Chromosome 15q11.2-13.1 duplication (dup15q) syndrome is a clinically identifiable syndrome which results from duplications of chromosome 15q11.2-13.1. These duplications most commonly occur in one of two forms. These include an extra isodicentric 15 chromosome, abbreviated idic(15), which results in an individual having 47 or more chromosomes instead of the typical 46. Individuals with an interstitial duplication 15 are born with the typical 46 chromosomes but have a segment of duplicated material within their 15th chromosome.

On the eve of the Dup15q Alliance’s 2015 Stronger Together Conference, volunteers gathered in a spacious Orlando, Florida hotel to greet conference participants with name tags, schedules, and smiles. Out in the courtyard, kids from different countries played in the pools together. Upstairs, the room for the New Family Orientation filled with adults, kids and strollers. Adults chatted with those seated around them-strangers, yet already connected.

This issue of The Mirror builds on the momentum of the conference. In these pages, you will see the heart of the conference – the connections between families, affected individuals, research and medical practitioners, educators and specialists.

The Dup15q Alliance has now grown to 1,017 families, with over 300 families from outside the United States, including Saudi Arabia, Peru and Austria. We celebrate and support our international families with a dedicated session for conference participants from countries other than the United States to discuss current international activities and country based groups.

This conference had at least five families who attended with a service dog at their side. These calm dogs seemed to naturally lower anxiety and encourage social interactions with everyone around them.

Scientific interest and progress into dup15q is gaining momentum! Guy Calvert provides an excellent summary of the Dup15q Annual Scientific Meeting, and Carolyn Schanen introduces the first two Dup15q Alliance research grants. At the conference, rooms were also set up for researchers and technicians. Individuals with dup15q syndrome and family members attending the conference participated in research studies on site, instead of having to travel to specific research sites.

We appreciate everyone who contributed to the conference related fundraising successes! Links of Love, which ran from June to early August, raised more than $17,000. The Hometown Dinner Raffle and Silent Auction raised $9,000. Twenty people volunteered at the conference store over four days, and sold 220 t-shirts, the entire inventory of silver bracelets, and much more. You’ll find a financial update from the Dup15q Alliance in this issue.

Thank you to all who made the 2015 conference such a success: every participant, presenter sponsors, raffle donors and ticket salespeople, room monitors, store and registration clerks, Board and Conference Committee members, our DJ (who drove his sound system 3,016 miles), and many others!

Special thanks to the K4 Team: Kim, Kadi, Karen and Katie, for their long-term commitment to our international family conference.

For families touched by dup15q syndrome, our lives are not always filled with ease and comfort. From the strength of 353 conference participants and presenters who came together in Orlando to all of you, enjoy this issue of the Mirror. Each person’s journey’s with dup15q syndrome is different, but we are stronger together.

Hoping to see you in 2017 in Los Angeles, California.
2015 Annual dup15q Scientific Meeting

By Guy Cavert, DUPE15Q Alliance Research Chair

Dup15q Neurons

Stormy Chamberlain’s team at the University of Connecticut produces neurons from dup15q stem cells donated skin and blood – those who donated blood at our family meeting this year directly supported this work. The ideal control system for comparison would be neurons with the same genetic make-up, without the duplicated material. So - with the help of the Dup15q Alliance registry - Chamberlain discovered and reached out to the families who are mosaic for dup15q syndrome (i.e. have some dup15q cells and some normal cells) and received generous skin and blood donations. She is now attempting to derive neurons from matched pairs of normal and dup15q cells.

Meanwhile, Chamberlain has also identified some compounds that restore UBE3A protein levels to normal in her dup15q neurons. Two of her UConn colleagues, Eric Levine and Les Loew, are now attempting to characterize the dup15q neurons. They have found some encouraging leads. Levine and his team observed that a current passed through dup15q neurons elicits a different electrophysiological response than the Angelman neurons or normal neurons. That may sound rather abstract - far removed from the everyday experience - but at the cellular level it is the beginning of a possibly resuable phenotype.

UBE3A

Jason Yi, a postdoctoral researcher in Mark Zylka’s lab at the University of North Carolina, presented his findings on properties of a key gene called UBE3A, which is located in the critical 15q11.2-13.1 duplication region. Dr Yi’s work (which has since been published in the journal Cell) represents a substantial advance in the understanding of how UBE3A is controlled at the protein level. Although many genes are in the dup15q11-13 region, there is intense interest in UBE3A because deletion of the maternal UBE3A copy causes Angelman syndrome and duplication of the maternal UBE3A copy occurs in most cases of dup15q syndrome. This study showed that UBE3A can be modified to be either active or inactive. This has not been previously known, and is big news. If ongoing over-expression of UBE3A leads to hyperactivity of UBE3A function in dup15q, then some kind of chemical off-switch or tuning dial would certainly come in. Yi and his collaborators have designed a potential drug, which could be developed as a treatment for depression, that may help to regulate UBE3A activity and potentially impact some symptoms of dup15q syndrome. A natural next step would be to try this and similar medications out on well-matched systems of dup15q syndrome, to see if those systems can be “rescued” (i.e. restored to normal).

Regarding the model systems, the good news is that there are several alternative systems under development - ranging from animal models (flies and mice) that have been doctored in the critical 15q11.2-13.1 region to mathematical models that have been developed to over-express UBE3A, to human brain neurons that were harvested from the stem cells of actual people with dup15q syndrome (and therefore have the same genetic duplication that those individuals have). True, none of these models are fully characterized yet, meaning no one has established definitive phenotypes that are caused by the duplication and which scientists can then attempt to rescue. But some models are at least partially characterized and can give critical insights into the molecular mechanisms of dup15q.

Mathematical Models

Olena Marchenko, a graduate student working in Les Loew’s lab to fit mathematical models of cellular dynamics to dup15q neurons, dropped a quiet bombshell while describing her equations. Marchenko was interested in the neuron’s dendrites - branched tendrils-like extensions that transmit electrical signals between neural cells. Such neural networks are the basic building blocks of thinking, learning, dreaming, pretty much everything the brain does. The dendrites themselves, if overly dense or too numerous, can generate a multitude of tiny spines. We could leave it at “multitude”, but the relative number of spines sometimes turns out to be quite important. So the bombshell: Marchenko and Loew found that young neurons grown from dup15q cells have a higher than normal density of dendritic filopodia - think of these as baby dendritic spines. We could leave it at “multitude”, but the relative number of spines turns out to be quite important. So the bombshell: Marchenko and Loew found that young neurons grown from dup15q cells have a higher than normal density of dendritic filopodia - think of these as baby dendritic spines. The density difference could be due to the presence of additional dendrites, or changes in the number of spines on each dendrite. This could be due to the presence of additional dendrites, or changes in the number of spines on each dendrite. Marchenko’s findings suggest that the increased dendritic complexity in dup15q neurons could contribute to the cognitive and behavioral phenotypes observed in dup15q individuals.
In May, 2015 the Dup15q Alliance announced its first Request for Applications (RFA) for grants to fund research specifically for dup15q syndrome. The grant program supports scientists early in their research careers by providing training grants to graduate students, post-doctoral fellows, or medical students pursuing research into dup15q-related fields.

The response to the RFA was excellent. We received 10 applications that were very competitive and focused on a number of topics directly related to dup15q. A group of seven scientists and clinicians reviewed the applications and selected the top two for funding. It was a tough decision because of the high quality of the proposals. We extend our congratulations to the winners, Kevin Hope and James Fink (and their mentors!)

Kevin Hope: Investigation of Synergistic Interactions Among Genes in Dup15q

Kevin is a neuroscience graduate student working with Lawrence T. Reiter, PhD at the University of Tennessee Health Science Center, in Memphis, TN. He was awarded 4 years of funding for his ongoing studies on dup15q syndrome.

Kevin’s PhD thesis project aims to find out which genes in the duplication act together, resulting in the major clinical features of dup15q syndrome. Many genes are located in the segment of chromosome 15q duplicated in both idi (15) and int dup15 (1). So far, most of the research on the genetic basis of the syndrome has focused on a single gene, UBE3A (the gene that causes Angelman syndrome when it is not present). Kevin suspects that other genes in the region contribute to the complex spectrum of symptoms seen in dup15q syndrome. He has selected 4 genes commonly duplicated in most individuals with dup15q syndrome, and likely to impact the function of the nervous system. He wants to understand how these genes influence learning and memory, autism behaviors, and seizures by duplicating and deleting them in Drosophila (fruit flies). Why fruit flies, you ask? First, it is relatively easy to change the dosage and part of the body where the genes are active. Second, they reproduce quickly, so Kevin can create many strains of flies that have different combinations of gene duplications/deletions to test for potential interactions between the genes. Third, you might be surprised to know that fruit flies display complex social and learning behaviors, and can even be triggered to have seizures like mice and people. Thus, Kevin can measure how changing the dosage and combinations of these genes affects the nervous system.

The review committee was very excited about the potential that this study holds for creating a model system that can be used to screen for new therapeutics - potentially by modifying gene function - noting that the fly model of Fragile X syndrome has been a powerful tool for new therapeutics - potentially by modifying gene function - study holds for creating a model system that can be used to screen for new treatments? Both of James’ proposal focuses on understanding what causes the increased risk for seizures in dup15q syndrome. Brain neurons are electrically active cells that send highly coordinated impulses among complicated networks of cells. Seizures often arise when regulatory processes are not functioning normally, or when connections are not formed properly. Although seizures are a major problem for many individuals with dup15q syndrome, we don’t understand how the duplications chromosomes influence the brain to make it more vulnerable. James’ work will use a technique that allows him to convert skin cells from dup15q patients into neurons that he can grow in the lab. Because seizures involve the whole brain, you might wonder how James can study seizures ‘in a dish’. He can do this by measuring the electrical activity (excitability) of the neurons, how they interact, and whether they are accurately regulating the signals transmitted between cells to determine whether there is something fundamentally different with the dup15q neurons compared to normal neurons. James’ work has broader implications, because accurate regulation of the interactions among brain neurons is critical for learning and memory, language, autism, and even muscle tone.

James’ research project also got the review committee excited because using neurons grown from actual dup15q patients to understand the processes that could be causing seizures is truly innovative. This research could provide the groundwork to eventually test different types of compounds or drugs to see if they can correct processes that are functioning abnormally, which could potentially lead to new treatments for dup15q syndrome.

Directly funding research empowers the Alliance to drive work into areas that are important to dup15q syndrome. In the review process used to select the winners we asked – would the work impact our understanding of the syndrome? Could it potentially generate model systems to screen for new treatments? Both of the grants awarded meet those goals. The grant winners are at an influential stage in their careers, and these grants could spark long-term commitments to dup15q research. Training grants allow the mentor to invest in new dup15q projects, and generate results that can be used to apply for large-scale funding by agencies such as the National Institutes of Health. It is exciting that the Alliance is now in a position to drive the direction and quality of research that hold promise for improving the lives of individuals with dup15q syndrome.
The Beauty of dup15q

The Dup15q Alliance is fortunate to have a longstanding relationship with Rick Guidotti. Rick is the founder and director of Positive Exposure (www.positiveexposure.org), an innovative arts, education and advocacy organization. Rick’s photos capture the beauty and joy of people living with genetic, physical, cognitive and behavioral difference. It is always a treat to see the beauty of dup15q as captured by Rick, and here are some of the Stronger Together conference photos from our remarkable friend.
We are transitioning from being a family run organization to one that can clearly sustain itself and maintain professional leadership. Our financial position is strong. Our balance sheet at the end of August has slightly over $406,000. We still have the large conference hotel bill to pay as well as several other conference related expenses, but we remain in good financial standing because of the generosity including ongoing and gifts of time and talent. We are committed to funding the development of a Dup15q Alliance and gifts of time and talent. We are happy to have Kadi as our Executive Director, but know that, at some point, we will transition to a full-time director. Kim is awesome providing support and leadership behind the scenes, making sure that everything from the website, to fundraising mailings, to conference details are all taken care of in a professional manner. In addition, we are engaging other families to assist with tasks including mailings as well as more complicated projects like our walks and fundraising events. All of these require additional funds, but if we are to grow as an organization we need to think differently about leadership, funding, and succession plans. We are budgeting with that in mind, and currently have nearly $100K budgeted for such purposes. We don’t have them all staffed so we won’t spend that much, but we felt we needed to be ready to make those moves when the time was right. We budgeted $15K this year to maintain professional leadership, and $25K per year grants awarded at the conference (see Carolyn Schanen’s Dup15q Alliance Funds Research Article for more on this). One of these is a three-year grant from the other four funded grants. In addition, we are investing $48K in funding the development of a data base for our Dup15q clinics so that we can share information to understand and treat individuals. In addition, we are investing $48K in funding the development of a database for our Dup15q clinics so that we can share information to understand and treat individuals. We budgeted for such positions. We need to get them as quickly as possible. We have engaged a number of different professionals to work on an ongoing basis to develop our Dup15q Alliance. We are considering the establishment of a Dup15q Alliance in other countries as they develop their organizations and websites. Government and medical decisions are made very differently throughout the world, so we need to be prepared to assist those organizations as they grow rather than just presume that our models work everywhere.

If you have any questions about the budget or our thought processes on developing it, please feel free to contact me at tom.doyle@dup15q.org. I would be happy to answer any questions.

Thanks so much to everyone who has and who continues to support the Dup15q Alliance through your generous donations, fundraising, and gifts of time and talent. We obviously couldn’t do it without you. Together we can make a difference!
I will never forget the phone call from the pediatric neurologist at 9 a.m. on a Monday morning in November 2010, when he neither I nor Susan had any idea that the blood test would give us real answers. Rather, we thought it just another routine test. At 12 ¾ months of age, the Pediatric Neurologist suggested that a chromosomal microarray analysis be obtained. At the time, typical developmental milestones for a one year old. Hoeldon was eligible for early intervention services through DDD, three months to decide what to do next. At 12 months, although able to sit independently, Hoeldon was still nowhere near

A DOC band is a funny looking white helmet used to reshape the skull. He wore this helmet for a few months. In the month well check, the pediatrician noticed that he was not enjoying his baths and being held and talked to. At his 4 month well check, the pediatrician noticed that he was not rolling over and seemed to have very low muscle tone. We were referred to physical therapy. We were also referred to a pediatric neurologist. Hoeldon appeared normal, so we were not anxious.

The geneticist suggested we visit the Unique Rare Chromosome website. Unique eventually led us to the Dup15q Alliance, although we did not become much involved with it. We seemed to us at the time that this was a condition which was not going to change and that there was little we could do. It seemed that therapies would do little and with Hoeldon going full-time while battling our own demons, Hoeldon made little or no improvement. He did attend two years of a public, mixed class (typical and non-typical) pre-school with regular visits from speech, occupational and physical therapists. The next few years saw Susan and I struggle individually with our own personal, emotional, and mental, and career difficulties while at the same time facing an apparently irreparable domestic situation. Through all, God has looked after Hoeldon in ways that can only be described as miraculous. I had no idea...

In August 2014, I assumed responsibility for Hoeldon on a full-time basis. Hoeldon was speaking, sitting a lot and spent his pre-school hours at a typical daycare, much of it stimming on his own. It was quite a challenge to only look in one direction and sleep with his head in one position. Every time Hoeldon's diaper was changed, Susan and I would struggle to ensure that he was not breathing. While this sent my shock and fear to levels I did not know could attain in two seconds time, the medical staff quickly resolved the situation, and all was well within a few minutes. Hoeldon was a beautiful baby. I was excited to be a father again. At the hospital, before completing the birth registration, the staff tried to convince me that the common spelling was ‘Holden’. I insisted on spelling it ‘Hoeldon’, not realizing it was a unique name I had no idea...

Hoeldon was a good eater. He slept in Mom and Dad’s room in the same bassinet that his older sister and brother Nick slept in as babies. Hoeldon was a happy baby, and enjoyed his baths and being held and talked to. At his 4 month well check, the pediatrician noticed that he was not rolling over and seemed to have very low muscle tone. We were referred to physical therapy. We were also referred to a pediatric neurologist. Hoeldon appeared normal, so we were not anxious.

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**Dup15q Alliance** is a nonprofit organization that provides family support and promotes awareness, research and targeted treatments for chromosome 15q11.2-13.1 duplication syndrome (dup15q).

Dup15q Alliance offers help and hope for those with dup15q syndrome.

**HOLIDAYS ARE COMING!**

And what better gift than one that supports the Dup15q Alliance and helps raise awareness of dup15q syndrome? The Alliance store has several new items. Check them out!

- Silver Believe Bracelet
- International Believe Shirts (youth and ladies)
- Fleece Zip Ups
- Baseball hats
- Golf Shirts
- License Plate Covers
- Drawstring Bags
- Water bottles

Order your Alliance merchandise at [http://www.dup15q.org/store/](http://www.dup15q.org/store/)

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