The Center for Cornelia de Lange Syndrome and Related Diagnoses at The Children’s Hospital of Philadelphia exists to provide clinical care and to improve the lives of children and adults with Cornelia de Lange syndrome (CdLS) and related diagnoses.

The Center is the culmination of years of dedicated work of a core team of clinicians and investigators at Children’s Hospital coupled with the passion and vision of parents and families of children born with Cornelia de Lange syndrome and related diagnoses. The seed for this Center was planted when Frank Mairano, whose daughter, Lisa, had Cornelia de Lange syndrome, asked us shortly after her death: “How do we stop our kids from hurting?” The Center was established to develop a comprehensive approach to treating and understanding, on a clinical and molecular level, developmental diagnoses. Our Center provides a setting where individuals can receive coordinated care and comprehensive services, and clinicians have the opportunity to translate clinical and laboratory research into improved management and therapeutics.

Our Multidisciplinary Clinic works under the hypothesis that by understanding the clinical issues children with specific developmental diagnoses face and training experts in relevant specialties to proactively manage these issues, we can optimize the quality of life and cognitive outcomes of these children. Our team has a high level of expertise and professional experience specific to these rare conditions. To provide the best medical care, we collaborate across many specialties, so every patient has an individualized plan for care. The Center seeks to provide a medical “home” for individuals with developmental diagnoses and their families. The clinic caters to families from all over the world that may come for a diagnosis, for answers to questions their local physicians are at a loss to explain, or for targeted medical and surgical care. All families return home with a care plan for their children and a medical resource that is a phone call away.

Equal to its clinical activities is the Center’s research. Identifying the underlying causative genes for these diagnoses and the pathways in which they work, while daunting in and of itself, is just the beginning of our mission to translate this knowledge into novel diagnostic, management and, eventually, therapeutic modalities.

The Children’s Hospital of Philadelphia, with its tremendous clinical, research and administrative resources, has embraced the vision of the Center, supported its mission and enabled its growth during our six years of operation. Over the past few years we have had the joy and privilege to meet and work with families from all over the country and the world. We are committed to providing continued support through managed medical care and scientific research.
It has been another exciting year of successes and growth for the Center for Cornelia de Lange Syndrome and Related Diagnoses here at CHOP. These successes have come in the form of high-impact novel discoveries and scientific publications, as well as in less flashy, but no less impactful, management breakthroughs for individual families. The missions of the Center are reflected in these breakthroughs — striving to be at the forefront of research and novel therapeutic development, but equally dedicated to the day-to-day care and management of the individuals and families affected by these diagnoses.

Imagine three families’ multiyear search for answers for the many clinical and developmental issues facing their children. By applying cutting-edge diagnostic and research methodologies, the team at the Center for CdLS and Related Diagnoses was able to end their diagnostic odyssey. Outlined in the pages of this Annual Report you will read about our team’s discovery of a novel diagnosis, “CHOPS syndrome,” and what connects this diagnosis to CdLS, both clinically and molecularly. This discovery implicates a critical biological pathway with a human developmental diagnosis for the first time and sheds light on how disrupting this and other associated pathways, such as the cohesin pathway involved in CdLS, causes human disorders.

Imagine one family’s struggle for answers about the medical needs for its young child and the potential life-saving care plan offered through the Center’s clinicians and counselors. You can read Patrick’s story on Page 3.

Imagine a clinician who has dedicated more than 70 years of his life to the care of individuals with genetic conditions, and who still, in his 90s, is actively involved in helping children with the diagnoses he originally described. You can read about the symposium honoring Philip Pallister, M.D., on Page 10.

Through large and small advances, the Center for CdLS and Related Diagnoses continues to grow and expand its reach and mission. Its dedicated funding and endowment allow it to face new clinical challenges and to capitalize on novel technologies to advance its clinical and research missions. The Center’s successes are a testament not only to our amazing clinicians and basic scientists, but also to the families that have participated in establishing the Center through their generous fiscal support, as well as the families who contribute to our clinical understanding of these diagnoses simply by allowing us the privilege of participating in their children’s care.

For all of this we are eternally grateful.

Here’s to another amazing year and beyond!

Ian Krantz, M.D.
Director
Meet Landon

Adapted from submissions by Nicole Hollner, Landon’s mother

Landon, who was featured on the cover of the 2013 Annual Report, is now 19 months old and weighs 19 pounds! Since last year, we have increased his in-home therapies to include speech (three times a week), special education (two times a week), and occupational therapy, physical therapy, and aqua physical therapy (once a week). We have been putting a lot of emphasis on speech and physical therapy. Since last year, he has had his feeding tube removed and has been eating great by mouth with the exception of liquids. Landon still has sleep apnea, but it appears to slowly improve with each sleep study.

One of the biggest changes happened this past September, when Landon became a big brother to his perfectly healthy brother Levi!

We are so grateful to the wonderful people at the Center for all of their help, support and guidance as we, and so many other families, continue on this journey with our precious children. The Center is an invaluable resource to our children’s healthcare team at home and to us and other parents who always have questions or concerns. We look forward to visiting the Center at The Children’s Hospital of Philadelphia soon.
Meet Patrick

Adapted from submissions by Annie Kelley, Patrick’s mother

My son, Patrick, was diagnosed with Pallister-Killian syndrome (PKS) when he was 10 months old. From birth, we just knew something wasn’t quite right. He had a “look” to him, which included low-set ears, wide-set eyes and sparse hair growth. He was not making any of his milestones, such as crawling, grabbing toys or tracking. He also struggled with nursing and taking a bottle. He had very low muscle tone and bouts of severe constipation. We started physical therapy and were referred to genetics.

The day we walked into our geneticists’ office, they were pretty certain Patrick had PKS, which was confirmed quickly by blood tests. We knew nothing about it. Our research led us to PKS Kids. The organization had the most information on its pkskids.org website and offered a lot of parent support. We read about Dr. Krantz and the research being done at CHOP. My family met Dr. Krantz and the CHOP team at the 2012 PKS Kids Face2Face conference in Washington, D.C. We were thrilled to attend the conference, and little did we know how valuable Dr. Krantz’s knowledge would be for Patrick.

When Dr. Krantz spoke, he made the point that all our kids should be tested for intestinal malrotation, which we’d never heard of. We quickly made an appointment with a local GI doctor and requested an upper GI test. We were told Patrick did not need it because he was not vomiting. After we moved to Michigan to be closer to family, our new pediatrician ordered the upper GI without question. Within minutes of starting the test, the radiologist said Patrick definitely had malrotation. Patrick had LADD surgery, with two hernia repairs and appendix removal. He recovered beautifully.

Had Dr. Krantz not told us about malrotation, we would never have known until Patrick had a complication. We are truly so thankful to Dr. Krantz and the CHOP team for what they do for kids with PKS. Now, Patrick is receiving great care and doing fantastic. He’s 4½ years old and can sit on the floor unassisted, drink from his sippy cup, reach and hold some of his favorite toys, and stand with assistance. We are hopeful Patrick will continue progressing with the help of his teachers, therapists and doctors.
The Center for CdLS and Related Diagnoses continues to offer clinical care and research opportunities to its families locally, nationally and internationally. This past year, we have had families from across the United States and from countries throughout the world, including Qatar, Colombia and Kuwait, travel to CHOP or contact our team to seek an expert opinion. For families unable to visit for an in-person evaluation by our multidisciplinary team, we offer a virtual consult via our “telemedicine” program. Many families and clinicians also contact us regarding research opportunities. Last year, families from many countries, including Latvia and Georgia, enrolled in our research program.

The CHOP CdLS team also had the opportunity to travel to the National CdLS Foundation biennial scientific symposia and family conference in Costa Mesa, Calif., in June 2014. Throughout the conference, the team met with families to offer clinical care and research opportunities. Center director Ian Krantz, M.D., Matthew Deardorff, M.D., Ph.D., Mary Pipan, M.D., Kathleen Loomes, M.D., Sarah Noon, M.S., and additional research team members attended. Dr. Krantz and Laura Bettini, M.D., also had the opportunity to attend the PKS Kids 2014 Face2Face meeting in Chicago. More than 47 families and 200 individuals were in attendance. The CHOP team is looking forward to attending the next CdLS and PKS meetings in 2016!
CORE TEAM

Matthew A. Deardorff, M.D., Ph.D. ■ Attending physician, Clinical Genetics ■ Dr. Deardorff is a clinical geneticist who has worked at CHOP for 13 years. He has his own lab and does research to uncover the causes and mechanisms of the group of diagnoses now referred to as cohesinopathies, under which CdLS falls.

Monica Gaskill, B.S. ■ Junior research associate ■ Monica Gaskill began working in the Krantz lab in October 2014. She graduated from Thomas Jefferson University in August 2014 with a degree in biotechnology.

Ann Tokay Harrington, P.T., D.P.T., Ph.D. ■ Physical therapist ■ Dr. Harrington has been at CHOP for 10 years and joined the CdLS team in 2012. She plays a vital role in the CdLS Multidisciplinary Clinic, providing therapeutic recommendations based on individual concerns and those common to CdLS and related diagnoses.

Pamela Herrera, B.S. ■ Junior research associate ■ Pamela Herrera joined the lab in fall 2014 and is primarily focused on studying Cornelia de Lange syndrome using induced pluripotent stem cells (iPSC). Pamela graduated from the University of Connecticut in 2012 with a bachelor’s degree in environmental science, ecology and evolutionary biology.

Laird G. Jackson, M.D. ■ Professor, Drexel University College of Medicine ■ Dr. Jackson began his research on CdLS more than 30 years ago. His foresight in collecting familial blood samples made today’s research possible. He plays a significant role in the work at CHOP. His current interests are in implementing the development of a CdLS patient registry and database in collaboration with the National Institutes of Health Office of Rare Diseases Research.

Maninder Kaur, M.S. ■ Senior research associate ■ Maninder Kaur received her master’s degree in human genetics and began working in Dr. Krantz’s laboratory in 2002. She has been involved in various aspects of scientific CdLS research over the last dozen years.

Ian D. Krantz, M.D. ■ Attending physician, Clinical Genetics ■ Dr. Krantz, Center director, has worked at CHOP for 20 years. In collaboration with Dr. Jackson, his team began work to find the underlying etiology for CdLS and has since identified several causative genes that led to the discovery of a novel pathway in human development. His lab is also studying other multisystem developmental diagnoses through clinical and basic science research.

Kathleen M. Loomes, M.D. ■ Attending physician, Gastroenterology ■ Dr. Loomes is a gastroenterologist who has been at CHOP for 18 years. She has extensive experience treating and managing individuals with CdLS. In addition to clinical work with CdLS, she researches pediatric liver disease.

Jason Mills, Ph.D. ■ Scientist ■ Dr. Mills is a biomedical researcher who joined the Krantz laboratory in July 2013. He is involved in developing a human therapeutic model for studying Cornelia de Lange syndrome using patient-specific induced pluripotent stem cells (iPSC).

Sarah E. Noon, M.S. ■ Genetic counselor, Clinical Genetics ■ Sarah Noon started at CHOP as a genetic counselor in 2012. She is the clinical director for the Center, serving as the primary contact for families interested in visiting the Multidisciplinary Clinic and participating in research.

Mary Pipan, M.D. ■ Attending physician, Developmental and Behavioral Pediatrics ■ Dr. Pipan is a developmental pediatrician who specializes in the developmental and behavioral aspects of genetic disorders. Dr. Pipan is also director of the Trisomy 21 Program at CHOP and serves as the child development specialist for CHOP’s 22q and You Center.
MEET THE TEAM continued

TEAM TRAINEES ■ A core mission of the Center is to mentor some of the best and brightest future research experts and clinicians.

CURRENT TRAINEE
Yaning Wu, Ph.D. ■ Postdoctoral research fellow, Genetics ■ Dr. Wu received her Ph.D. from the University of Texas at Austin, where her research established a Drosophila model for Angelman syndrome. She worked as a postdoctoral fellow for four years at M.D. Anderson Cancer Center and joined Dr. Krantz’s laboratory in 2013.

PAST TRAINEES
Kosuke Izumi, M.D., Ph.D. ■ Clinical fellow, Genetics ■ As a Clinical Genetics fellow, Dr. Izumi worked at CHOP for two years. He also was a research fellow in Dr. Krantz’s laboratory in the Human Genetics Division, focusing on understanding the mechanism of genetic syndromes including CdLS, Pallister-Killian syndrome and CdLS-related diagnoses.

Jinglan Liu, M.D., Ph.D. ■ Postdoctoral research fellow, Cytogenetics ■ Dr. Liu worked in Dr. Krantz’s laboratory from 2006 to 2009 as a clinical cytogenetics fellow. She is now the director of the Clinical and Molecular Cytogenetic Laboratory at Drexel University and is currently affiliated with St. Christopher’s Hospital for Children.

Dongbin Xu, Ph.D. ■ Postdoctoral research fellow, Genetics ■ Dr. Xu worked in Dr. Krantz’s laboratory for four years. He established two research models involving fruit flies and stem cells to better understand the molecular mechanism of CdLS

TEAM MEMBER HIGHLIGHT
Sarah Noon, M.S. ■ Genetic counselor, clinical director and research coordinator ■ Sarah Noon received her undergraduate training from Boston College and earned her master’s in genetic counseling from the University of Pittsburgh in 2012. Since being recruited to the CdLS Center in the summer of 2012, her focus has been on expanding clinical and research programs of the Center.

Sarah oversees all administrative and patient care operations for the Center. She is the primary contact for families interested in our monthly multidisciplinary clinics, serving as a resource before, during and after their visit. Sarah also assists families interested in enrolling in CHOP’s CdLS research studies or participating in our telemedicine/virtual consultation program. Sarah is the primary mentor and thesis supervisor for students participating in the Marie Barr Genetic Counseling Award (see related story on Page 14) and is spearheading several research projects related to the care and management of children with CdLS. Sarah also has taken on oversight of the National Institutes of Health grants that help support the research mission of the Center. In her three years at CHOP, Sarah has proven to be an indispensible member of the CdLS team and has contributed to every aspect of the Center’s mission and development.

“It is a privilege to work with the CdLS team at CHOP and the families of the Center, who are an inspiration to all and bring so much joy to the work that the Center accomplishes,” says Sarah.
FAMILIES HELPING FAMILIES

The national Cornelia de Lange Syndrome Foundation in Avon, Conn., is an integral resource for families, providing support and education. At the Center for CdLS and Related Diagnoses at CHOP, we strive to collaborate with the CdLS Foundation to provide the best possible medical care and support for families. Beginning in spring 2014, parents from the Philadelphia region who have children with CdLS were trained by the Foundation as volunteer representatives of the Foundation.

The trained volunteers attend monthly multidisciplinary clinics at CHOP, where they serve as a resource for families, providing emotional support and explaining the services available through the CdLS Foundation. Families have the opportunity to attend a pre-clinic lunch to meet the CdLS Foundation volunteers and other families attending clinic that day. The parent volunteers, Beth Patitucci and Liz Geraghty, have become an invaluable resource to clinic families, providing a unique sense of comfort and support to our clinic. The Center is thrilled to offer this new service.

MEET BETH PATITUCCI:
“I am married to Paul Patitucci and am the mother to three boys: Justin, 26, Joe, 15 and Andrew, 13, who has Cornelia de Lange syndrome. I’ve been an awareness coordinator and regional coordinator for the CdLS Foundation for several years. I was excited about the opportunity to participate as a parent volunteer at CHOP’s CdLS clinics. I know firsthand how difficult and scary it can sometimes be to raise and take care of a child with Cornelia de Lange syndrome. I’m thrilled the clinic is in place to help families get some answers and guidance directly from professionals who are experts on the syndrome. I’m very happy to be part of the process to help families feel more connected and not so alone in their journey. I also appreciate the opportunity to try to make the clinic experience a little more pleasant by providing whatever support I can, including helping out with the kids, connecting families with the CdLS Foundation, sharing my own experiences or just lending an ear. We’ve been fortunate to have such great connections and support raising Andrew; I’m more than happy for the opportunity to give back and offer hope. It's not often easy living with CdLS, but it is incredibly rewarding!”

MEET LIZ GERAGHTY:
“I was born in England, but did most of my growing up in New Jersey, where I currently reside. I am married and a mother of three children; two boys, ages 27 and 26, and one girl, age 24. My daughter, Bozena, has Cornelia de Lange syndrome. She lived her first 3½ years at Children’s Specialized Hospital, N.J., came home for 15 years and has resided for the past five years at Matheny Hospital, N.J. Bozena was diagnosed with CdLS at 2 months old. This was new to me, and I did not know how to react. But knowledge is power, and I embarked on a journey, reaching out to physicians and the CdLS Foundation to learn as much as possible. I found a family that embraced me and became a part of helping me raise my daughter. Having her at home was not always easy. I learned a lot about family sacrifice, support (or lack thereof), social scrutiny and, at times, the emotional roller coaster, but I also learned about acceptance and love no matter what. Bozena’s current residence, Matheny Hospital, is now a part of our family. I am actively involved in various committees and serve on the board of trustees there. I miss my daughter being home, but I miss her in a good way, like my sons. Not having Bozena at home has given me the gift of time, and I am truly grateful to use that time in giving back the knowledge I have learned from her.”
Always More to Discover

Over the past several years our understanding of CdLS and the genetic basis of CdLS has rapidly changed. It has been 10 years since the discovery of the first gene associated with CdLS. Since this initial discovery, a total of five genes (NIPBL, SMC1A, SMC3, RAD21 and HDAC8) have been identified. All are involved in the regulation of structural integrity of the cohesin complex. These five genes account for approximately 70 percent of individuals with CdLS. The remaining 30 percent of CdLS cases may be due to another gene yet to be discovered or a different mechanism such as mosaicism, which was most recently described in individuals with CdLS. Individuals who are mosaic have a change in a gene that occurs in some but not all of their cells.

Our research program continues to study the mechanisms involved in CdLS and the growing group of diagnoses called the “cohesinopathies.” Through our research program we are able to study CdLS using several different models. Animal models are a powerful tool, given their similarity to humans, that can be readily used to study a disease process. Both Yaning Wu, Ph.D., a postdoctoral student at CHOP, and collaborator Dale Dorsett, Ph.D., a professor at Saint Louis University, are Drosophila geneticists who study Drosophila (fruit fly) models of CdLS. Collaborators Anne Calof, Ph.D., Arthur Lander, M.D., Ph.D., and Thomas Schilling, Ph.D., from the University of California, Irvine, study mouse and zebrafish models of CdLS. These animal models have been critical in advancing our understanding of the developmental and behavioral aspects of CdLS.

Additionally, Jason Mills, Ph.D., a research scientist in the Krantz lab at CHOP, has extensive experience working with human induced pluripotent stem (iPS) cells. These cells serve as a human model for studying how certain tissues — such as cardiac, blood and brain tissues — develop in order to better understand the mechanism of cohesin in patients with CdLS. These iPS cells have the ability to make any cell in the body and are therefore a powerful tool used to study cohesin and CdLS.

Our research is supported by the National Institute of Child Health and Development (NICHD) PO1HD052860 “NIPBL, Cohesin, and Related Structural Birth Defects,” the Doris Duke Charitable Foundation “HDAC8, Cohesin and Human Disease,” the CdLS Foundation, and the PKS Kids Foundation. Most recently, Dr. Mills was awarded a two-year U01 sub-award to study hematopoiesis in patients with CdLS carrying NIPBL mutations with a focus on megakaryocyte development.
ONGOING RESEARCH PROJECTS

MOLECULAR STUDIES
- Molecular etiologies of CdLS
- Novel gene discovery in CdLS
- Development of induced pluripotent stem (iPS) cell models for CdLS and other diagnoses
- Fruit fly (Drosophila) model development for use in testing pharmacologic agents as therapeutics for cognitive and behavioral aspects of CdLS
- Role of cohesin (protein complex) in basic cellular mechanisms, including gene regulation and X-inactivation
- Cohesin gene disruption identification in diagnoses related to CdLS (cohesinopathies)
- Molecular characterization of a novel cohesinopathy “CHOPS syndrome”
- Role of the super elongation complex (SEC) in cohesin function
- Delineation of a 12p critical region in Pallister Killian syndrome (PKS)
- Identification of downstream effectors of the genes on 12p by genome-wide expression in PKS

CLINICAL STUDIES
- Benefits and limitations of a multidisciplinary approach to managing individuals with CdLS or a related diagnosis
- Immunodeficiency in CdLS
- Genotype/phenotype correlation in CdLS
- Limb characterization in CdLS
- NIPBL mosaicism in CdLS
- Autism in CdLS
- Natural history and phenotype characterization of CHOPS syndrome
- Natural history and phenotype characterization of PKS
- Diagnostic modalities using genome wide arrays in PKS
- Natural history and phenotype characterization of 9q subtelomeric deletion syndrome

RESEARCH COLLABORATORS
The CHOP research team collaborates with other researchers across the country and the world. Working together, we have made greater advancements in the field of cohesin biology and the translation of basic science discoveries into clinical application than we could alone. Several research groups the CHOP team collaborates with include:

Anne L. Calof, Ph.D.
Arthur D. Lander, M.D., Ph.D.
Thomas F. Schilling, Ph.D.
Department of Developmental and Cell Biology
University of California, Irvine

Dale Dorsett, Ph.D.
Edward A. Doisy
Department of Biochemistry and Molecular Biology
Saint Louis University School of Medicine

Antonio Musio, Ph.D.
Istituto di Ricerca Genetica e Biomedica
Pisa, Italy

Kerstin Wendt, Ph.D.
Department of Cell Biology, Erasmus Medical Center
Rotterdam, The Netherlands

Kosuke Izumi, M.D., Ph.D.
Katsuhiko Shirahige, Ph.D.
Laboratory of Genome Structure and Function
Research Center for Epigenetic Disease
Institute of Molecular and Cellular Biosciences
The University of Tokyo, Japan

Frank Kaiser, Ph.D.
Institut für Humangenetik Lübeck
Universität zu Lübeck, Germany

Feliciano Ramos, M.D.
Juan Pie, M.D., Ph.D.
Unit of Clinical Genetics and Functional Genomics
Departments of Pharmacology-Physiology and Pediatrics,
Medical School, University of Zaragoza, Spain
On July 11, 2014, we were privileged to attend an extraordinary event at Shodair Hospital in Helena, Mont., to honor and pay tribute to a true giant in medical genetics, Philip David Pallister, M.D. Friends, family and colleagues attended the Conference on Clinical Genetics to honor Dr. Pallister’s many accomplishments and contributions to the field of human genetics. Presentations highlighting his many landmark findings were given by physicians and scientists who are not only luminaries in the field, but who have also been inspired, mentored and befriended by Dr. Pallister in many different ways.

Ian Krantz, M.D., gave a presentation titled “Pallister-Killian Syndrome — Clinical and Basic Science Investigations.” It highlighted the novel clinical and molecular insights arising from recent work that stemmed from Dr. Pallister’s first description of this diagnosis in 1977 and subsequent identification of the underlying cytogenetic etiology, and his continued clinical interest and support of the newly formed PKS Kids Foundation. There are few medical geneticists in the world who can look back on a 70-year career — at least 50 years in genetics — with scientific accomplishments of fundamental biologic importance.

Devanshi Mehta is an undergraduate student at the University of Pennsylvania in the Biological Basis of Behavior program with an aspiration of going to medical school and becoming a pediatric geneticist. Before coming to Penn, Devanshi was involved in a variety of research projects at Rutgers University. At the Ernst Mario School of Pharmacy, she studied chemical biology, and at the Department of Graduate Studies in Psychology, she studied the influence of mentors on youth development, authoring a manuscript for publication in the journal Child & Family Behavior Therapy. The wealth of knowledge acquired from this experience sparked a greater interest in getting involved in research at the undergraduate level.

Devanshi was originally interested in the field of oncology as a medical career. However, she hit a turning point when she shadowed Ian Krantz, M.D., in the CdLS Multidisciplinary Clinic at The Children’s Hospital of Philadelphia. After seeing the complexity of CdLS, observing the challenges of treatment, and interacting with the families and patients, Devanshi turned toward the field of genetics. She realized how much families valued research, how much she learned in every interaction, and how she had the potential to help these families in return. She chose to use her passions in research and medicine by joining the Krantz laboratory to learn more about CdLS and find answers to its complexities.

Devanshi has worked to characterize limb development and to quantify NIPBL gene expression levels on a severity scale. The goal is to use these profiles as a diagnostic and therapeutic tool for the cognitive and behavioral aspects of CdLS. She had the opportunity to attend and present her work at the National CdLS Meeting in Costa Mesa, Calif., this past year — a transformative experience for her. After being inaugurated into the National Honor Society in Neuroscience, Devanshi decided to focus her research on the neuroscience aspect of CdLS. She is currently studying neural differentiation in CdLS using induced pluripotent stem cells (iPSCs). She hopes using the iPSC model will eventually lead to the development of therapeutics for CdLS.
CHOPS SYNDROME

Since birth, Leta (age 17), Liam (14) and Nadira (10) have been living a diagnostic odyssey. All three children first presented to our multispecialty CdLS clinic due to a concern for Cornelia de Lange syndrome. Though all three children had some overlap with CdLS, the diagnosis of CdLS did not explain all their clinical findings. For years these children underwent test after test and met with many different specialists within CHOP and throughout the surrounding area in hopes of finding an answer for their medical issues. Clinicians were at a loss to explain the reason for Leta’s, Liam’s and Nadira’s symptoms. Today, with the use of modern technology in genetics and the efforts of Ian Krantz, M.D., Kosuke Izumi, M.D., Ph.D., and a long list of clinical and research collaborators, we have an answer.

New technology allows exome sequencing, 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. Exome sequencing is used for those 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. Leta, Liam and Nadira underwent exome sequencing as part of CdLS research at CHOP. Through the collaborative efforts of Drs. Krantz and Izumi, a de novo mutation (new gene change) was identified in the AFF4 gene in all three patients. This discovery had not been previously characterized. The change in AFF4 identified in Leta, Liam and Nadira is believed to be the underlying genetic cause for their symptoms.

The AFF4 gene plays a role in turning on and off other genes, functioning as a master switch or regulator. The mutation in the AFF4 gene identified in Leta, Liam and Nadira 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. This is the first time AFF4 has been associated with a human diagnosis, and this discovery has led to a new genetic diagnosis named “CHOPS syndrome.” The first three patients 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 and course facies, H for heart defects, O for obesity, P for pulmonary involvement and S for short stature and skeletal dysplasia. The Krantz laboratory, along with Drs. Katsuhiko Shirahige and Izumi at the University of Tokyo, has been studying CHOPS syndrome and the mechanism of AFF4 for the past two years. Their findings and this new diagnosis have recently been accepted for publication in Nature Genetics (Izumi et. al., 2015).

This has certainly been a long journey for these three families, one paved with many uncertainties and unknowns. However, now we have an answer. Though Leta, Liam and Nadira are the first three individuals to be described as having CHOPS syndrome, we believe there are many more affected individuals throughout the country and the world who may have a similar story and are yet to be identified.
REACHING OUT FOR SUPPORT KEY TO ACCEPTING CdLS DIAGNOSIS

Mike and Lisa Lewin are loving parents who do everything possible to improve the quality of life for their 2-year-old daughter, Lauren, who was diagnosed with Cornelia de Lange syndrome (CdLS) at 36 hours old. Lisa is honest in telling how difficult it was for her to accept Lauren’s diagnosis and to allow herself to reach out for support.

“I felt my world was coming down,” Lisa says now. “Parenthood is hard enough when things go smoothly. For me, the first months after Lauren’s birth were darkness and stress. I wasn’t prepared for it; I didn’t think I could parent her.”

Today, Lisa has embraced what it means to have a child with CdLS. She is active in CdLS fund- and awareness-raising activities. She offers support to other families that have children with CdLS through Facebook groups, the CdLS Foundation and the Center for Cornelia de Lange Syndrome and Related Diagnoses at The Children’s Hospital of Philadelphia.

Her journey from darkness to light was more like a sunrise than flipping a light switch. CHOP and its Center for CdLS were instrumental in her transformation.

When Lisa called the Center for CdLS, the first person she spoke with was genetic counselor Sarah Noon, M.S. “The way Sarah speaks to you and her disposition immediately put you at ease,” Lisa says. “Even though it took a few months until we met, I was comfortable with her from the beginning. All during Lauren’s first year, whenever she passed a milestone, I’d take a picture and send it to Sarah. We developed a trusting relationship.”

Building trusting relationships was repeated with all of Lauren’s care providers at CHOP. “At CHOP, everyone explains things,” Lisa says. “Not coming from a medical background, there was so much we didn’t understand. People took time with us and didn’t make us feel rushed.”
There was much to explain. Lauren was born at 39 weeks at Virtua Voorhees Hospital, one of CHOP’s partner community hospitals. She weighed 4 pounds, 13 ounces. “They suspected immediately that something was wrong,” Lisa remembers. While she was still in recovery from the C-section, a doctor started talking about chromosomal concerns related to Lauren’s full head of hair, full eyebrows and long eyelashes. “I couldn’t comprehend how those could be a bad thing,” Lisa says.

A CHOP cardiologist, Aaron Dorfman, M.D., happened to be on call at Voorhees and checked out Lauren’s heart when she was a few hours old. She was later diagnosed with patent ductus arteriosus and narrowing of the aortic arch. Neither required surgery. Lauren continues to see Dr. Dorfman for yearly checkups.

Lauren spent three weeks in the Virtua Voorhees newborn intensive care unit, mostly because of feeding issues. Switching formulas helped, so she could go home. But it wasn’t until Lauren, at 8 weeks old, had an appointment with gastroenterologist Kathleen Loomes, M.D., who treated her with omeprazole, that her reflux abated.

During her first six months, Lauren also saw CHOP specialists in Audiology, Genetics, Neurosurgery, Urology, Cardiology, Gastroenterology and Otolaryngology, in addition to her pediatrician for weight checks, well baby checkups and immunizations. “Because multiple systems are involved with CdLS, we had so many different appointments,” Lisa says. “After six months, things started to settle down. That’s when I feel I really got to know Lauren and open my heart fully to her.”

Lauren has attended the CdLS Multidisciplinary Clinic twice, with another visit coming up. She started physical and occupational therapy at 14 months old and is soon to start speech therapy. She has appointments with most of her specialists at the CHOP Specialty Care Center at Virtua Voorhees, so care is convenient to the family’s Laurel Springs, N.J., home. Lauren’s CHOP doctors also coordinate and share information with her local pediatrician, so he is familiar with her current treatments.

As Lauren’s medical needs were addressed, Lisa’s personality “as someone who connects” began to return. “In the beginning, I didn’t reach out,” she says. “I didn’t join the parents’ group on Facebook; I didn’t use the resources at the CdLS Foundation. But after a few months I wanted that connection. I was ready for it.”

Lewin joined the Facebook group and connected with other parents, seeking out those whose children were developing similarly to Lauren. One was Nicole Hollner of New York, whose son is also a CHOP patient. (See story on Page 2.) “Our children were born a week apart,” Lisa says. “Nicole was going through many of the same issues with her son.”

As Lisa has been supported by other parents, her knowledge and confidence have grown to the point where she’s reaching out to other families and getting involved in any way she can. In July, she told her family’s story to 300 people at a CdLS fundraising event.

“We’re doing great now,” Lisa says. “Lauren has made me strong in a way I never knew possible so I can stand up and be her advocate. She taught me to take each day at a time, and that is a gift from her I will be forever grateful for.”
Marie Barr was one of the first genetic counselors in the Philadelphia area. Starting as the chief technician for the cytogenetics laboratory at Jefferson Medical College (now Thomas Jefferson University), she soon became involved in counseling families who had children with Down syndrome and other cytogenetic conditions. Marie developed the Jefferson prenatal diagnosis program with Ronald Wapner, M.D., and Laird Jackson, M.D., that in 1983 led to the development of one of the earliest CVS (chorionic villus sampling) programs in the United States and the world. One of Marie’s passions was her work with Cornelia de Lange syndrome patients, both in counseling and helping families. Marie attended family gatherings to collect research samples that finally led to the discovery of the first gene associated with CdLS in 2004. She was the first president of the CdLS Foundation Board. CHOP’s Center for CdLS and Related Diagnoses-sponsored award for an Arcadia University student is also fitting as Marie was a longtime friend of Deborah Enpuh, both before and after Deborah founded the Arcadia Genetic Counseling program. The two met frequently to discuss experiences, frustrations and plans to better help their genetic counseling patients.

The Marie Barr Genetic Counseling Award, initiated in 2014 and supported by the Center, will be awarded annually to a first-year graduate student in the genetic counseling master’s program at Arcadia University. The mission of the award is to promote the development of expertise in genetic counseling issues related to rare developmental diagnoses. Students work with members of the Center for CdLS to gain an understanding of the molecular etiology, clinical complexities, and targeted management of individuals with CdLS and related diagnoses. Under the direction of the CHOP team, award recipients will develop and conduct a thesis project focused on CdLS or a related diagnosis. Winners will receive a tuition stipend to support their genetic counseling education.

The first recipient of the Marie Barr Award is Kathleen January, now in her second year in the genetic counseling program at Arcadia. Kathleen graduated from Boston University in 2010 with a bachelor’s degree in biology, then spent three years working with leukemia and lymphoma patients as a senior research program coordinator in the Department of Oncology, Division of Hematologic Malignancies at Johns Hopkins University School of Medicine.

Throughout her graduate education, she developed an interest in rare and complex multisystem developmental diagnoses. Kathleen’s thesis is focused on studying the perceived strengths and limitations of a multidisciplinary approach to caring for individuals with CdLS and related diagnoses. Kathleen was fortunate to attend the National CdLS Foundation meeting in Costa Mesa, Calif., this past summer to further her research studies. In her future career as a genetic counselor, she aims to improve the lives of children and adults with these conditions and their families.


Since the opening of the Center for Cornelia de Lange Syndrome and Related Diagnoses in December 2009, our goal has been to raise a $5 million endowment. Thanks to the generous donations of several families and the support of The Children’s Hospital of Philadelphia, we reached our first level of endowment in 2013, raising $2 million. Once we reach our goal and become a fully funded Center, the endowment will generate $250,000 in operating funds each year. These funds will support costs for personnel, patient care, family programs, education, outreach and research initiatives.

The first level of the endowment has allowed for the creation of various educational and family support programs such as the Laird and Marie Jackson Lectureship, the Marie Barr Genetic Counseling Award, and the pre-clinic Meet-and-Greet Luncheons with CdLS Foundation volunteers.

In the summer of 2016, we will be hosting our first annual Cool Cars for Kids fundraiser and awareness event at the Fred Simeone Museum in Philadelphia. The event will be open to all — families of the Center, members of the CHOP community and the public — and will feature a display of custom, antique and classic automobiles along with activities for families and children. The goal is to provide a fun event for families and the public while publicizing the work of the Center and increasing awareness of the issues faced by children and adults with developmental disorders. For anyone interested in assisting with supporting or planning the event, please contact Sarah Noon, M.S., noons@email.chop.edu.
We are committed to reaching our $5 million endowment goal, which will allow us to continue and expand activities in support of the Center’s mission of providing specialized clinical care and advancing medical research. We would like to thank the CdLS Foundation and PKS Kids Foundation for their continued support. We are truly appreciative of the donors who have enabled us to reach our first level of endowment.

For more information about supporting the Center for Cornelia de Lange Syndrome and Related Diagnoses, please contact Mika Harding at 267-426-6461 or hardingm@email.chop.edu.
For more information about the Center for Cornelia de Lange Syndrome and Related Diagnoses, call Sarah Noon at 215-590-4248 or email cdlscenter@email.chop.edu.

Matthew A. Deardorff, M.D., Ph.D., a member of the Center for Cornelia de Lange Syndrome and Related Diagnoses team, playing peekaboo with Andrew, when he was 6.