R.C.P.U. NEWSLETTER

Director: Roberto Zori, M.D.
Editor: Jennifer Mueller, M.S.,C.G.C.

R.C. Philips Research and Education Unit
Vol. XXVIII No.1 **A statewide commitment to the problems of mental retardation** **December 2016**

R.C. Philips Unit ♦Division of Genetics and Metabolism♦ PO BOX 100296 ♦ Gainesville, FL 32610 ♦ (352)294-5050
Website: http://www.peds.ufl.edu/divisions/genetics/newsletters.htm

Cornelia de Lange Syndrome

Jennifer Mueller, M.S.,C.G.C.

Introduction and Historical Background

Cornelia de Lange syndrome (CdLS) is a multisystemic genetic condition involving skeletal anomalies of the arms and hands, intellectual disability, growth related issues (less than the 5th percentile on the growth curve), distinct facial appearance, behavior issues including autism spectrum features, short stature, digestive problems, seizures, hearing loss, genital, heart and eye issues.

The earliest probable case of CdLS dates back to 1849, in which German anatomist, Wilhelm Vrolik, described a child who had features including oligodactyly (missing fingers). It was not until 1916 that German physician, Winfried Robert Clemens Brachmann, detailed this condition in a 19-day old infant who died of pneumonia while he was practicing at the Children's Hospital of Dresden. Dr. Brachmann's studies were quickly interrupted by World War I and he was sadly killed in action.

Recognition and description of this genetic condition was propelled forward by Dutch pediatrician, Cornelia Catharina de Lange. Dr. Cornelia de Lange was a pioneer in the field of pediatrics and her studies took her abroad to Zurich, Switzerland and later to Emma Kinderziekenhuis, Amsterdam's Children's Hospital. In 1933, she encountered two unrelated females who came to the hospital within weeks of each other. Dr. de Lange noted that this 17-month infant and 6-month old baby bore a remarkable resemblance to each other and similar medical issues. Recording her observations in detail, she later presented a third case to the Amsterdam Neurological society in 1941.

Dr. Cornelia Catharina de Lange

Dr. de Lange's contributions to the medical field earned her knighthood from the Dutch government in 1947. Decades after her death, researchers discovered the first gene (*NIPBL*) associated with CdLS in 2004. Since that time, four more genes have been identified- *SMC1A*, *HDAC8*, *SMC3*, and *RAD21*. Seen across all ethnic backgrounds, approximately 1 in 10,000-30,000 individuals are born with CdLS.

Clinical Features

One of the diagnostic challenges for physicians and healthcare providers is the broad spectrum and variable severity of clinical features seen in CdLS, especially those children and adults who present

with a mild phenotype. These individuals will often have many of the characteristic facial features but lack the extent or severity of limb involvement and other congenital issues. Learning disabilities can be mild and in fact, some individuals will have essentially normal intelligence. There are individuals with this syndrome who live independently and have children of their own. In the following section, we will review the natural history and classical features but by no means is this an exhaustive description of the syndrome.

Pregnancy through Childhood

During pregnancy, babies with CdLS may plot small by the second trimester. Congenital issues involving the heart, palate, diaphragm and other organs are often detected by high resolution ultrasound.

At birth, babies with CdLS may plot below the fifth percentile for all their growth parameters and remain proportionately short throughout their lives. Newborns who are severely affected have a low-pitched cry which goes away during infancy. Approximately 25% of babies with CdLS have congenital heart disease including ventricular septal defects, atrial septal defects, pulmonic stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, and bicuspid aortic valve. Renal abnormalities also occur, as well as undescended testes in almost 75%. Cutis marmorata (a blue/red, lacy appearance of skin when a newborn is exposed to cold) happens in 60% of babies.

Gastroesophageal reflux disease (GERD) occurs in almost all individuals with CdLS. Other issues include pyloric stenosis (the opening between stomach and small intestine is thick), intestinal malrotation (2%), and congenital diaphragmatic hernia in 1% (CDH- hole in the diaphragm allowing movement of abdominal contents into the chest cavity). The combination of GERD, small mouth and jaw, bowel motility, and oral muscles issues contribute to these feeding issues, which in some cases will require G-tube placement for adequate caloric intake.

Almost 95% of babies have limb differences with relative sparing of the lower limbs. Severe upper extremity limb differences are seen in 25%. Limb differences are symmetric or asymmetric, and range from severe reduction with complete absence of the forearm and missing digits to small hands or even milder features like proximal placement of the thumbs or curving of the fifth finger. Lower extremity differences include small feet, club foot, webbing between the second and middle toes, etc.

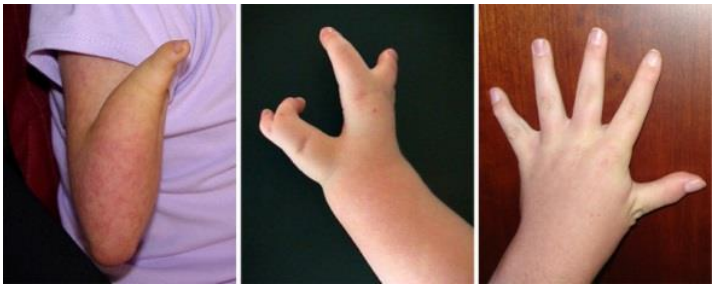

Photo credit: GeneReviews:
https://www.ncbi.nlm.nih.gov/books/NBK1104/

The classic craniofacial features associated with CdLS include arched eyebrows or eyebrows which grow together (synophrs), long and thick eyelashes, small and widely-spaced teeth, short neck, small chin, small head size (microcephaly), low-set ears, wide nasal bridge, small and upturned nose, long, smooth philtrum (area between upper lip and nose) and thin vermilion border (border between upper lip and surrounding skin) with downturned corners of mouth, high and arched palate with clefts (30%), dental crowding, and excessive body hair or hair in locations where it is normally absent or minimal.

Photo Credit: Cornelia de Lange Foundation:
http://calendar.cdlsusa.org/2011/12/one-love-one-heart-1.htm

In terms of hearing and vision, sensorineural (cochlear and nerve pathways to the brain) hearing loss occurs in 80-90% of children and 40% have hearing loss in the profound range. Conductive (outer and middle ear) hearing loss also occurs but may be subsequent to frequent ear infections. About half have ptosis (droopiness of eyelid), as well as nearsightedness (60%), nystagmus, eyelid inflammation, glaucoma, block of the tear ducts, small cornea, astigmatism, optic atrophy, coloboma of the optic nerve (missing tissue in the structure of the eye), etc.

Some individuals have thrombocytopenia (low blood platelet count), impaired T-cell function and antibody deficiency with issues including recurrent infections, chronic ear infections, viral respiratory infections, and pneumonia.

Most individuals with classic CdLS have severe-to-profound intellectual disabilities. IQs range from 30 to 102 with a mean of 53. However, some individuals will have milder intellectual disabilities depending on the type of pathogenic variant and gene this variant occurs in (see Genotype-Phenotype Correlations). In addition to delayed motor milestones, studies demonstrate that about half of children over the age of four years old can construct sentences of two or more words. About 5% have normal language abilities and the remaining third may have up to two word phrases. Of note, comprehension and receptive language (what a child understands) is higher than expressive language (verbal communication). Parental anecdotes suggest that the use of sign language improves communication, as well as behaviors, by using another means of expressing needs and other issues.

Autism spectrum disorders are common (including high pain tolerance, self-destructive behaviors, avoidance of physical and social interaction) and behaviors are exacerbated by impaired expressive language. Additional behaviors include hyperactivity, compulsiveness, aggression, and sleep disturbances. Seizures occur in about 25% of children.

Puberty and Adulthood

Onset and course of puberty is similar to that of the general population. Fertility also appears to be essentially normal or slightly decreased in both males and females. However, some females will not have menstrual periods. Parents and care providers note mood swings and aggression, as well as unexplained pain episodes in their teens. An additional challenge is navigating the beginning of menstruation- especially in daughters with intellectual disabilities or impaired communication. Families may benefit from discussion with their healthcare providers and behavioral therapists as they face these issues.

As adults, constipation persists and GERD and seizures can become worse. Caregivers report that behavior issues including anxiety and aggression may increase and are challenging to handle. Some adults will develop peripheral neuropathy, retinal detachment of the eye with severe nearsightedness, leg length discrepancy and scoliosis. About 20% have truncal obesity. Women may have irregular or no menses. In terms of appearance, adults have prematurely graying hair and coarsening of their facial features.

Research by Beck and Fenger (1985) and later by Jackson et al. (1993) demonstrated that the most common cause of death in individuals with CdLS was due to aspiration pneumonia, followed by congenital heart disease, intestinal obstruction, and recurrent apneas.

Management and Surveillance

Management of CdLS depends on a multidisciplinary effort of specialists which includes but is not limited to gastroenterology, nutrition, audiology, ophthalmology, cardiology, neurology, nephrology, urology, hemoncology, genetics, and therapists (speech, occupational, physical, and behavioral). Treatment is based on the individual's clinical presentation and standard treatment methods are recommended. However, attention is required with anesthesia due to a risk for malignant hyperthermia (rise in body temperature and muscle contraction due to certain drugs used for anesthesia) and management of children with small airways. Guidelines recommend annual monitoring of growth, developmental milestones, routine monitoring of existing cardiac and renal anomalies, and regular follow-up with ophthalmology and audiology.

The Genetics and Testing

Pathogenic variants in the *NIPBL (*60% of all cases)*, SMC1A* (~5%)*, HDAC8* (~4%)*, SMC3* (1-2%), and *RAD21* (<1%) genes are all known to cause Cornelia de Lange syndrome. We still have not identified the genetic cause in about 30% of individuals with CdLS. These five genes have an important role in the cohesion complex, which aids in regulating the structure and organization of our chromosomes (organized structure that contains most of our genes), stabilizes the genetic information of cells, and in the repair of DNA that that been damaged. Importantly, it also has a role in guiding the development of the face, limbs, and other portions of our bodies. Genetic alterations to these genes affect the body during early development and lead to the features we see in CdLS.

Molecular testing is appropriate in individuals who have a clinical diagnosis of CdLS. Testing in a stepwise fashion, *NIPBL* should be sequenced (a test that examines the building blocks of the gene) to identify a pathogenic (CdLS causing) genetic change. If this testing is normal, deletion/duplication analysis (testing for gains and losses within the gene) of *NIPBL* is usually the next step, followed by sequencing and deletion/duplication analysis of *SMC1A*. If the results are normal and the clinical features are highly suggestive, testing is available for the other three genes. Two points to consider in testing for this condition is that somatic mosaicism (multiple different cell lines throughout the body but not the egg or sperm cells) has been reported in

NIPBL. A buccal swab can be sent with peripheral blood to exclude this possibility when sequencing *NIPBL*. Additionally, if this molecular testing is normal, a chromosome microarray can be considered since whole gene deletions of *NIPBL* are associated with CdLS. Additionally, a chromosome microarray will further rule-out other microdeletion or microduplication syndromes that mimic CdLS. Nowadays, multi-gene panels are available that include all five genes. Sensitivity of the panels will vary depending on the lab but may prove more cost effective than serial testing.

Genetic Counseling Issues

Cornelia de Lange syndrome is inherited in both an autosomal dominant and X-linked pattern. Genetic alterations in *NIPBL*, *RAD21*, and *SMC3* follow an autosomal dominant inheritance pattern and *SMC1A* and *HDAC8* with X-linked inheritance. Prenatal genetic testing is available when the familial pathogenic variant is known. Preconception and prenatal genetic counselors can guide families through the benefits and limitations of testing.

Autosomal Dominant

The majority of genetic changes to *NIPBL*, *RAD21* or *SMC3* are brand new (*de novo*) and have not been inherited from a parent. The penetrance, or likelihood an individual will present with CdLS, is very high with all these genes and 100% in individuals with *NIPBL* variants. Due to the possibility of germline mosaicism (genetic alterations contained only within the sperm or egg of a parent), the recurrence chances is about 1.5% to have another child with CdLS if the parents are clinically unaffected with normal molecular testing. In rare cases, mildly affected individuals have children of their own. In these instances, there is a 50% recurrence chance to have a child with CdLS.

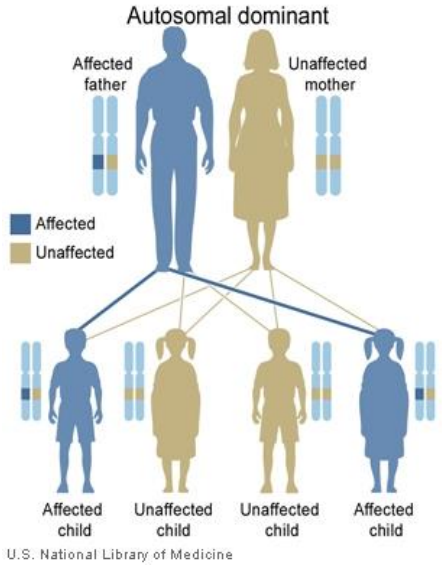

Photo credit: U.S. National Library of Medicine

X-linked Inheritance

The majority of cases of CdLS that are X-linked, demonstrate a brand new genetic alteration in which the mother is not a carrier. However, the mother's carrier status should be determined and again, germline mosaicism should be considered. If the mother is a carrier, she has a 50% chance of passing the pathogenic variant with each pregnancy. Males who inherit the pathogenic variant will have CdLS. Females who inherit the pathogenic variant will be carriers and usually not affected due to X-inactivation. X-inactivation describes the process by which females have one of their two X-chromosomes randomly inactivated or silenced. Mildly affected males with X-linked CdLS will pass the pathogenic variant to their daughters and none of their sons.

Of note, unlike typical X-linked inheritance, there are reports of carriers of *SMC1A* variants who have mild presentations because *SMC1A* does not undergo X-inactivation. However, there are so few cases and limited information, we do not fully understand this process in CdLS.

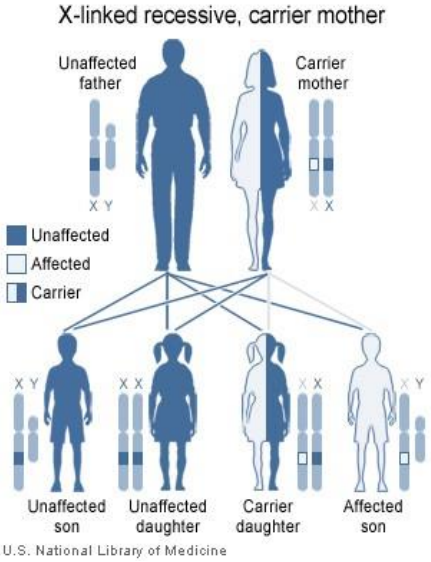

Photo Credit: U.S. National Library of Medicine

Genotype-Phenotype Correlations

The clinical features and severity of CdLS are quite varied and influenced by both the specific gene in which the pathogenic variant occurs and the impact the genetic change has upon the gene's function. Consideration of these phenotypic-genotypic correlations should be taken into account when providing genetic counseling. Milder clinical presentations are reported in individuals who have genetic changes that preserve some protein function (ex. missense changes). Furthermore, milder features have been reported in individuals with *SMC1A*, *RAD21*, and *SMC3* pathogenic variants.

Individuals with *RAD21* pathogenic variants often have milder intellectual deficiency and are born without major structural differences. However, facial features, growth issues, and minor skeletal issues overlap the classic features of this condition.

Intellectual disabilities are usually in the moderate to severe range in people with *SMC1A* and *SMC3* variants, but these individuals may have improved growth and less severe structural anomalies. Facial appearance can differ and is defined by a broader and longer nasal bridge and slightly flatter and broader eyebrows. Furthermore, people who have CdLS due to *SMC3* pathogenic variants are at an increased chance to have a heart defect (~ 60%) but may have either entirely absent or very subtle synophrys. Additionally, the philtrum may look normal but long and the nose is wider and bulbous. Significant intellectual disabilities occur within males with *HDAC8* variants, but the clinical spectrum includes improved growth and head size, friendly personalities, delayed closure of the anterior fontanelle (soft spot on head), hypertelorism (widely spaced eyes), wide nose, skin pigmentation marbling, and dental abnormalities. Clinical presentation in females will be influence by X-inactivation.

Support Organizations

Support Organizations serve an important role for families to connect to other families who have children with CdLS. Major support groups include:

Cornelia de Lange Syndrome Foundation, Inc.
302 West Main Street #100
Avon, CT 06001
Phone: 800-223-8355 (Toll-free Support Line); 860-676-8166
Fax: 860-676-8337
Email: info@cdlsusa.org
www.cdlsusa.org

CdLS World
Website: www.cdlsworld.org

Conclusion

As we continue through the 21st century, we learn ever more about Cornelia de Lange syndrome. Discovery of new genes, delineating genotype-phenotype correlations, next generation sequencing and whole exome sequencing to identify those who have been clinically missed or misdiagnosed has expanded our knowledge by leaps and bounds. These advances serve as an ever constant reminder for healthcare providers to stay abreast on the latest literature, genetic technology, and available clinical trials in order to provide our families with accurate and exceptional care.

References

Cornelia De Lange Foundation: http://www.cdlsusa.org/

Beck B, Fenger K. Mortality, pathological findings and causes of death in the de Lange syndrome. *Acta Paediatr Scand*. 1985;74:765–9.

Deardorff MA, Kaur M, Yaeger D, Rampuria A, Korolev S, Pie J, Gil-Rodríguez C, Arnedo M, Loeys B, Kline AD, Wilson M, Lillquist K, Siu V, Ramos FJ, Musio A, Jackson LS, Dorsett D, Krantz ID. Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of cornelia de Lange syndrome with predominant mental retardation. Am J Hum Genet. 2007 Mar;80(3):485-94..

GeneReviews on Cornelia de Lange Syndrome: http://www.ncbi.nlm.nih.gov/books/NBK1104/

Gooban MT. Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. Am J Med Genet. 1993; 47:1059-1063.

Jackson L, Kline AD, Barr MA, Koch S. de Lange syndrome: a clinical review of 310 individuals. *Am J Med Genet*. 1993 Nov 15;47(7):940-6.

Kline AD, Grados M, Sponseller P, Levy HP, Blagowidow N, Schoedel C, Rampolla J, Clemens DK, Krantz I, Kimball A, Pichard C, Tuchman D. Natural history of aging in Cornelia de Lange syndrome. Am J Med Genet C Semin Med Genetics. 2007 Aug 15;145C(3):248-60.

Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. Cornelia de Lange syndrome: clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Genet A*. 2007 Jun 15;143A(12):1287-96.

Schrier SA, Sherer I, Deardorff MA, Clark D, Audette L, Gillis L, Kline AD, Ernst L, Loomes K, Krantz ID, Jackson LG. Causes of death and autopsy findings in a large study cohort of individuals with Cornelia de Lange syndrome and review of the literature*. Am J Med Genet A*. 2011 December ; 155(12): 3007–3024.

Selicorni A, Russo S, Gervasini C, Castronovo P, Milani D, Cavalleri F, Bentivegna A, Masciadri M, Domi A, Divizia MT, Sforzini C, Tarantino E, Memo L, Scarano G, Larizza L. Clinical score of 62 Italian patients with Cornelia de Lange syndrome and correlations with the presence and type of NIPBL

mutation. *Clin Genet*. 2007 Aug;72(2):98-108.

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health. The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes. Pediatric Genetics University of Florida Box 100296 Gainesville, FL 32610. The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

Acknowledgments

The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children’s Medical Services.