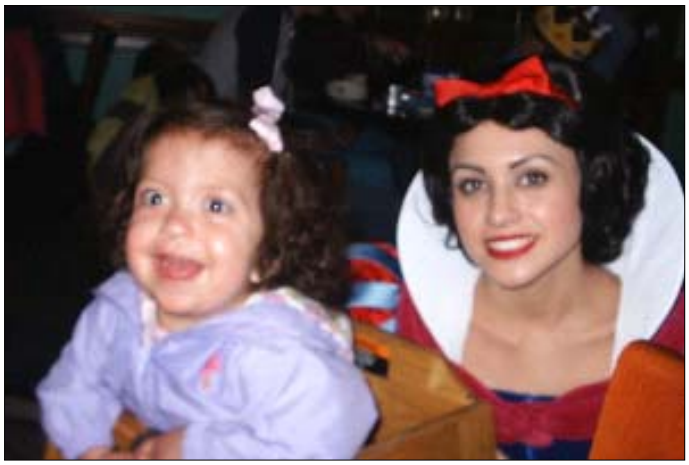
Cliffy Conger at Winter Special Olympics event where he won the gold medal for his skiing



Stephanie Kohler

Owen Wild and Ethan

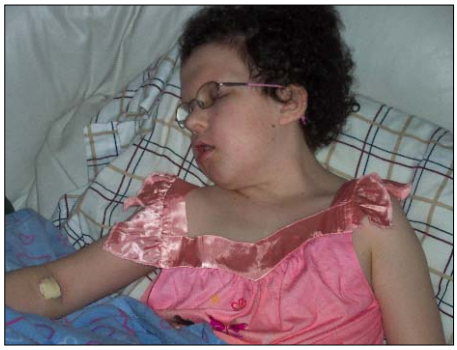
Jared Stowell on his 11th birthday with Kyle, Jennifer and schoolteacher Mr. Heidrich and his wife



Stela Molinar with Snow White at Disneyland

Nancy Newton at Rotary Club camp in Australia

Kinley Greenhaw in her Easter dress



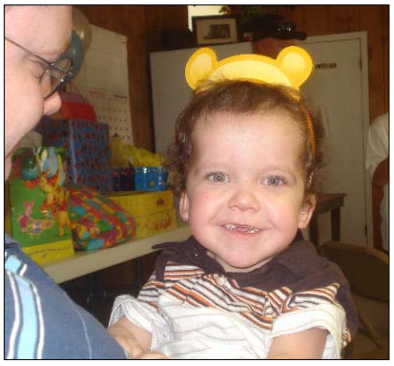
Kaci Smith resting after having six teeth removed

Brenan Wilson helping daddy with the new swingset

Nathaniel Epstein's big smile

Meg Young and her papa

Josh Schrock at the Winter Special Olympics bowling event



Avery Clark wearing Pooh ears at his friend Brandon's birthday party

Brennan Skipper at school receiving physical therapy

Jenna Braun 8 yrs. old from Rosholt, SD

CFC Research Progresses Rapidly Since 2006 Gene Discoveries (continued)

Use of 3D Digital Surface Photogrametry to Capture, Visualize and Analyze Dysmorphic Facial Features

Investigator: Professor Peter Hammond, UCL Institute of Child Health, London

Of the 5,000 documented genetic conditions in the medical and scientific literature, about 700 involve some effect on facial development that causes mild to severe facial dysmorphology. We have developed novel techniques for building 3D computer models of face shape that visualize face shape differences, assist in the early stages of diagnosis and contribute to studies linking gene alterations to the observable features of a condition. Useful results have been obtained in Noonan, Smith-Magenis, Williams-Beuren, Cornelia de Lange, 22q11 deletion, Fragile X, Angelman and Jacobsen syndromes as well as Autism Spectrum Disorder. Facial appearance in Noonan, CFC and Costello syndromes is an important clue in early stages of diagnosis but for some children and for clinicians with less experience it is difficult to interpret the facial clues. We aim to make a detailed comparison of facial morphology in these conditions.

We will capture and analyze 3D facial images of children and adults with CFC syndrome and compare them with existing collections of images of individuals with Costello and Noonan syndrome, as well as age/sex/ethnicity matched controls. We will build dense surface models of face shape variation in these three conditions and controls. Findings will be presented in 2009 at the joint syndrome conference.

SOS1 Gene Mutation Studies

Investigator: Dr. Amy Roberts
Harvard Medical School – Partners HealthCare Center for Genetics and Genomics, Boston, MA

Patients with cardiofaciocutaneous syndrome (CFC) share many physical, cardiac, cutaneous, growth, and developmental features in common with patients with a related condition, Noonan syndrome. Our research group has recently discovered that mutations in a gene known as *SOS1*are the cause of approximately 10% of cases of Noonan syndrome (with mutations in the *PTPN11* and *KRAS* genes previously found to cause an estimated 50% and 1% of cases of Noonan syndrome, respectively). For patients with CFC, mutations in the *BRAF, KRAS, MEK1,* and *MEK2* genes are known to cause CFC in a significant number of cases, but the genetic cause of CFC in some patients remains unknown. Previous research has shown that mutations in *PTPN11* do not cause CFC. We propose performing *SOS1* gene mutation analysis studies on patients with CFC who tested negative for mutations in the known "CFC genes" to determine if this recently identified cause of Noonan syndrome might also be the cause of some cases of CFC.

Cardiofaciocutaneous syndrome (CFC) is a genetically heterogeneous condition, meaning that mutations (i.e. DNA sequence changes) in more than one gene have been shown to cause the condition. Some patients who have been diagnosed with CFC on the basis of their clinical features do not have identifiable mutations in any of the known CFC genes: *BRAF, KRAS, MEK1,* or *MEK2*.

Gene discovery is a complicated process that can be approached in many different ways. One approach is to look for gene mutations in genes that have been found to cause conditions related to CFC, like Noonan syndrome. In the past, patients with Noonan syndrome have been found to have mutations in the *PTPN11* and *KRAS* genes. Our research group recently discovered that a third gene, *SOS1*, causes Noonan syndrome in approximately 10% of patients. Interestingly, many of the NS patients with an *SOS1* mutation have cutaneous findings similar to those found in children with CFC. The genes that cause NS and the genes that cause CFC all encode protein products that are important to the same cellular pathway (i.e, both sets of genes play a similar function in the body). This fact explains why patients with CFC and Noonan syndrome have many features in common.

We propose testing samples from patients with a clinical diagnosis of CFC who have had negative *BRAF, KRAS, MEK1,*and *MEK2* gene studies to determine if any of the patients have identifiable *SOS1* gene mutations. Because of the clinical overlap of features seen in CFC and Noonan syndrome, and because many NS children with an *SOS1* mutation have CFC-like cutaneous manifestations, *SOS1* gene sequencing is a logical approach to attempt to identify additional genetic causes of CFC.

It is important to identify the causes of CFC for a variety of reasons. Having access to genetic testing to confirm a clinical diagnosis of CFC can help ensure that a patient receives appropriate medical management and can

reduce the need for additional unnecessary tests that may be costly and/or invasive. Genetic test results can also help families better understand the chances for other people in the family to have the condition. In addition, when gene mutations that cause a condition are identified, it is sometimes possible to correlate certain clinical features (such as cardiac defects) with specific mutations. This information aids in the medical management and counseling provided to patients and their families. Finally, the more researchers know about the genetic causes of CFC, the better they are able to understand the underlying pathways that could someday be utilized to develop treatment options.

Communication and adaptive behavior in individuals with Cardio-facio-cutaneous syndrome

Investigators: Rene Pierpont, MS, Mark Seidenberg, PhD, and Mary Ella Pierpont, MD
University of Wisconsin, Madison, WI
Children's Hospital of Minnesota, St. Paul, MN

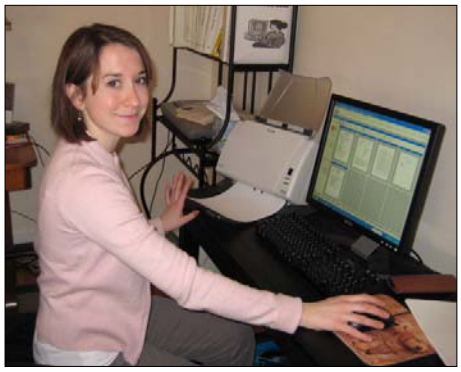
Cardio-facio-cutaneous syndrome is associated with variable learning disabilities, but outcomes in speech and language have not been well documented. Our research has begun to investigate how communicative development in CFC syndrome differs from the typical learning trajectory. We are examining communication skills in relation to other adaptive behaviors such as social and motor skills, as well as several of the medical characteristics that frequently accompany CFC syndrome. This research may help us to determine which factors may place an individual at risk for difficulties in language development and which factors enable more advanced levels of communication. An eventual goal of this research program is to suggest methods to foster these skills in individuals for whom speech and language is a challenge. Early identification of speech and language related issues may be a key to providing children with the best possible learning opportunities.

Our research has been conducted primarily through surveys completed by families of individuals with CFC syndrome. At the 2007 CFC international meeting, and in subsequent work with additional families, we have been able to collect surveys from nearly 30 families! We are currently in the final stages of the study and are looking forward to distributing our research findings in the coming months. We appreciate very much the time and efforts of all of the individuals who have participated!

For further information about our research program, or to learn about avenues for participation in our studies, please contact Rene Pierpont at: eipierpont@wisc.edu.

CFC International Interns on board with Research Programs

CFC International is thrilled to introduce Amber Chavalier and Lisa Hein, two college interns and Luba Djurdjinovic, the Program Director at The Comprehensive Community Based Genetic Services of Ferre Institute in Binghamton, NY, who are assisting us with our research projects. Ms. Chavalier is a graduate of Virginia University and is continuing her education for a degree in Genetic Counseling. Mrs. Hein is a senior at Binghamton University majoring in Human Development. Both interns are busy working on the research projects. Mrs. Hein is blinding the newest CFC Clinical Data that parents have sent to CFC International. Ms. Chavalier is scanning the blinded clinical data and transferring it into a PDF format. She is also creating a computer file folder for each CFC child and has created sub-specialty folders within each child's mail folder. This will allow researchers to access a particular medical area for their research project. Luba has generously offered the use of their special document scanner that converts our paper data into digital files that can be stored, searched and retrieved from a centralized, electronic storage location. CFC International couldn't have taken on this extensive project without the support of Luba Djurdjinovic and the dedicated interns Amber Chavalier and Lisa Hein.



Amber Chavalier

Mouse Models and CFC

By: Kyle Stowell

The 2007 Nobel Prize in medicine was awarded to three individuals for their work on developing the ability to introduce a specific genetic mutation in mice – mouse modeling. One of these people was Mario Capecchi, a professor and researcher at the University of Utah in Salt Lake City Utah. I was able to find Mr. Capecchi's contact information and make an appointment to visit with him about his research.

On Thursday, 3 April, I found my way to Mario's office at the Institute of Human Genetics at the "U". Mario is a very soft-spoken humble man. I shared with him a photo of Jared and Cliffy and showed him the graphics from the

Science magazine gene discovery article. I showed him the diagram of the MAPK pathway, which he was very familiar with.

Mario explained to me the process of making a mouse model. Once a mutation has been identified, they can create a small segment of DNA that contains the mutation. They place a marker at the beginning of the DNA segment that causes the mutation to be inactive. Also, a segment is placed after the mutation that causes any affected tissues to glow under a black light. This DNA segment is then placed in a one cell embryo.

I was told that one of the most important factors in determining the effects of a genetic mutation is when the mutation is introduced. In the case of our kids, however, the mutation is present from the very beginning. So every cell in the body has a copy of the mutation.

When the mouse reaches the desired age, the mouse is injected with a molecule that causes the "inactive" marker to be reversed so that the mutation is then active. The effects of the mutation can then be observed in ways that can't happen in humans. The mouse can be dissected and the tissues placed under a black light, where the affected cells actually glow.

Mario thought that there was a good possibility that a BRAF mouse model already exists. There are about 11,000 different mouse models in existence. He thought a thorough study of a BRAF mouse would be helpful to CFC research. Researchers typically have areas of the human genome that they are interested in. The MAPK pathway is not his specialty. However, he knows many researchers who work with mouse models and offered to make additional contacts should we offer seed money for research. He was also impressed that our organization has a support group made up of interested parents along with our own DNA Biobank.

His final comment as I left his office was that with parents involved who are highly motivated to help out their children, these rare syndromes will continue to see growing progress in knowledge and treatment options.

Prenatal Manifestations in the CFC Syndrome

Investigators: Dr. Katherine Rauen and Dr. Susan Tran
University of California San Francisco, San Francisco, CA

CFC Syndrome is characterized by typical craniofacial features, cardiac defects, short stature and developmental delay. The genetic basis of CFC was recently identified. Knowing the causative genes for CFC now allows us to reevaluate the clinical characteristics of this rare syndrome. While the features of CFC have been described in children and adults, little is known about the features that may potentially be present prenatally. Now that the causative genes for CFC have been identified, we are attempting to gain a better understanding of the potential prenatal findings. In particular, we are interested in the percentage of mutation positive individuals with prenatal findings and defining exactly what the findings are, such as congenital heart defects, amniotic fluid abnormalities, fetal edema and abnormalities of fetal movement. We hope this study will help us understand the prenatal features of CFC so that physicians may one day diagnose CFC in utero and, therefore, provide better anticipatory guidance to their patients. In addition, clearly defining the prenatal manifestations of CFC syndrome and the natural history of the findings may assist in defining criteria for clinical diagnosis of CFC syndrome as compared to other syndromes of the Ras/MAPK pathway. It will also assist in understanding the pathophysiology of the MAPK pathway in human development.

The Spectrum of Dermatologic Findings in 52 Mutation Positive Individuals With Cardio-facio-cutaneous Syndrome.

Dawn H. Siegel, MD1 and Kate Rauen, MD2
1Oregon Health & Science University, Portland, OR
2University of California San Francisco, San Francisco, CA

Cardio-facio-cutaneous syndrome is a multiple congenital anomaly syndrome characterized by abnormalities of the skin and hair, congenital heart defects, failure to thrive and a distinctive facial phenotype. This study seeks to evaluate the skin manifestations in the mutation positive cohort registered with CFC International. The authors designed a two part survey asking a number of questions about the skin of the individuals with CFC. The surveys were distributed to the subjects via CFC International, then anonymous surveys were returned to the authors. Photographs were also reviewed when possible. When available, notes and biopsies were also reviewed from the dermatology visits.

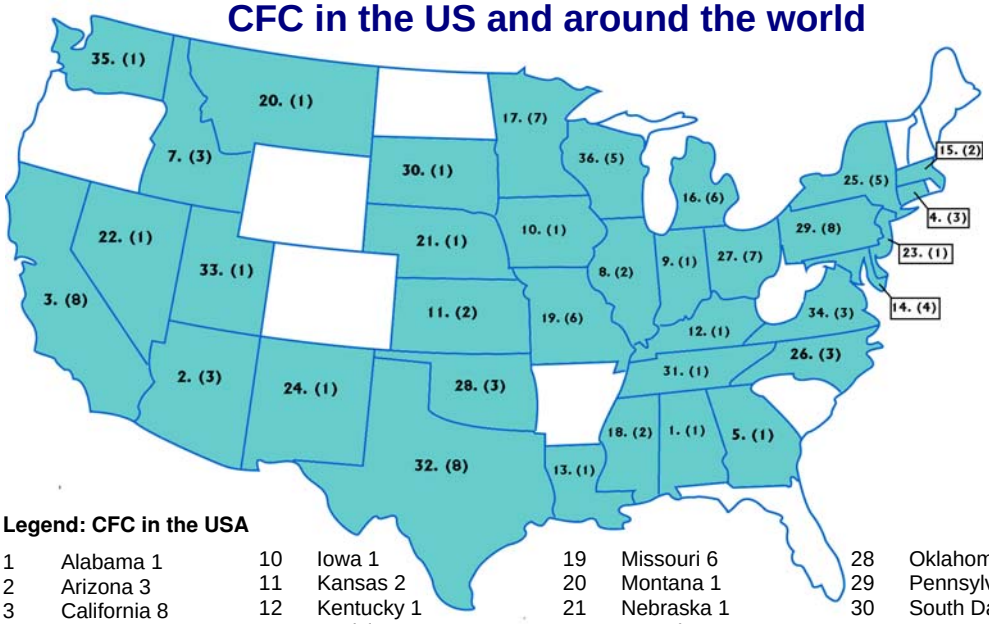
Surveys were returned from 52 subjects who had positive mutation testing for BRAF, MEK1 or MEK2. The results were used to create a database of the skin features. Eruptive melanocytic nevi were one of the most striking features. Several individuals had greater than 50 nevi and 100 nevi. No melanomas were reported. Hemangiomas

also occurred in this population more frequently than in the general population. Keratosis pilaris, sparse eyebrows or absent eyebrows were frequent. Many additional interesting skin findings were seen and are still being analyzed for the manuscript.

Thank you very much to all of the families who took the time to complete the surveys! We could not have done this study without your support. We believe this paper will provide valuable information on the skin features of CFC syndrome. We will be submitting the manuscript for publication in a peer reviewed dermatology journal in the next few weeks!

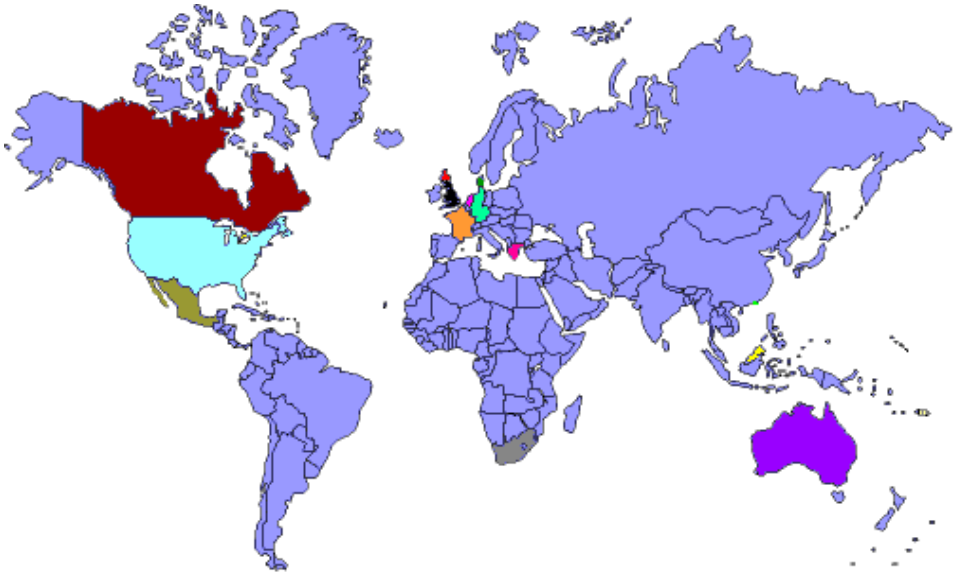
Where do we all come from?

CFC in the US and around the world



Legend: CFC in the USA

1	Alabama 1	10	Iowa 1	19	Missouri 6	28	Oklahoma 3
2	Arizona 3	11	Kansas 2	20	Montana 1	29	Pennsylvania 8
3	California 8	12	Kentucky 1	21	Nebraska 1	30	South Dakota 1
4	Connecticut 3	13	Louisiana 1	22	Nevada 1	31	Tennessee 1
5	Georgia 1	14	Maryland 4	23	New Jersey 1	32	Texas 8
6	Hawaii 2	15	Mass. 2	24	New Mexico 1	33	Utah 1
7	Idaho 3	16	Michigan 6	25	New York 5	34	Virginia 3
8	Illinois 2	17	Minnesota 7	26	North Carolina 3	35	Washington 1
9	Indiana 1	18	Mississippi 2	27	Ohio 7	36	Wisconsin 5



Legend: CFC Worldwide

- Australia 5
- Canada 5
- Denmark 1
- England 10
- France 1
- Germany 1
- Greece 1
- Hong Kong 1
- Malaysia 1
- Mexico 1
- Netherlands 3
- Samoa 1
- Scotland 2
- S. Africa 1
- USA 101

CFC International Annual Report 2007

Caring, Facilitating & Connecting

Our Vision

A world in which no one will be isolated from appropriate diagnosis and treatment.

Our Mission

Forging a path to improve lives through family support, research and education.

Our Programs:

Patient Registry

Cardio-Facio-Cutaneous (CFC) Syndrome is a very rare condition. To better understand the characteristics and natural course of CFC syndrome, an International Registry has been established. The Registry offers essential resources for the study of CFC Syndrome by providing centralized information and medical records on CFC individuals from around the world. Confidentiality of personal information regarding incidence, genetics, clinical course, and prognosis is provided to professionals and families. The Registry also serves to improve communication of ideas among interested researchers, and to ensure rapid distribution of any new information that may benefit patients or their families.

BioBank

CFC International is a founding member of the Genetic Alliance BioBank, which was established in 2004, and now holds the world's largest collection of blood and tissue from people affected by CFC and their immediate relatives. It is the only centralized repository in the world. Access to a large number of samples, combined with comprehensive clinical data and photographs, is a key resource for CFC researchers. These resources played an integral role in the research work associated with the CFC gene discoveries and will continue to do so for future research programs, including development of treatment programs.

Family Conference with Clinical Evaluations

Every two years CFC International brings physicians, clinical and scientific researchers and families together. Clinics are offered at no cost to affected children. Families hear about research advancements directly from the researchers. Resource materials are provided for affected families to better assist them in caring for a person with this rare disorder.

Family Support

Welcome Packet

Upon registration and completion of the CFC registry, a welcome packet is mailed to families. This includes contact information, past newsletters, CFC brochure, Parent's Guide and other resource materials. There is no fee to join CFC International and support of our members is sponsored through the kindness and generosity of our donors.

List Serve

CFC International hosts a computerized list serve, which offers immediate distribution of a message to the entire CFC International community. These messages and questions are considered and answered by fellow family members of CFC syndrome children and adults. While CFC International does not endorse opinions as medical advice, the list serve offers support and informed opinions by people who know this disease firsthand.

Newsletter

Three editions of "The CFC Chronicle" were published in 2007 (May, August & December) and mailed to more than 735 families, friends, doctors and researchers. The newsletter is also available online through the CFC website. It offers the most up to date news about research, family issues, educational concerns, events and issues about CFC syndrome.

2007 Highlights

- Many more children confirmed with the official CFC diagnosis through DNA testing.
- The CFC International Biobank holds samples from 69 affected individuals and their biological parents.

CFC International Annual Report 2007

Caring, Facilitating & Connecting

- CFC International now serves over 140 members from 15 countries around the world: Australia, Canada, Denmark, England, France, Germany, Greece, Hong Kong, Malaysia, Mexico, Netherlands, Samoa, Scotland, South Africa, and USA.
- In July 2007, 48 families & extended family members from around the globe and throughout the USA attended the 4th International CFC Conference & Medical Clinic program in Orlando, Florida. Overseas families traveled from Australia, Canada, England and Samoa. Doctors and medical advisors included representatives from Brazil, Canada, England, Italy and the USA. This conference was unique in the number of extended family members who attended, including 37 siblings, 18 grandparents, 6 aunts and 1 uncle.
- In 2007, welcome packets were shipped to 27 new families who contacted our organization.
- A Three part series written by author & parent, Ian Brown ran in the Toronto Globe and Mail. Ian described his experiences of raising a child with CFC Syndrome.
- CFC parents Anthony & Nevada Verrino were featured on a PBS Frontline TV show titled, "The Undertaking".
- The CFC International website underwent a new design look.
- During 2007, four research proposals were presented to the CFC International Biobank Scientific Advisory Board for access to clinical data. All projects were approved.
- Throughout 2007, three outreach talks were presented at Atascadero State Hospital, California by CFC International Vice-President Molly Santa Cruz.
- CFC International funded $16,369 for research programs (BioBank) in 2007.
- Thirteen family/friends fundraisers were held during 2007 raising a total of $74,601:
  - $6,159 5th Annual Toast the Angels wine tasting & dinner hosted by the Conger family, New York
  - $600 Binghamton, NY Cruisin' Buddies car club annual Memory Cruise
  - $1,700 Chicago Marathon Fundraiser - Kayra Johnson
  - $10,404 Chili Bowl hosted by the Doyle family, Ohio
  - $300 Ross County, Ohio 4-H
  - $260 Macy's Shop for a Cause
  - $440 McVay family pillow case sales
  - $10,000 Olsen grandparents matching funds for CFC International Conference Silent Auction
  - $22,744 A Night of Fun hosted by the Lydiksen Family in Connecticut
  - $7,202 3rd Annual CFC Golf Tournament in honor of Ronnie Zeunen, Jr., North Carolina
  - $9,202 Hickman Family Golf Tournament in honor of Jacelyn Hickman, Connecticut
  - $4,165 Brockwell family United Way appeal campaign
  - $1,425 Tobby family Christmas appeal

Several families have made pledges to provide financial help on a yearly basis.
We are very grateful for their generosity and continued support!

CFC International Income and Expenses 2007:

INCOME 2007		**EXPENSES 2007**	
Contributions	$140,301	Program Services	$63,801
Other	$6,149	Management & General	$21,531
		Fundraising	$1,406
Total Support & Revenue	**$146,450**	**Total Expenses**	**$86,738**

CFC international

183 Brown Road
Vestal, NY 13850

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RETURN SERVICE REQUESTED

Our vision is a world in which no one will be isolated from appropriate diagnosis and treatment.

Would you like to contribute to CFC International?

Your donation and support will help:

- families to receive information about CFC syndrome;
- publish our newsletter;
- fund the biannual International CFC Family Conference & Clinic Program;
- maintain the CFC Biobank, which is critical to future research.

Enclosed please find a check in the amount of $ _____

Gift in Honor of _____

Gift in Memory of _____

Please make checks payable to CFC International & mail to: 183 Brown Road
Vestal, NY 13850

Name: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____

Email: _____