Shortly after the death of 34-year-old Lisa Mairano from Cornelia de Lange syndrome in 2007, her father, Frank, asked her medical team, “How do we stop our kids from hurting?” That question planted the seed for the Center for Cornelia de Lange Syndrome and Related Diagnoses at The Children’s Hospital of Philadelphia.

The culmination of years of dedicated work by a core team of CHOP clinicians and investigators, coupled with the passion of our patients’ families, the Center was established to provide a comprehensive approach to understanding and treating developmental diagnoses.

The Center seeks to provide a “medical home” for our patients. We believe that by understanding the clinical issues children with specific developmental diagnoses face, and by training experts in relevant specialties to proactively manage these issues, we can optimize cognitive outcomes and quality of life.

We serve families from all over the world that may come to us for diagnosis, seeking answers their local physicians are at a loss to provide, or for targeted medical and surgical care. Families return home with an individualized plan of care for their child and a medical resource that is just a phone call away.

Also essential to the Center’s work is research. Identifying the underlying genes that cause these diagnoses and the pathways in which they work is at the core of our mission to translate scientific discovery into novel diagnostic, management and, eventually, therapeutic tools.

The Children’s Hospital of Philadelphia, with its tremendous clinical, research and administrative resources, has embraced the Center’s vision and supported its growth. Over the past five years, we have had the joy and privilege to work with so many wonderful families and children — and we are committed to providing ongoing support through innovative medical care and research.
What an exciting time in the medical field and specifically in the area of medical genetics! The world of genetic and genomic diagnostics has been undergoing a paradigm shift around us with the introduction of new technologies that allow for screening of all 20,000-plus genes in the human genome in a single test (called “whole exome” or “whole genome” sequencing).

We have already begun to feel the impact of this on the Center for Cornelia de Lange Syndrome and Related Diagnoses, with increasing referrals of children with variable clinical presentations found on these new genome-scale diagnostic platforms with mutations in the CdLS genes. Many of these children were diagnosed with CdLS prior to genetic testing, while others have very atypical presentations for whom targeted testing of the CdLS genes would never have been thought of clinically, and are only being identified by these new tests. While on one hand these tests “democratize” genetic testing by allowing all clinicians to order wide spectrum genetic diagnostic tests, they are, at the same time, also pushing the boundaries of our understanding of what is CdLS. Our Center is optimally situated to respond to these new demands and serve as the medical home and referral base for individuals diagnosed on these platforms. We not only provide answers for the families, but we also learn from these families and transform what we know and how we approach the diagnosis of CdLS.

At the same time, these new diagnostic tools are being applied by our researchers to search for answers for families with a child with CdLS or a related diagnosis of an unexplained origin. This work has led to several novel observations and new genes being added to our growing pantheon of CdLS-related genes.

These breakthroughs and increasing clinical demands will challenge us moving forward to broaden the spectrum of those individuals and families that fall under the Center’s umbrella. We are also beholden to help in applying the comprehensive care and translational research model so successfully developed (and constantly being tweaked and optimized) in the Center to benefit other unrelated patient populations with multisystem developmental diagnoses.

The recent establishment of the first level of endowment for the Center for Cornelia de Lange Syndrome and Related Diagnoses has allowed us to gain a foothold of permanence and to turn our dreams for the future into an active reality. I am continually amazed by the dedicated physicians at CHOP, the CdLS Foundation, and collaborators from around the world who give of their time and share their insight to make the mission of this Center happen. I am equally inspired by the families that have given so much — emotionally, intellectually and fiscally — to create this Center that stands as a testament of their love and dedication to their children.

This has been another year of new clinical insights, cutting-edge medical management and ground-breaking research leading to new gene discoveries and first steps towards developing therapeutics for CdLS and related diagnoses.

Here’s to another amazing year and beyond!

Ian Krantz, M.D.
Medical Director, Center for Cornelia de Lange Syndrome and Related Diagnoses
The biggest thing Megan Ramsey has taught those around her during her 35 years is this: Be patient, then watch out.

She didn’t start talking until she was 5 year old, “but she hasn’t stopped since,” according to her mother, Diana. Due in part to a partial cleft palate and swallowing issues, it took Megan a year and a half to learn to eat solid food, but she has eaten independently once she got the hang of it. She didn’t walk until 4½, and then became a whirlwind who loves to dance.

“Early on, when I was working to get Megan services at a public school, one school psychologist told me, ‘A word of caution: If we let Megan think she is normal, she is liable to try to do things she really can’t do.’ I told her, ‘Why don’t we let Megan decide what she can and can’t do.’ Specialists tried to limit her, but Megan is an indomitable spirit,” Diana says.

Diana, an educator herself, was a powerful advocate for her daughter and worked tirelessly so Megan could achieve her potential despite being born with Cornelia de Lange syndrome (CdLS). “I had a voice and I used it,” Diane says. “I decided to be optimistic and to do whatever I could so Megan would feel hopeful and happy.”

For example, Diana created assistive devices when none existed to help Megan sit at the table because she didn’t have the balance and muscular control to sit on her own. When Megan started kindergarten, Diana suggested that she use a box under her feet to support her sitting because her legs weren’t long enough to reach the floor, even in the smallest chair. Megan’s family included her in all they could and as a result, “the town council made a proclamation, and the whole town adopted her,” Diana says.

Megan eventually attended Midland School, a nonprofit special education school in New Jersey, and now lives in a residential facility for adults with mental disabilities. The group home provides the environment Megan needs and her family can’t provide. “It takes a team to manage Megan; it’s not a one- or two-person job,” Diana says. “On a bad day, Megan might have multiple meltdowns, and the behavior specialists and staff are prepared to handle that. Megan feels very independent living in her group home community. She’s happy. Megan loves the people there, and they love her back! Of course she loves to come home for a visit, but she’s fine with going back.”

Megan is followed at the Center for Cornelia de Lange Syndrome and Related Diagnoses at The Children’s Hospital of Philadelphia in the CdLS Clinic, which treats adults as well as children.

The Ramseys were connected to the Center even before it officially existed. When Megan was born 35 years ago in Allentown, Pa., few doctors even knew about CdLS. But Laird Jackson, M.D., then at Thomas Jefferson University Hospital, did. As part of a March of Dimes-funded program, he traveled to hospitals all over Southeastern Pennsylvania and New Jersey to see babies with birth defects and visited Megan in the intensive care unit. “As a mom, all I knew was that Megan struggled to breathe and had oddly shaped hands,” Diana says. Jackson gave the family the diagnosis.

“She was a chubby baby so she didn’t show the classic facial features,” Jackson remembers. Because he had “read a few articles,” he became a de facto CdLS expert, and when a handful of families with children with CdLS banded together to create the CdLS Foundation, Jackson was the medical director.
Jackson, now a professor at the Drexel University School of Medicine, later connected with CHOP’s Ian Krantz, M.D., and the pair discovered the first CdLS gene in 2004. They continue to collaborate on research, and Jackson consults on CHOP patients and supports the Clinic. The Ramseys had stayed in touch with Jackson over the years and came to Philadelphia in 2004 to celebrate the gene discovery.

“First there was Dr. Jackson,” Diana says. “I remember when Ian came in as a young doctor. I’m so grateful this small group of doctors was motivated to passionately work on a disease that won’t make them famous, but is so meaningful to us. The kindness they have shown to their patients and their families is amazing.”

Megan and her mother, Diana Ramsey, who was a powerful advocate for her daughter Megan, giving Natalie Iannacone, clinical support advocate, a hug, has been connected to CHOP even before the CdLS Center was created.
CHOP’s Center for Cornelia de Lange Syndrome and Related Diagnoses continues to provide clinical care and research opportunities to patients and families from all over the country and the world (see below). This past year, we had families from many different states and various countries, including Egypt and the Dominican Republic, travel to CHOP for our multidisciplinary clinic or to enroll in our research studies.

The Center’s team has also been invited to present our research at family meetings, scientific meetings and universities across the United States and in several countries including Australia, England, Germany, Israel, Italy and Spain. The CHOP team had a busy year meeting with various research collaborators to share our scientific findings, gaining insight into other researchers’ discoveries and expanding in our research activities.

This past summer Ian Krantz, M.D., and Matthew Deardorff, M.D., Ph.D., attended the fourth biannual “Cohesin Biology and Cohesinopathy” meeting in Certosa, Italy, meeting with several
of our international collaborators. This meeting has become the cornerstone of the cohesin biology community and has been essential for establishing working collaborations. Dr. Krantz also attended the first family meeting for the Italian PKS Foundation in Bologna, Italy, in September 2013, providing clinical care and research enrollment opportunities to families in attendance.

In December, several members from the CHOP research team traveled to California to meet with Anne L. Calof, Ph.D., and Arthur D. Lander, M.D., Ph.D., from the University of California, Irvine, and Dale Dorsett, Ph.D., from the University of St. Louis, who are close collaborators involved in our research grant provided by the National Institute of Child Health and Development. Attendees shared our respective progress and discussed new plans and future direction for research efforts. This June, the CHOP team will be attending the CdLS Foundation biennial national family conference in Cost Mesa, Calif., and the PKS Kids Foundation family meeting in Chicago, Ill. We look forward to seeing many of you there!
Gastroenterologist Kathleen Loomes, M.D., with Nevaeh, 4, is a member of the multidisciplinary team that sees patients in the CdLS Clinic.
Children or adults who visit our CdLS Multidisciplinary Clinic see many of the doctors and therapists on the core team. We arrange appointments with other specialties as needed. In addition to this list, there are many other CHOP doctors who see patients through the Center.

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 12 years. He currently 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. He received this year’s Dr. Laird Jackson Award from the CdLS Foundation, recognizing significant medical or scientific contributions toward understanding CdLS.

**Ann Tokay Harrington, P.T., D.P.T., Ph.D. • Physical therapist**
Ann has been at CHOP for nine years and joined the 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.

**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 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 decade.

**Ian D. Krantz, M.D. • Attending physician, Clinical Genetics**
Dr. Krantz, Center director, has worked at CHOP for 19 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 17 years. She has extensive experience in 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).

Team continued >
CORE TEAM continued

Mary Pipan, M.D. • Attending physician, Child Development and Rehabilitative Medicine
Dr. Pipan is a developmental pediatrician who specializes in the developmental and behavioral aspects of genetic disorders. Dr. Pipan is also the clinical director of the Trisomy 21 Program at CHOP and serves as the child development specialist for CHOP’s 22q and You Center.

Sarah E. Noon, M.S. • Genetic counselor, Clinical Genetics
Sarah 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.

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

PRESENT 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 the past four years at M.D. Anderson Cancer Center and recently joined Dr. Krantz’s laboratory.

PAST TRAINEES

Kosuke Izumi, M.D., Ph.D. • Clinical fellow, Genetics
Dr. Izumi was a Clinical Genetics fellow who worked at CHOP for two years. He also worked as 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 and to provide platforms for exploring potential therapeutic drugs.

CONSULTING TEAM

Richard S. Davidson, M.D.  
Division of Orthopedic Surgery  
Deborah A. Driscoll, M.D.  
Chair, Department of Obstetrics and Gynecology, Penn Medicine, CHOP Attending Physician  
John A. Germiller, M.D.  
Division of Otolaryngology  
Elizabeth Goldmuntz, M.D.  
Division of Cardiology  
Soma Jyonouchi, M.D.  
Division of Allergy and Immunology  
James A. Katowitz, M.D.  
Division of Ophthalmology  
Andrea Kelly, M.D., M.S.C.E.  
Division of Endocrinology  
Sudha Kessler, M.D.  
Division of Neurology  
Michele Lambert, M.D.  
Division of Hematology  
Rochelle G. Lindemeyer, D.M.D.  
Division of Dentistry  
Kevin E.C. Meyers, M.B.B.Ch.  
Division of Nephrology  
Monte D. Mills, M.D.  
Division of Ophthalmology  
Stephen A. Zderic, M.D.  
Division of Urology
Yaning Wu, Ph.D. • Postdoctoral Genetics research fellow

Dr. Wu is a postdoctoral genetics research fellow at Children’s Hospital who joined the Krantz laboratory in September 2012. She received her Ph.D. in molecular biology from the University of Texas at Austin in 2007. Additional training includes a master’s in biochemistry and molecular biology from Peking Medical College in China in 2000 and a degree in clinical medicine from China Medical University in 1997. As part of Dr. Wu’s doctoral research at UT-Austin, she developed a *Drosophila* model for Angelman syndrome, a neurodevelopmental disorder caused by a deficiency in the UBE3A ligase. Dr. Wu identified that Angelman syndrome fly models displayed deficits in learning, memory, locomotion coordination and circadian rhythms which are also observed in humans who have a diagnosis of Angelman syndrome.

Dr. Wu chose to continue her research and training at CHOP due to its world-renowned reputation and her interest in working on CdLS. Dr. Wu is very interested in how her *Drosophila* research is related to human disease and is particularly interested in using a fly model to study CdLS, given the heterogeneous etiology and multisystemic findings present with this diagnosis. Her research is focused on analyzing the neurological features of various fly models for CdLS such as disruptive sleep patterns, reduced learning and deficits in short-term memory. Dr. Wu is also investigating the genes and pathways that are differentially expressed or regulated by the cohesin pathway in CdLS fly models as it relates to brain development and pathogenesis of CdLS. This past year, she was one of four researchers awarded a research grant by the national Cornelia de Lange Syndrome Foundation in Avon, Conn. The four researchers selected by the foundation will share a $23,000 grant to study various aspects of CdLS. Dr. Wu’s project will use fruit fly CdLS models to reveal the genes and pathways downstream of CdLS-like mutations in hopes of developing therapeutic drugs screens in the future.

Jason Mills, Ph.D. • Scientist

Dr. Mills received his undergraduate and graduate degrees from the University of Delaware. While there, he used primary tissue to develop a novel co-culture system that studied the regulation of growth and maintenance of adult keratinocyte (skin cell) stem cells in vitro. As part of Dr. Mills’ postdoctoral studies at CHOP, he was the sole researcher responsible for the generation of induced pluripotent stem cells (iPSCs) and spent the last four years exploring the mechanisms by which hematopoietic developmental potential varies across and within genetic background.

Dr. Mills’ current study of cohesinopathies was greatly influenced by a personal connection he has with CHOP. His godson was diagnosed with nemaline myopathy, a skeletal muscle disorder, at the age of 6 months and spent a large portion of his early childhood at CHOP. Dr. Mills recalls that the medical staff treated everyone like family, which made it easier to spend months at a time at CHOP. He spent nights and weekends in the Hospital during his undergraduate years, and remembers thinking how wonderful CHOP was. In 2009, Dr. Mills was offered a postdoctoral position at CHOP in the newly established human embryonic and iPSC core facility. This position provided technical training in the area of pluripotent stem cells, but also allowed him to collaborate with a number of world leaders in genetics, hematology, oncology, ophthalmology, neurology and developmental biology here at CHOP. Dr. Mills joined the Krantz laboratory this past summer, bringing extensive experience in human ES/iPSC maintenance and differentiation, genetic manipulation of ES/iPSCs (viral and direct-targeting), generation of iPSCs, animal models for transplantation and diseases, molecular biology, genetics, and epigenetics. His current work focuses on using iPSCs, patient-specific cell lines, to study cohesinopathies. These cells have the capability to make any cell type in the entire body, making them a powerful tool to study the development of normal and diseased tissues. He is currently studying how cardiac, blood and brain tissues develop in order to understand the mechanism of how cohesin affects patients with cohesinopathies. We hope this work will provide a foundation for identification of novel therapeutics to treat patients with cohesinopathies.
All members of the CdLS Clinic team check each patient’s electronic medical record to see updates from the last visit. Since Nevaeh has problems with digestion, which is typical for children with CdLS, gastroenterologist Kathleen M. Loomes, M.D., examines her belly.

A DAY IN THE LIFE

Nevaeh’s parents, Jeremy and Devon Schaffer, have brought Nevaeh, 4, to the CdLS Multidisciplinary Clinic from their Emmaus, Pa., home since her CdLS diagnosis at 2 years old.

In addition to the specialists who rotate through her exam room during Clinic, Nevaeh is also followed at CHOP by Audiology, Cardiology and speech therapy.

All families leave the Clinic with an individualized care plan for their child.

Physical therapist Ann Harrington, P.T., D.P.T., Ph.D., checks Nevaeh’s legs and her walking and climbing. Children with CdLS often have limb differences. Nevaeh didn’t walk on her own until she was 3, but is racing around these days.
Seeing how Nevaeh draws with a marker and “feeds” a doll with a spoon gives developmental pediatrician Mary Pipan, M.D., insight into her eye-hand coordination and fine motor skills dexterity. Developmental delays are common in children with CdLS, but vary in severity.

Ian Krantz, M.D., medical director of the CdLS Center, sees each patient in Clinic to gain an overall sense of the child’s development and specific issues. Dr. Krantz checks Nevaeh’s mouth (a high or cleft palate and small, widely spaced teeth are CdLS characteristics) and her strength, while talking with her parents about changes in her health and behavior since her previous Clinic visit.
The first gene known to be associated with CdLS, \textit{NIPBL}, was discovered in 2004. Since then four more genes have been identified in the involvement of CdLS including \textit{SMC1A}, \textit{SMC3}, \textit{HDAC8} and \textit{RAD21}, with \textit{HDAC8} and \textit{RAD21} being discovered in the past two years. Changes in these five genes are found in approximately 65 percent of individuals with CdLS, with the vast majority being caused by mutations in \textit{NIPBL}.

This leaves approximately 35 percent of individuals with CdLS without an identifiable underlying etiology suggesting there are still mechanisms involved in CdLS yet to be discovered. Our research program continues to study the role of these genes and characterize the function of how an altered cohesin pathway is implicated in CdLS.

In addition to understanding the molecular basis of CdLS, we continue to collect clinical information to better understand genotype-phenotype correlations. Our database continues to grow with more than 1,800 entries from more than 650 families. In addition to CdLS, we are also interested in investigating other multisystemic developmental diagnoses such as Pallister-Killian syndrome, Coffin-Siris syndrome and chromosomal deletion/duplication syndromes.

**Inspiring talented young physicians and medical students to study CdLS:**

\textbf{Richard Tilton, B.S. • Medical Student}

Ricky was first introduced to the world of CdLS research in the summer of 2011 when he worked in Dr. Krantz’s laboratory between his first and second years of medical school at Temple University School of Medicine. Ricky was the recipient of a research fellowship from the American Pediatric Society and Society for Pediatric Research to spend a year continuing his research work on CdLS. One of Ricky’s research projects focused on developing a fruit fly model to study heart differences observed in CdLS. Additionally, he has been involved in projects that use next generation sequencing to look for novel genes that cause CdLS. Ricky is finishing his research fellowship in March 2014 and will be entering his fourth year of medical school this spring.

“Meeting the children and their families in the CdLS clinic has added so much meaning to my research. It is incredibly motivating to see how our research is directly helping our patients, and I am honored to be part of such a great team!”

\textbf{Laura Bettini, M.D. • Physician}

Dr. Bettini graduated from the Medical School at University of Milan, Italy, in July 2013. She previously studied with Angelo Selicorni, M.D., director of a CdLS multidisciplinary clinic in Monza, Italy. Dr. Bettini has a particular interest in developmental diagnoses, and as part of her training she undertook a thesis project related to Cornelia de Lange syndrome. Dr. Bettini joined the Krantz laboratory this past March with an interest in developing a career as a physician-scientist studying the clinical and molecular aspects of CdLS. During her time here at CHOP, she will be working on a basic science project studying induced pluripotent stem cells and CdLS.

“I am very happy to be here at CHOP working in Dr. Krantz’s lab, and I’m excited to learn more about the basic science of CdLS. It will be an honor for me to have the opportunity to meet the children and families of the Center.”
Matthew Deardorff, M.D., Ph.D., (front) demonstrates the lab’s new digital droplet PCR machine to (from left) Jay Mills, Ph.D.; Mani Kaur, M.S.; Ricky Tilton, B.S.; and Yaning Wu, Ph.D.
Our research program is funded by the National Institute of Child Health and Development P01HD052860 “NIPBL, Cohesin, and Related Structural Birth Defects.” Matthew Deardorff, M.D., Ph.D., is also the recipient of a Doris Duke Charitable Foundation Clinical Scientist Development Award entitled “HDAC8, Cohesin and Human Disease.” Our research has also been supported by the CdLS Foundation and PKS Kids Foundation. Several of our current projects include:

Molecular and Cellular Studies
- Molecular etiologies of structural birth defects in CdLS
- Novel gene discovery in CdLS
- Development of induced pluripotent stem cell (iPSC) 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 (cohensinopathies)
- Diagnostic modalities using genome-wide arrays in Pallister-Killian syndrome (PKS)
- Delineation of a 12p critical region in PKS
- Identification of downstream effectors of the genes on 12p by genome-wide expression in PKS

Clinical Studies
- Immunodeficiency in CdLS
- Genotype/phenotype correlation in CdLS
- Limb characterization in CdLS
- Autism in CdLS
- Natural history and phenotype characterization of PKS
- Natural history and phenotype characterization of 9q subtelomeric deletion syndrome

Collaborators
The CHOP research team is involved with additional CdLS and related projects through collaborative efforts with other scientific researchers throughout the country and the world. Collaboration with other researchers, who specialize in various areas, has allowed for great advancements in increasing our understanding, making new discoveries, and ultimately improving the lives of individuals and families affected by these conditions. 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

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

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
CdLS and Mosaicism: A New Mechanism

A recent study led by Dr. Raoul Hennekam in the Netherlands (Huisman et al., *Journal of Medical Genetics*, 2013:50:339-344) has found that mosaicism for *NIPBL* mutations may be found in up to 30 percent of individuals with CdLS who have tested negative in the blood for mutations in the known CdLS genes. Mosaicism means that an individual has a change in a gene which is present in only some but not all of the cells in the body. If an individual is mosaic for a change in *NIPBL*, we may not be able to identify this change by testing only the blood; instead, we may need to test other cells from other tissues. The easiest cells to collect are cells from the inside of the cheek called buccal cells. These cells can be collected by performing a swab of the inner cheek with a small Q-tip-like brush. Dr. Hennekam’s study is critical in that it has demonstrated that a fairly high number of individuals with CdLS may be mosaic for a mutation in the *NIPBL* gene. Therefore, even though testing for this gene in the blood may be within normal limits, complete testing would require examining buccal cells as well to rule out that a mutation in *NIPBL* does not exist in other tissues.

Our Center is interested in understanding the frequency of *NIPBL* mosaicism in individuals with CdLS who have had normal testing in their blood. For families interested in participating in this mosaicism project please contact Sarah Noon, genetic counselor, at 215-590-4248 or noons@email.chop.edu.

Immunological Findings in CdLS

CdLS is caused by disruption of the cohesin complex which plays a key role in gene regulation of human development. Cohesin, however, has additional roles including involvement in the immune system. Recurrent infections have been frequently reported in individuals with CdLS and are a common cause of morbidity. A study led by CHOP immunologist Soma Jyonouchi, M.D., (Jyonouchi et al., *Pediatrics*, 2013:132(2):e484-489) examined 45 patients with CdLS to assess the frequency and types of infections observed in CdLS and determine if an underlying immunodeficiency is associated with this diagnosis.

Recurrent infections are commonly reported at a high frequency in individuals with CdLS. Out of the individuals involved in this study, the most commonly reported infections included recurrent ear infections, viral respiratory infections, pneumonia and sinus infections. Additional infections included recurrent oral candidiasis, bacterial sepsis and recurrent bacterial skin infections. Out of the 45 patients studied, 27 underwent immunological screening. Out of the 27 evaluated, nine cases of antibody deficiency were identified in individuals with a more severe form of CdLS. Screening of individuals with milder forms of CdLS have thus far not revealed any immunologic abnormalities. This was the first study to reveal a high frequency of antibody deficiency in patients with severe CdLS, supporting the need for immunological screening and management of immunodeficiency in patients with a strong history of severe or recurrent infections. Additional studies are needed to determine the mechanism of antibody deficiency in CdLS and understand the full spectrum of immunodeficiency associated with this diagnosis.
Kellie and Michael Feehan have a parenting philosophy for their 6-year-old son Connor: “We don’t put him in a box,” says Kellie. “We expect him to do everything a typical kid would do, and if he has trouble, we adjust.”

Connor has Cornelia de Lange syndrome (CdLS), a genetic condition that affects multiple organ systems. He is treated by Ian Krantz, M.D., medical director of the Center for Cornelia de Lange Syndrome and Related Diagnoses at Children’s Hospital, and during CdLS Clinic, he sees GI and Developmental Pediatrics specialists. They have referred him to CHOP specialists in Ophthalmology, Genetics, Audiology and Allergy. Connor also receives physical, occupational and speech therapy.

“He has needs that aren’t typical of other kids, and we get him the help he needs,” Kellie says. “He’ll discover his limitations at some point. But because he’s pretty mildly affected, we’d be foolish to limit his potential. We don’t know any other way to parent.”

Three days a week, Connor attends First Step Preschool at The Arc of Chester County. On the two other weekdays he attends a mainstream preschool near his home in Chester Springs, Pa. “He loves school now, but it has been a struggle because he has started to show some social anxiety,” Kellie says. “He’s doing pretty well, which is awesome.”

His parents plan to send him to kindergarten — and beyond — in their local school district. “Our hope is for him to be in the typical classroom and have him pulled out [for special education] as needed,” Kellie says.

Because Connor doesn’t have the more classic CdLS physical features, his diagnosis was late in coming. He had severe feeding issues as an infant. He was finally diagnosed with gastroesophageal reflux disease (GERD) at 6 months, but he still wasn’t eating well or growing. At 11 months, his pediatrician referred the family to CHOP for a genetic workup.

“When they told us he had Cornelia de Lange syndrome, we had never heard of it,” Kellie says. They soon learned that Connor’s problems with feeding, development, small size, ptosis (drooping eye lids, which required surgery) and delayed speech are all potentially caused by CdLS.

His GERD is controlled with daily doses of Prevacid. “While he’s been a terrible eater most of his life, in the last year he’s begun to eat better,” Kellie says. “We still deal with some behavioral issues at mealtime.” To further complicate eating, Connor is allergic to milk, eggs, cashews and mustard, and would be happy to exist on his favorite foods — meatloaf and Oreos.

After years of therapy, Connor’s speech has improved greatly, although his articulation decreases when he talks faster. Like many children with CdLS, he has behavioral issues. “It can be tough at times. He has a hard time focusing, and he can get really frustrated,” Kellie says. “We’re working on it; there’s progress.”

With help from Dr. Krantz, the CdLS team and other CHOP specialists, the Feehans are optimistic about Connor’s future. “We feel very lucky to live so close to CHOP; we’ve met people who come to the clinic from states away,” Kellie says. “We would have a hard time making a move away from this area.”


The National CdLS Foundation and CHOP: Achieving Together

By Marie Concklin-Malloy, Executive Director, Cornelia de Lange Syndrome Foundation

The staff at the Cornelia de Lange Syndrome (CdLS) Foundation has viewed the Center for Cornelia de Lange Syndrome and Related Diagnoses at Children’s Hospital as an important resource since its inception. Through medical care and scientific discovery, the dedicated group of clinicians and investigators at the Center continues to advance our understanding and management of the syndrome.

Both the Center and the Foundation share a common goal: To help people affected by CdLS live longer, healthier, happier lives. The Center does that through medical care and research; the Foundation through emotional support and education. By working together and sharing resources and referrals, it’s a win-win for all people with CdLS.

Above: Executive Director Marie Concklin-Malloy (green jacket) and the staff of the Cornelia de Lange Syndrome Foundation


June 7, 2013, marked the first annual Laird and Marie Jackson Lectureship of the Center for CdLS and Related Diagnoses. The lectureship series is named after Laird Jackson, M.D., and his wife, Marie Jackson. Dr. Jackson is currently a professor of genetics in the Department of OB/GYN at Drexel University College of Medicine. Dr. Jackson is also a colleague in the Division of Human Genetics at CHOP whose initial interest in CdLS decades ago sparked the beginnings of great advances in research and medical care for children and adults with CdLS. Dr. and Mrs. Jackson were instrumental in the formation of CHOP’s Center for CdLS and Related Diagnoses, and they have also been involved with the national CdLS Foundation.

The inaugural lecture was given by Dale Dorsett, Ph.D., a professor of biochemistry and molecular biology at Saint Louis University School of Medicine and a close collaborator of the Center. His research interests involve understanding how chromosome structure controls gene expression during development of the fruit fly (Drosophila). His discovery of the Nipped-B gene in Drosophila has been integral in developing an understanding of the molecular mechanism involved in CdLS.

Dr. Dorsett’s lecture, Using Drosophila to Understand the Molecular Mechanisms Underlying Cornelia de Lange Syndrome, focused on the importance and usefulness of using animal models as a tool for studying genetic diagnoses in humans. Various clinicians and researchers throughout the CHOP and University of Pennsylvania community as well as many families of the Center attended. The lecture was followed by a reception to celebrate and thank the families that contributed to reaching the Center’s first level of endowment.

Thank you to all who attended the event, and we look forward to seeing you at the next lecture, planned for the fall of 2014.
At the beginning of 2013 we were thrilled to announce the Center reached its first level of endowment. We have raised $2 million, and our goal is to reach a $5 million endowment level. Reaching our $5 million endowment goal will allow the Center to function as a fully funded center providing $250,000 in operating funds each year. The interest generated from the $5 million endowment will support operating costs for personnel, research, family programs and patient care. The endowed fund will also support outreach and educational activities of the Center and already has allowed for the creation of the annual Laird and Marie Jackson Lectureship, which was launched in 2013.

The Center will also be awarding a research scholarship to support a CdLS or related diagnosis thesis project of a genetic counseling student from the graduate program at Arcadia University in Glenside, Pa. The research award will be named after Marie Barr, a genetic counselor who worked closely with CdLS families and was involved in the early days of the establishment of the CdLS Foundation. It is through your generous donations that we are able to continue to spread awareness, expand our research activities and offer specialized medical care.

We would like to thank the many donors of the Center who have made reaching this first goal a possibility. We are grateful for each gift that helps support our work. We would also like to thank the national CdLS Foundation and the PKS Kids Foundation for their continued support. We are excited about the future of the Center and optimistic as we continue our fundraising efforts to meet our goal of a $5 million endowment.

For more information about supporting the Center for Cornelia de Lange Syndrome and Related Diagnoses, please contact Dan Agoglia at 267-426-6461 or agogliad@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.