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.

http://www.dup15q.org
Since 2011, I’ve had the privilege to organize and chronicle four annual Dup15q Alliance research meetings, each time bringing together 50-100 of the best minds engaged with dup15q research. As both an armchair biologist and parent to a child with dup15q syndrome, I’ve been both delighted at the accelerated pace of progress over these years, and frustrated that it still takes so long to identify targeted treatments. Every year we hear of new incremental insights, each tantalizing in their promise, but often raising more questions than they answer.

This year’s meeting felt different somehow. It wasn’t that the work from past years was any less valuable, nor that this year brought with it any definitive answers for targeted treatments. The thing that impressed me most was that suddenly many of those incremental insights seemed connected to each other. It was as if everyone had decided to sit down and fit together the pieces of the dup15q jigsaw puzzle and, this year, at long last, had finally gotten past laying out the edge pieces. The final picture remains unclear, but at least it’s starting to take shape.

### 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 was not 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 handy. Yi and his co-workers also demonstrated that UBE3A is a plausible treatment for depression, that may help to regulate UBE3A activity and potentially impact some symptoms of dup15q, including seizures, autism, and so on that with dup15q syndrome experience - but at the cellular level it is the beginning of a possibly rescuable phenotype.

### Mathematical Models

Olena Marchenko, a postgraduate student working in Les Loew’s lab at Lees’ove in Belgium to fit mathematical models of cell dynamics to dup15q neurons, dropped a quiet bombshell while describing her equations. Marchenko was interested in the neuron’s dendrites - branched tendrils-like structures - in a mouse model of Dravet syndrome - a rare and intractable epilepsy disorder. Dr. Kalamele was able to induce seizures in the mice while tracking their bioelectrical activity. In many cases it was observed that the mice died exhibiting a characteristic period of bradycardia (slowed heart rate). For the clinicians in the audience, who had patiently sat through the entire previous day of molecular research presentations, it was a moment where someone had fired a starter pistol - a spontaneous and energetic discussion ensued about the findings and their relevance to dup15q.

Professional Advisory Board members Dimitrios Arkil (who runs the Minneapolis dup15q clinic) and Ron Thibert (of the dup15q clinic at Massachusetts General in Boston) reported on their joint work regarding VNS performance and characteristic sleep patterns on EEG in dup15q patients. Arkil reported survey findings on the efficacy and safety of vagus nerve stimulator (VNS) treatment in children with dup15q syndrome and medically resistant seizures. Seventeen families responded to the survey, and the overall conclusion was that VNS was safe and well tolerated. Thibert presented a deeper analysis of sleep EEG patterns in dup15q. First reports on sleep patterns were presented in 2012 based on an initial group of children seen at Dr Thibert’s clinic. The latest data was gathered from individuals seen at dup15q clinics all around the country as part of a multi-center study. The most unique findings were three separate patterns present in a certain percentage of children with dup15q. One pattern is characterized by high beta activity and another by alpha-delta sleep, which is an uncommon pattern of fast and slow activity on EEG present at the same time and has been associated with autonomic dysfunction in the general population. The third pattern is one of very high amplitude, very high frequency alpha pattern. This is an unclear significance, but very likely associated with seizures, and may be unique to dup15q.

Shafali Jeste, from UCLA, also presented analysis on EEG patterns - in this case using a more advanced technology to look at the characteristic beta oscillations found in dup15q kids. Her preliminary work shows that this pattern is more intense for isodicentric duplications compared to interstitials, and that a group, children with dup15q show an EEG pattern that is distinct from children with non-syndromic autism. That means this intense beta wave pattern is so far a true biomarker of dup15q syndrome and not autism, per se. Jeste noted that the pattern was most pronounced in the kids who were more challenged in verbal and motor skills, but this relationship may be related to both type of duplication. Dr. Jeste’s group collected EEG data from 25 more children with dup15q at the family meeting in order to better understand this biomarker. Meanwhile Connie Kasari, also at UCLA, presented insights from her pilot study on JASPER-based interventions (intensive one-on-one therapies) with some of the same kids. The interventions were generally and measurably beneficial, but it was clear that a handful of sessions was insufficient. One of the finest and possibly most valuable moments of the research meeting was an entirely off-menu event. Midway through the second morning, the meeting adjourned briefly so that the researchers and clinicians could walk downstairs to watch the opening parade of the family conference. In an emotionally charged scene, the crowd erupted in cheers as 63 individuals with dup15q and their families marched through the town to take their place at the front. For many of the basic science researchers and Dup15q families, this was his first opportunity to work on something with the potential to directly impact their loved ones. For us, like many of us, many of us, the dup15q puzzle has a very personal feel.
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 and 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 dup15q. 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 people with 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 in flies. 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 approach for identifying new drugs to use to improve symptoms for that disorder.

James Fink: **Hypersensitivity in Human Stem Cell-Derived Neurons from 15q Duplication Syndrome Patients**

James is a graduate student working with Eric Levine, PhD, in the Department of Neurosciences at the University of Connecticut Health Science Center in Farmington, CT. The grant will provide funding for 3 years of research. 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 result 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 duplicated chromosome influences 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 empowered 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 these 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.
The Dup15q Alliance takes the responsibility of handling the resources that you have entrusted to us very seriously. As of this writing, our financial position is strong. Our balance sheet at the end of August has slightly over $496,000. We all 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 and continued support. Our financial position is strong. We currently have nearly $100K of additional funds, but if we are to move when the time is right. We budgeted $15K this year to support dup15q related events. All of these require fundraising mailings, to conference mailings and fundraising events. All of these require...
I had no idea...  

By ROBERT SWITKSY, RISING HIS SON IN SCOTTSDALE, AZ

I thought it would be wonderful to have another child. I had no idea...  

I had no idea how far from any dreams of what I considered ‘normal’ I would find my life. I had no idea of the joys that I would experience in not ‘normal’...  

Susan and I each had two children from prior marriages. Susan had a daughter (9) and a son (12) while I had sons (10 and 11) at the time we discovered Susan was with child. I came from a family of 5 children; we had both been single parents for most of our older children’s lives. This seemed to be the opportunity for a wonderful new chapter for us and our children.  

Hoeldon Day Swinsky was born in September, 2009, at 5 pounds and 10.2 ounces, and 18 3/4 inches long. He needed help with oxygen right after birth as he was not breathing. While this sent my shock and fear to levels I did not know I 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 told me to convince me that the common spelling was ‘Holden’. I insisted on spelling it ‘Hoeldon’, not realizing it was a unique name for a very unique baby. I had no idea...  

Hoeldon was a good eater. He slept in Mom and Dad’s room in the same bassinet that his sister Lauren 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.  

The physical therapist suggested to Susan that she call DDD (Department of Developmental Disabilities) for Hoeldon. Susan said, “No, that’s for people in wheelchairs with a disability.” A month later the therapist suggested calling DDD (Department of Developmental Disabilities) for Hoeldon.  

The geneticist suggested we visit the Unique Rare Chromosome website. Unique eventually led us to the Dupl5q 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 his arrival going by leaving only the most fulfilling parts behind with our 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 saw Susan and I struggle individually with our own personal, emotional, and medical difficulties while at the same time facing an apparently irreparable domestic situation. Through this 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. I realized that he was spending a lot and spent his after pre-school hours at a typical daycare, much of it his own doing. It was quite a challenge for me. Due to my own struggles, and our domestic situation, I had rarely seen Hoeldon for more than court ordered Saturday afternoon visitation for the prior three years. I had not played an active role in his caregiving nor advocacy. I wish I had seen the importance of advocating for my son, for his therapies and for his opportunity to progress past what I thought was a static prognosis. I had no idea of his potential to bring purpose and joy to my life, and to grow and thrive in his own life. I had no idea of the tremendous support of the myriad individuals who together actually are the Dupl 5q Alliance; the caregivers, friends and therapists that God would send to help me help Hoeldon... I had no idea...  

Happily, Susan and her older children are in Hoeldon’s life. He loves and needs them very much. We communicate about Hoeldon’s schooling, therapy and medical needs.  

This August, Hoeldon started v-day kindergarten at the Arizona Autism Charter School. The school is the only charter school in Arizona for autistic students. It is in its 2nd year of operations; admissions are by lottery, and we were on a wait list. The curriculum is delivered via Applied Behavior Analysis (ABA). Board Certified Behavior Analyst supervise teachers and staff; class size maximum is 9:1. Hoeldon is in the “Simplicity” curriculum. The school provides PT, OT and Speech therapy. Through a combination of DDD funding, and insurance I have arranged for Hoeldon to also receive outside speech therapy, physical therapy, occupational therapy, and will soon begin outside ABA therapy. These days, Hoeldon talks and laughs a lot, approaches and says “hello” to strangers everywhere he goes (yes, ya, I know….) enjoys his trampoline, Lego’s (does not build anything yet), Sponge Bob, playing with landscape stones, and most of all swimming… I had no idea...
**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.

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**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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[http://www.dup15q.org](http://www.dup15q.org)