CHOPS SYNDROME NEWSLETTER

FACTS / FEATURES / THE FUTURE

What is CHOPS Syndrome?

CHOPS SYNDROME is caused by a rare *de novo* genetic mutation of the AFF4 gene that was only recently discovered in 2012 at The Children's Hospital of Philadelphia. CHOPS is an acronym for the main characteristics of this new syndrome:

(C) Cognitive Delays
(H) Heart defects
(O) Obesity
(P) Pulmonary Issues
(S) Short stature

Meet the Experts

Dr. Ian Krantz and Dr. Kosuke Izumi - discoverers of CHOPS Syndrome, are Pediatric Clinical Geneticists at the Children's Hospital of Philadelphia.

CHOPS SYNDROME SYMPOSIUM 2019
July 12th-14th 2019
Philadelphia,PA

Join us this summer for the first CHOPS family gathering

It all began here…

CHOPS Syndrome was diagnosed at Children's Hospital of Philadelphia (CHOP) when one doctor, Dr. Ian Krantz, had a hunch about three kids that seemed like they had similar medical and physical attributes that no other syndrome could explain. His hunch led to a genetic sequencing exome study, which two years later would prove to find a perfect match. Three kids, all living within 100 miles of each other, indeed shared the exact same genetic mutation. For Liam, Leta and Nadira the medical mystery was solved and a new syndrome was discovered. Since then, our CHOPS family has grown slowly. There are at least 12 kids in the world diagnosed with this syndrome. And we are excited to be publishing our very first newsletter. There is still much to learn about CHOPS Syndrome and the various manifestations of it, but we are all on this journey together.

A Letter from Dr. Krantz

Genomic Era of Medicine

It is very exciting to be able to contribute to the first CHOPS Family Newsletter. Finding answers for families and individuals with rare and undiagnosed disorders is extremely valuable and our team has been fortunate to be able to do this for families with CHOPS Syndrome. Finding an answer for families serves multiple purposes:

1) It ends the diagnostic odyssey – often eliminating the need for additional procedures and tests that can be stressful and painful for the affected child or adult.
2) It provides a definitive answer for families which allows them to identify other individuals with the exact same diagnosis and to form a community that is invaluable for support and advocacy.
3) It allows concrete information for recurrence risk counseling for families (which in the case of CHOPS Syndrome is extremely low given that all identified individuals have a new, or *de novo*, change in the causative gene and is not something inherited from a parent).
4) Through the identification of other affected individuals of different ages and backgrounds it allows us to understand the natural history of the condition and improve our medical management as well as give families more information about prognosis.
5) It helps the psychological healing process for many families who believe their child's diagnosis was somehow their fault or due to something they "passed on" to them.
6) It sets the ground work for understanding how the clinical features relate to the basic molecular cause which we hope will lead to targeted therapeutics at some point based on this information.

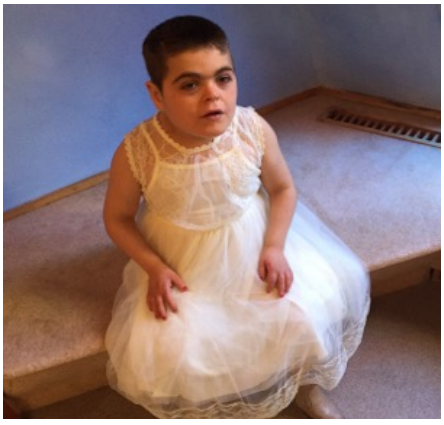
Pictured above: Aspen Hunt (top); Taylor Davis (bottom)

The field of medical genetics has been rapidly changing over the past few years with the introduction of new technology. In fact, when we look back at this era of medicine it will likely be known as the "Genomic Era" given the contribution that genetics and sequencing the genome (all of our genetic material including all of our genes) has made to our understanding of medical conditions. One of the breakthrough technologies that allowed for the identification of the underlying cause of CHOPS Syndrome was something called exome sequencing. Exome sequencing is a technique that unlike traditional genetic testing, which screens one gene at a time or a panel of related genes, screens all of an individual's ~20,000 genes at once. This process is used for individuals who have a medical history and exam strongly suggestive of an underlying genetic etiology, but for whom all testing thus far has not been diagnostic. When this type of testing was in a research stage we hoped it would help us find answers for three exceptional and unrelated children in our care at CHOP. All three children; Liam, Leta, and Nadira were referred to our Center here at CHOP because they had traits similar to a diagnosis called Cornelia de Lange Syndrome (CdLS). When, over the course of more than 10 years we met Liam, Leta and Nadira – we knew they didn't quite fit into the CdLS diagnosis and in fact had clinical issues that made them more similar to each other than to any known diagnosis. In 2013 we asked the three families to contribute DNA from their children and themselves to a research study here at CHOP. Dr. Kosuke Izumi, a postdoctoral fellow in my research lab, was able to use exome sequencing to identify *de novo* (new) mutations (or gene changes) in the AFF4 gene in Liam, Leta and Nadira, and thus they became the very first three children diagnosed with CHOPS Syndrome.

The *AFF4* gene, functioning as a master switch or regulator, plays an important role in turning on and off hundreds of other genes. Mutations in the *AFF4* gene prevents AFF4 from being able to turn other genes on and off at the appropriate times during development. This misregulation has a critical impact on development and cognitive function. The discovery was the first time *AFF4* had been associated with a human diagnosis and has led to a new genetic diagnosis named "CHOPS" Syndrome. The first three children diagnosed with this syndrome are fittingly CHOP patients and the word "CHOPS" is an acronym describing the major clinical features associated with the diagnosis. 'C" for cognitive impairment, "H" for heart defects and hearing loss, "O" for obesity/overweight, "P" for pulmonary issues and "S" for short stature. The Krantz and Izumi Laboratories along with Dr. Shirahige at the University of Tokyo have been studying CHOPS Syndrome and the mechanism of AFF4 for the past few years. Their research findings and this new diagnosis was accepted for publication in Nature Genetics in 2015 [Izumi et al. 2015]. CHOPS Syndrome has some overlap with CdLS but presents with different facial features, pulmonary involvement, obesity and skeletal differences that make it distinct. Dr. Izumi, who is now on the faculty at CHOP and the University of Pennsylvania, is continuing to study the genetics of CHOPS Syndrome and is leading efforts to collect clinical data on newly diagnosed children with CHOPS Syndrome. The hope is to gain a better understanding of the natural history of this novel diagnosis. Since the initial publication of this paper 4 years ago, we have learned about at least 10 additional children with CHOPS Syndrome. We expect that once clinicians, through the increasing use of exome sequencing, begin to better recognize the clinical features of this new diagnosis, we will continue to identify more and more families. The ultimate goals of Dr. Izumi's research is to improve the CHOPS Syndrome medical care and treatments. None of this work could be done without the inspirational and humbling support of the CHOPS Syndrome families. Their willingness to share their clinical information and participate has fueled the research process. We look forward to our continued collaboration and shared goal of improving the lives of children and adults with CHOPS Syndrome.

Dr. Ian Krantz, MD
Pediatric Geneticist

LETA'S STORY



Leta Moseley

Leta is the second to oldest child diagnosed with CHOPS Syndrome. She was born in 1997 and for the first 16 years of her life, all we knew was that she had an undiagnosed genetic anomaly under the category of Pervasive Developmental Delay. Beyond that geneticists were stymied. Born in the dark ages of genetic medicine, Leta is a trailblazer and will hopefully be able to help younger kids, receiving an earlier diagnosis, know more about the syndrome and what to expect both developmentally and medically. Leta did not walk until she was 3 1/2 yrs old, is only 3'10" tall, is predominately non-verbal and has battled multiple pneumonias and respiratory infections throughout her life. To finally find a syndrome and meet other kids who share it, has been an amazing gift to our family. This diagnosis is not only helping us to compare medical notes, but has helped by giving us a support system of like minded people that understand our hopes and fears. Every child on the CHOPS spectrum seems to have certain traits: pulmonary issues, developmental delays, short stature, but from what I can gather so far, they also share some striking and wonderful personality characteristics in common. Leta is incredibly social, has an uncanny sense of humor, and has an enormous heart. She is mayor of any room she enters and is the one you will most likely never forget when you leave that room. Leta is the heart and soul of our family and is an inspiration to most people she meets. Two years ago I wrote a letter the newest family diagnosed with CHOPS Syndrome on my blog: www.savingleta.com. I thought it might be helpful for all newly diagnosed families to read and understand how very special these kids are.

Lainey Moseley, mother of Leta Moseley

A MEDICAL ODYSSEY PUT TO REST

Sarah Raible, MS, LCGC

For the past few years a major focus of our team has been to better define the different clinical issues that are seen in CHOPS syndrome. It is through the generosity and willingness of the current families that we have been able to gather information, medical records, and surveys to gain a deeper understanding of the clinical spectrum of this diagnosis. We are so appreciative and thankful for your help and commitment to our research.

From this research, we have characterized CHOPS syndrome as a distinct genetic diagnosis that includes short stature, characteristic facial features (synophrys or connecting eyebrows, arched eyebrows, long eyelashes, upturned nasal tip with anteverted nares and coarse, full facies), congenital heart defects, pulmonary involvement, brachydactyly (shortened fingers) and other skeletal involvement, genitourinary issues, and developmental delay/ intellectual disability. Congenital heart disease, pulmonary, and skeletal issues are the most common complications. The most common congenital heart defects observed were PDA (patent ductus arteriosus) and VSD (ventricular septal defect). Pulmonary issues most commonly manifested as chronic lung disease, of undetermined etiology, and skeletal involvement included brachydactyly and abnormally shaped vertebral bodies. CHOPS syndrome, though clinically distinct, has some overlap with a different diagnosis called Cornelia de Lange syndrome (CdLS). Obesity and food seeking-behavior, pulmonary involvement, skeletal findings and distinct craniofacial features are the most notable features distinguishing CHOPS syndrome from CdLS. While individuals with CHOPS syndrome present with these four major distinguishing features, they still have some overlap with CdLS as many of the syndrome's other features such as microcephaly, developmental delay, intellectual disability, heart defects and hearing loss are also frequently observed in those with CdLS.

CHOPS syndrome is an autosomal dominant condition due to pathogenic changes (or mutations) in the *AFF4* gene. We all have two copies of every gene, one from our mother and one from our father. With autosomal dominant conditions, a change (or mutation) in just one copy of the gene is enough to cause signs and symptoms. Therefore, individuals with CHOPS syndrome are expected to have a de novo (or new and spontaneously occurring) gene change in AFF4. These genetic changes are typically not inherited from an unaffected parent. If a parent did carry the *AFF4* mutation we would expect them to also have signs and symptoms of the diagnosis.

If both parents are clinically unaffected, then the risk for future affected children is estimated to be ~1%. This risk is above the general population's risk due to the possibility of germline mosaicism. Germline mosaicism is a term to describe the situation in which all of the parents' non-sperm or non-egg cells do NOT contain the mutation, but some of the egg or sperm cells DO contain the mutation and therefore, there is a risk to have another affected child. While we have never seen a recurrence of CHOPS syndrome in a family, this theoretical low risk cannot be ruled out due to the rarity of this diagnosis and the small number of families identified to date.

In future pregnancies, serial ultrasound examinations may be performed to follow overall growth and the development of the heart and other structures affected in individuals with CHOPS syndrome. If a mutation in *AFF4* is identified, prenatal diagnosis of future pregnancies can be completed by performing a chorionic villus sampling (at 10-12 weeks gestation) or an amniocentesis (15-18 weeks gestation). Preimplantation genetic diagnosis (PGD) is also available for families in which the causative mutation has been identified. PGD is a procedure in which embryos are created outside of the body and one cell (in the first few stages of division) is biopsied to determine if the genetic change is present. Then, there is implantation of the embryos only if the mutation is not identified.

If an individual with CHOPS syndrome were to have children – with each pregnancy they would have a 50% chance of passing on the gene change (since they have one *AFF4* gene with the change/mutation and one without) to a child.

Though we have been able to gather a lot of information about CHOPS syndrome since it was first described in 2015, we still have a lot more to learn. Your participation in our research is key to advancing our knowledge to enable better management and clinical care for both the present and future families of the CHOPS syndrome community. We are so thankful for your involvement and our entire CHOP team looks forward to meeting many of you at the first CHOPS family meeting in the summer of 2019.

Sarah Raible, MS, LCGC
Genetic Counselor

ALEX GLIDDEN'S STORY

Alex Glidden and his mother Jenny Watts

Alex is our oldest child, born August 6th, 1991. We have 2 other children, 18 and 19 with no health issues (typical teenagers, though!). Alex was slow to feed as a baby, and needed lots of support in the first few days. He then went on to nurse really well. He was diagnosed with moderate hearing loss at about 18 months old, and now wears hearing aids in both ears. He walked at around 3.5 years with the help of a walking frame, and walked unassisted at approximately 5 years. Alex has always been behind in the milestones, diagnosed with moderate intellectual disability at around the same time.

He speaks with quite indistinct speech, but if people spend a bit of time with him they can usually understand him. He attended a special needs pre-school and then a special needs school until he was 19. For school he has attended a Day Options Service (Xlent Disability Services - they have a FB page), where I work now.

Alex has had every genetic test you can think of, urine tests, hair analyses, sleep studies (although Alex has an amazing ability to stay awake, so the overnight sleep studies were rarely successful!), scans and x-rays. Alex also seems to have an insatiable appetite which has necessitated padlocks on the fridge, freezer and pantry (Alex's dad, Neil was researching Prader Willi syndrome for some time); he has a liking to chew paper of any sort, usually toilet paper which can cause constipation! Plastic wrap seems to be his favorite though.

He has in the past had bad chest infections, also had an aspiration pneumonia caused by an anaesthetic for dental work, but has not had any ongoing breathing problems. He was 86 kgs (189 lbs) in weight, was on a diabetic medication because blood tests showed a protein had bonded with testosterone (a precursor to diabetes), had sleep apnea (hence the sleep studies) and wet the bed nearly every night, even though he was using a nasal spray (Minirin – to stop bed wetting). After his endocrinologist put him on a diet (oats for breakfast made with water, then skim milk, salad and protein for lunch (tuna, boiled eggs, chicken, etc.) and his favotite- veggie burgers and vegetables for tea. His weight is well managed now, so I can relax the meals a bit when we go out to eat, but still choose healthy options. He is now at 58 kg (127 lbs), and off all medications, sleeps better, gets up to use the toilet at night and goes straight back to bed, no more snoring and his blood tests are all completely normal. Alex seems to be the oldest know person with CHOPS although as the medical community becomes aware there will be more diagnosed. I was told by our geneticist that he thought there were perhaps 2 children in France with CHOPS.

So in a nutshell – this is our Alex, a happy, loving young man, who loves music, dancing, watching his siblings play sports, swims really well, can work the computer to a degree, doesn't like to walk too much but is happy to be encouraged along. I hope in the future, more will be known about this interesting syndrome that our children have.

Regards,
Jenny Watts (Alex Gladden's mom) Australia

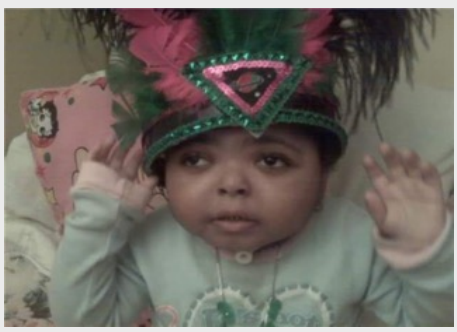
A CHOPS SYNDROME RESEARCH UPDATE
BY DR. KOSUKE IZUMI

After our first publication of CHOPS syndrome, our group has continued to conduct research on CHOPS syndrome. Although, we now understand that genetic changes in *AFF4* cause CHOPS syndrome, it remains unknown how these genetic changes cause symptoms such as obesity, lung disease, heart difference, short stature and so on. In order to identify a treatment for CHOPS syndrome, it is very important to understand how *AFF4* gene changes influence the way our body works. Our lab has been using cellular and animal model to understand the function of the gene.

AFF4's known function is to control genetic information usage (gene expression) in our body. Therefore, as a result of an *AFF4* gene change, one might expect to see gene expression differences in CHOPS syndrome. Utilizing the skin samples donated by children with CHOPS syndrome, we indeed observed gene expression changes unique to children with CHOPS syndrome.

We have also evaluated the effect of *AFF4* gene changes using an animal model. The AFF4 mouse model interestingly showed obesity, which is one of the main clinical symptoms of CHOPS syndrome. We are currently conducting research to understand how CHOPS syndrome's symptoms occur using this mouse model. Thank you very much for allowing me to work on CHOPS syndrome, and for your continued support towards our work.

Ko Izumi, MD, PhD
Assistant Professor of Pediatrics



Nadira Ashton

Teddy Lynn & Family

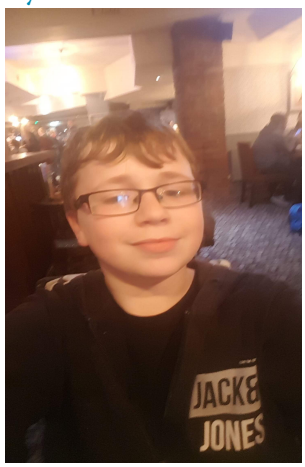
Jakob Engley

Ottilia Elfstrom

Leta Moseley

Avery Minnich and Family

Alex Glidden



Jake Matthews

Maddie Balon

Lucian Agulan

Eider Susperregi Basalo and Family

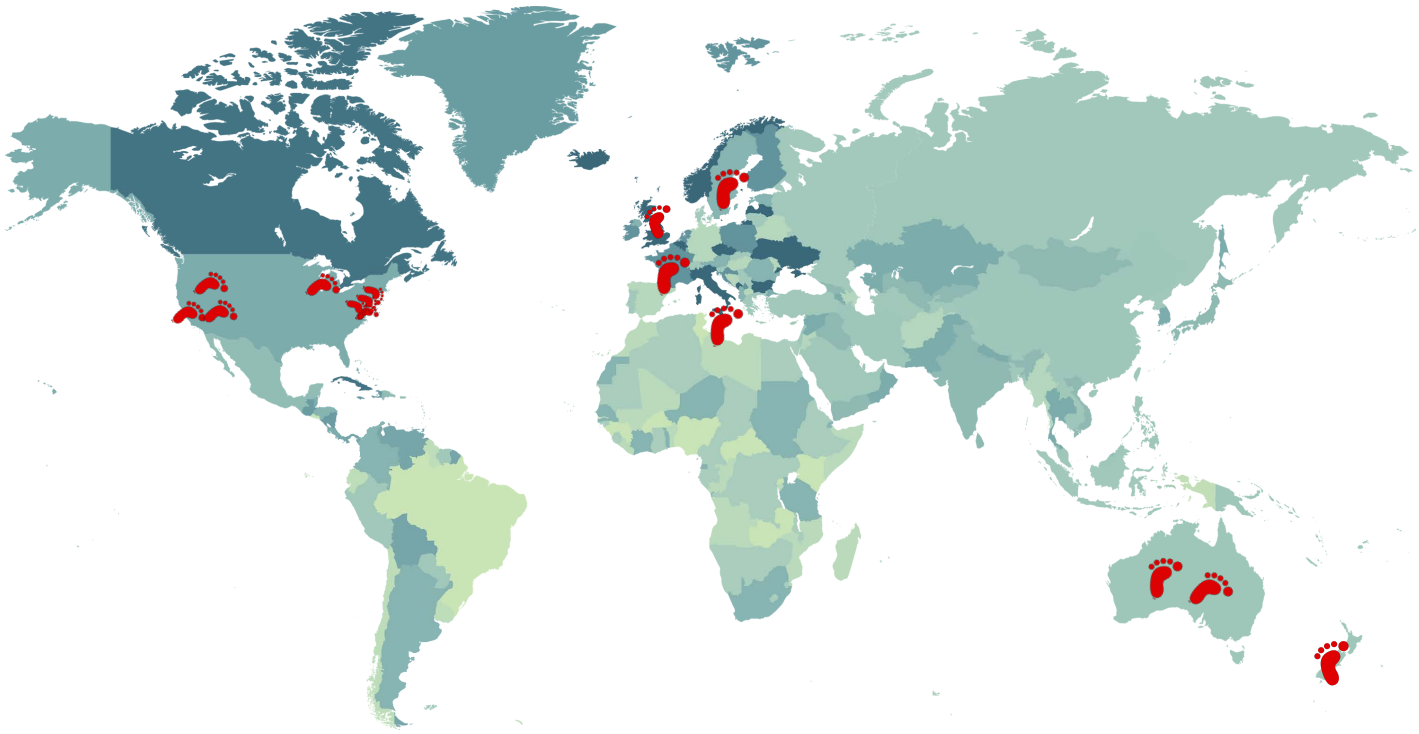
Moseley Family

Liam Hildebrand

Anthony Nelson

Making Footprints Across the Globe

Our CHOPS Members:



United States:

Chicago, IL: (Maddie) Jason and Kristin Balon
Brooklyn, NY: (Nadira) Melissa Ashton * deceased
Philadelphia, PA: (Leta) Lainey Moseley and Rick Moseley
West Chester, PA: (Liam) Kathleen Hildebrand
New Egypt, NJ: (Taylor) Jaime and Baldwin Davis
San Bernandino, CA: (Anthony) Stephanie Miller Nelson
Las Vegas, NV: (Avery) Amy Minnich
Washington, DC: (Teddy) Sanghee and Eric Lynn
Idaho Falls, ID: (Aspen) Kelsey and Bronson Hunt

CHOPS Syndrome Families share a Facebook Support Group. If your child has been recently diagnosed with CHOPS, please reach out to Lainey Moseley (lwmoseley@comcast.net) to be added to the private group.

Australia:
(Alex) Jenny Watts
(Jakob) Dani McLennan

New Zealand:
(Lucian) Belle Agulan

Sweden:
(Ottilia) Jeanette Elfstrom

France:
(Eider) Edurne Basalo and Josué Susperregi

United Kingdom:
(Jake) Judith Matthews

CONTACT:
For more information on **CHOPS SYNDROME:**

Lainey Moseley: lwmoseley@comcast.net

Sarah Raible, Genetic Counselor: raibles@email.chop.edu