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Clinical, Developmental and Molecular Update on Cornelia de Lange Syndrome and the Cohesin Complex: Abstracts from the 2014 Scientific and Educational Symposium

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Cornelia de Lange Syndrome (CdLS) is the most common example of disorders of the cohesin complex, or cohesinopathies. There are a myriad of clinical issues facing individuals with CdLS, particularly in the neurodevelopmental system, which also have implications for the parents and caretakers, involved professionals, therapists, and schools. Basic research in developmental and cell biology on cohesin is showing significant progress, with improved understanding of the mechanisms and the possibility of potential therapeutics. The following abstracts are presentations from the 6th Cornelia de Lange Syndrome Scientific and Educational Symposium, which took place on June 25–26, 2014, in conjunction with the Cornelia de Lange Syndrome Foundation National Meeting in Costa Mesa, CA. The Research Committee of the CdLS Foundation organizes the meeting, reviews and accepts abstracts, and subsequently disseminates the information to the families through members of the Clinical Advisory Board. In addition to the scientific and clinical discussions, there were educationally focused talks related to practical aspects of behavior and development. AMA CME credits were provided by Greater Baltimore Medical Center, Baltimore, MD. © 2015 Wiley Periodicals, Inc.

Key words: de Lange syndrome; CdLS; cohesin complex; cohesinopathy; intellectual disability; mice; zebrafish; drosophila

ABSTRACTS

Abnormalities of Limb Development in Vertebrate Animal Models of CdLS

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Recent studies implicate the cohesin complex in transcriptional control, potentially through influences on long-distance communication between DNA elements. Animal models of Cornelia de Lange Syndrome (CdLS), the most common “cohesinopathy,” provide a unique opportunity to investigate both how cohesin regulates transcription, and the physiological consequences of disrupting that action. CdLS is most commonly caused by haploinsufficiency for NIPBL, a protein important for loading cohesin onto chromosomes, and individuals with CdLS frequently exhibit limb defects, particularly forelimb reductions of varying severity. Although *Nipbl*-deficient mice (*Nipbl*^{+/-} mice), display no gross limb abnormalities, we find that *nipbl*-deficient zebrafish exhibit severe reduction defects of the pectoral fins, the homologues of the mammalian forelimb. These defects are preceded by dysregulated expression of key developmental genes in the early limb (fin) bud, including *fgfs* in the apical ectodermal ridge; and *shha*, *hand2*, and *hox* genes in limb mesenchyme. Intriguingly, a strikingly similar pattern of gene expression changes can be detected in the limb buds of *Nipbl*-haploinsufficient mice, although the magnitude of gene expression changes is smaller. Limb bud-specific expression of *Shh*

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and *Hox* genes is known to be controlled by long-range enhancer-promoter interactions, and the pattern of changes in *hox* expression that occurs in *Nipbl*-deficient fin buds—characterized by down-regulation of 5' *hox* genes and up-regulation of 3' *hox* genes—is consistent with the impairment of such long-range effects. Interestingly, knocking down expression of Med12—a subunit of the Mediator complex, which regulates promoter-enhancer communication and can co-localize with *Nipbl* on DNA—phenocopies morphological and transcriptional changes observed in *Nipbl*-deficient fin buds. Moreover, partial reductions of *Nipbl* and *Med12* interact synergistically, suggesting action in a common pathway. Overall, the data support the view that *Nipbl* and cohesin, most likely acting in concert with the Mediator complex, regulate limb-specific gene expression and limb development by influencing long-range chromosomal interactions, and suggest that these changes in expression in *Nipbl*-deficient limbs and fins are pathophysiologically significant in CdLS. *Supported by NIH grant P01-HD052860 to ALC and ADL.*

Evidence for Mitochondrial Dysfunction in Cornelia de Lange Syndrome

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Cornelia de Lange syndrome (CdLS), due to mutations in genes involved in the cohesin complex, affects nearly every body system, including the neurologic system with variable seizures, ophthalmologic and audiologic abnormalities, developmental and intellectual disability, and behavioral dysfunction (e.g., ADHD, self-injury, aggression and autism spectrum disorder). There is also evidence for premature aging in some body systems. It is known that there is a naturally high mutation rate in mitochondrial DNA which leads to somatic mutations that accumulate with age and contribute to aging. It has been reported that mutations in cohesin in yeast cells under oxidative stress cause mitochondrial dysfunction and apoptotic cell death. In addition, cell lines with mutations in *SMCIA*

and *SMC3* have been found to have down-regulation of proteins involved in defense against oxidative stress, suggesting its contribution to premature aging. Searching for possible causes of these led us to suspect mitochondrial dysfunction clinically in CdLS, with decreased protection against reactive oxygen species. There has been a confirmed association between autism and mitochondrial disease as well. Because of these reports, as well as the broad phenotype, multiple organ system involvement, and premature aging, investigation of mitochondrial function in CdLS was indicated.

We obtained blood samples from 22 patients with CdLS with a broad spectrum of involvement, including 13 typical and 9 atypical patients, 5 males and 17 females from 12 to 51 years of age. We measured plasma amino acids and tricarboxylic (citric) acid cycle intermediates on the blood samples. Plasma amino acids showed elevations of alanine in 62% and proline in 33%, recognized plasma markers for mitochondrial dysfunction, elevations of both glycine and alanine in 57%, characteristic of mitochondrial complex I deficiency, and the unusual finding of decreased asparagine in 82%, which reflects a low intracellular level of oxaloacetate, an integral part of the citric acid cycle. In terms of the citric acid cycle intermediates, 35% patients each had increased plasma levels of isocitrate (two quite extreme) or 2-ketoglutarate, abnormalities associated with impaired NADH dehydrogenase (complex I activity), and 41% showed elevations of succinate, a marker for mitochondrial oxidative damage. Urine organic acids were normal. Metabolic profile showed elevations of albumin, total protein or globulin in 33%, with the rest normal, and normal levels of CK, coenzyme Q10, selenium, and Vitamin E.

These results demonstrate impaired citric acid cycle function in plasma, and thus evidence for significant mitochondrial dysfunction and oxidative damage in about half of patients with CdLS, likely an underestimate of the total percentage affected. Because complex I is the rate-limiting step in the mitochondrial respiratory chain, many types of mitochondrial disease other than a mutation in a complex I protein gene can manifest functional complex I deficiency. As a result, decreased mitochondrial protein synthesis and increased production of reactive oxygen species would ensue. Although treating the primary cause of the reduced reactive oxygen species protection in CdLS would be difficult, there are antioxidant treatments effective in reducing oxidative damage and augmenting activity of complex I regardless of cause. These are being considered in patients with CdLS.

Identification and Manipulation of Molecular Pathways that Influence the Pathology Associated with Zebrafish Models for Cornelia de Lange Syndrome

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Background: Cornelia de Lange syndrome (CdLS) is a human disease characterized by defects in limb and craniofacial development and growth and mental retardation. CdLS is caused by mutations in several different cohesin genes. While the essential role of the cohesin complex in chromosome segregation has been

well characterized, it plays additional roles in DNA damage repair, chromosome condensation, genome organization, and gene expression. The developmental phenotypes of CdLS and other cohesinopathies suggest that gene expression is impaired by mutations in cohesin during embryogenesis. We set out to identify molecular pathways that are affected by these mutations with the aim of targeting these pathways with therapeutics.

Methodology/Principal Findings: To study development we used morphant zebrafish embryos for *Smc3*, *Rad21*, and *Nipbla/b*, all genes which when mutated lead to CdLS or a related syndrome. Here, we report that mTOR is inhibited in zebrafish morphants for *Smc3* and *Rad21*, but less so in *Nipbla/b*. *p53* activation is observed in *Smc3* and *Rad21* morphants. We tested the effect of inhibiting *p53* or stimulating *mTOR* on survival, size, apoptosis, mitotic index, heart, and craniofacial cartilage formation. All three morphants show some positive response to *mTOR* stimulation. Phenotypes associated with the *Smc3* morphant are partially rescued by *p53* inhibition.

Conclusions/Significance: Our data support the idea that reduction in cohesin is associated with translational defects. Our results are consistent with different gene morphants causing both overlapping and unique pathway signatures.

Heterozygous Drosophila Models for Cornelia de Lange Syndrome

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Cornelia de Lange syndrome (CdLS) is a multi-system genetic disorder. The most typical CdLS features include distinctive craniofacial appearance, growth and development delay, intellectual disability and upper limb abnormalities. Heterozygous mutations in *NIPBL* (*Nipped-B-Like*), *SMC1A*, *SMC3*, *Rad21*, and *HDAC8* account for 70% of CdLS cases overall, with *NIPBL* being by far the most common contributor. All these CdLS genes are highly conserved from yeast to humans and encode structural and regulatory components of the cohesin complex, which is long known for its canonical role in sister chromatid segregation during cell division. Prevailing research findings in CdLS patients and animal models suggest that global dysregulation of gene expression resulting from cohesin deficiency underlies the wide-spectrum of CdLS phenotypes, even though the downstream targets relevant to CdLS pathogenesis are still elusive. We have observed that, similar to CdLS cases, fly *Nipped-B* heterozygous mutants display disruptive sleep patterns, reduced learning, and defective short-term memory. In addition, heterozygous flies of strong *SMC1* and *HDAC8/Rpd3* alleles, but not *Rad21* or weak *SMC1* and *HDAC8/Rpd3* alleles, show defective learning. Such genotype-phenotype correlation is consistent with what has been reported in CdLS cases. These results confirm that the impact of cohesin haploinsufficiency on neurocognition is conserved between fly and human. We are currently trying to purify lineage specific neuronal nuclei tissues from both the wild-type and cohesin heterozygous mutant fly brains. RNA and

DNA isolated from these tissues will then be used for RNA-sequencing and chromatin immunoprecipitation analyses to profile cell-type-specific genome-wide expression and to determine the landscape of Nipped-B and cohesin binding throughout the genome. Genes and pathways differentially expressed or regulated by the cohesin pathway, between fly CdLS mutants and controls, will be assessed for their roles in brain development and in CdLS pathogenesis in future studies.

Airway and Anesthetic Management in Children and Adults with CdLS: Review of the Literature and Summary of Surveys

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Introduction : Cornelia de Lange syndrome (CdLS) patients are often characterized as having a difficult airway (DA) because of craniofacial malformations associated with the syndrome which render airway management difficult. In particular, CdLS patients present with small oral aperture which poses challenges direct laryngoscopy. Although the glottis may be visualized, intubation may prove challenging because the endotracheal tube (ETT) is difficult to place. Small oral aperture and ETT placement difficulties may also occur concomitantly necessitating the use of a specialized airway device (SAD) and/or video laryngoscopy techniques. Furthermore, oxygenation and ventilation can be difficult and patients stand the risk of desaturation even if an airway is established. Vomiting and subsequent aspiration also pose problems because of CdLS associated gastroesophageal reflux. In addition to laryngoscopic challenges, CdLS patients respond unpredictably to medication such as sedation, resulting in hyperactivity and/or paradoxical responses. CdLS patients require medications ranging from sedatives to general anesthetic agents for diagnostic studies and/or surgical procedures. This is a specific concern in CdLS patients because the syndrome's onset early in life and the need for surgical procedures into adulthood.

Methods: Quantitative data querying the incidence of peri-operative complications in CdLS patients was annotated by web-based survey and interviews with patient's families. The data were analyzed to elucidate which challenges and complications are specific to CdLS. Correlation study was performed to determine if DA is a sufficient model to design airway and anesthetic management protocols for CdLS patients.

Results: Data from 51 patients with CdLS reveal an increased incidence of problems related to intubation, ventilation, oxygenation, and aspiration (IVOA). Present in most cases was a narrower airway, requiring the insertion of smaller diameter ETTs. Intubation was difficult to the extent that some children required tracheostomy. Patients with CdLS have varied features relating to the airway and IVOA. Certain aspects related to airway and anesthetic care were over-represented. Regarding diagnostic procedures and surgeries, problems were not similar.

Discussion: Lack of depth in the literature hinders the development of a best practice in airway and anesthetic management of CdLS patients. Management strategies noted in the literature as successful in DA cases need to be assessed for their effectiveness in CdLS patients. Discrepancies between DA and CdLS cases need to be studied, as well as discrepancies between adult and pediatric

CdLS patients. Elucidating differences is significant because airway and anesthetic techniques may or may not become easier as the children grow older. Irrespective of age, however, many CdLS related complications are similar throughout their lifetime. Much information on CdLS is anecdotal; therefore a database should be developed from which the mechanism querying why and how complications occur may be studied. Specific protocols and best practices must be established to understand which interventions and outcomes are beneficial and decrease risk.

Cohesin and Polycomb: Cooperative Checks and Balances

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The cohesin complex mediates sister chromatid cohesion, which ensures accurate chromosome segregation upon cell division. Cohesin also directly controls transcription of genes important for growth and development via multiple mechanisms, such as facilitating looping between transcriptional enhancers and promoters. The Polycomb group complexes maintain gene silencing through multiple cell divisions during development. Genetic and molecular evidence from *Drosophila* shows that cohesin and the PRC1 PcG complex directly interact to control both gene silencing and transcription of active cohesin-binding genes. Cohesin directly recruits and sequesters the bulk of PRC1 at active genes, thereby indirectly controlling how much PRC1 is available for silencing. The PRC1 at active genes prevents promoter-proximal paused Pol II from elongating until it is properly phosphorylated, thereby facilitating the RNA processing needed to produce mRNA. This global balance between cohesin and PRC1 has important implications for the human developmental syndromes caused by modest reductions in cohesin function.

SMC3: Broadening Our Clinical Understanding

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Cornelia de Lange Syndrome (CdLS) and overlapping clinical phenotypes are caused by mutations in genes that encode core members or regulatory components of the cohesin complex. Most patients with typical CdLS have mutations in the *NIBPL* gene. Mutations in *SMC1A*, which encodes a core cohesin component, cause overlapping but less pronounced features, with respect to growth and facial findings. However, these individuals typically have significant cognitive involvement. To date, approximately 5% of patients with CdLS-like features have mutations in *SMC1A*.

In 2007, we identified an *SMC3* mutation in one individual. This man had features that were similar to those noted in subjects with *SMC1A* mutations. At that time, we speculated that because of the mild overlap with the facial features of CdLS and the significant cognitive findings, that *SMC1A* and *SMC3* may be a cause of isolated intellectual disability. Over the next few years, despite screening over 200 additional individuals with CdLS-like features for whom causative mutations had not been identified and 100 individuals with nonsyndromic intellectual disability, we did not identify additional patients with *SMC3* mutations.

Recently, testing for *SMC3* and exome sequencing have become clinically available. As a result of this, we have been able to work with diagnostic labs and global collaborators to identify a number of additional *SMC3* mutations. Patients with CdLS-like features are more likely to have missense mutations, although they do not appear to localize to a specific functional domain of the protein. A very small number of individuals have loss of function alleles. These individuals, while typically have milder growth abnormalities, do not have consistent phenotypic overlap with CdLS, or with each other.

These data suggest at least two things: 1. That mutations in the core cohesin complex cause phenotypic features that represent a subset of those caused by *NIPBL* mutations. 2. That we have a way to go to understand the human developmental effects of Cohesin mutations.

Gynecologic Characteristics and Concerns in CdLS Adolescents and Adults

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Gynecologic encounters with 207 CdLS adolescents and adults were reviewed; 61 females seen in the GBMC Adult CdLS clinic, 21 in contact by email through the CdLS Foundation, and 125 seen at national and international conferences.

The average age of menarche was 13.9 years, one year later than unaffected females. Pubertal changes (pubic hair, breast development) were reported from 3 years to concurrent with menarche. Five percent of individuals had delayed menarche (17 years or older) or primary amenorrhea. Five of the 20 female patients (25%) who had an ultrasound performed in our clinic, or record of a gynecologic ultrasound, had a bicornuate uterus. This is significantly greater than the population incidence of less than one percent.

Fifty-six percent of menstruating patients reported abnormal menses, including irregular cycles (24%), heavy menstrual flow (20%), both irregular cycles and heavy flow (8%), and secondary amenorrhea (3%). The most common hormonal treatment reported was the oral contraceptive pill (18%), most often given to control heavy menses. Depo-Provera use was reported in 17%, most often to suppress menses. Five percent took other hormonal medications, and 5% had had a hysterectomy.

The most common concern was regarding treatment for behavioral changes related to the menstrual cycle, including premenstrual syndrome and dysmenorrhea. There were also a number of inquiries related to menstruation. These included seeking information about medical and surgical options to suppress menses, and methods to

control irregular and/or heavy menstrual cycles. There were also questions regarding contraceptive options for both mildly, sexually active CdLS females to prevent pregnancy and severely affected CdLS females who could be vulnerable to sexual abuse.

Natural History of Young and Adult People Affected by Cornelia de Lange Syndrome: A Report of 46 Italian Patients

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Cornelia de Lange syndrome (CdLS) is a rare genetic condition characterized by a wide variability in term of both genetic and phenotypic expression. To the best of our knowledge, only one report regarding the natural history of aging in patients affected by CdLS has been published so far.

We describe the natural history of aging and of disease-derived major medical complications in a cohort of 46 young-adult patients affected by CdLS, ranging from 15 to 46 years of age. The mean age is 27.4 years. For all patients a clinical diagnosis has been made according to diagnostic criteria published by Kline and colleagues (2007). According to Kline's clinical score, 35% of patient presented a mild, 40% a moderate and 25% a severe phenotype. All patients were genetically tested. Fifty seven percent did not have a genetic mutation while the remaining 43% had a mutation in *NIPBL* or *SMC1A*, respectively (*NIPBL* mutation in 35% and *SMC1A* mutation in 8%).

Obesity developed in 37% of our patients, most commonly in the truncal region. Feeding problems persist throughout the life-span of the patients with 72% presenting with GERD. Eighty percent of these patients are being treated with medical approach, while 20% underwent a surgical intervention. Moreover, within those patients affected by GERD who underwent an EGDS, Barrett's esophagus was found in 13%. Hiatal hernia was found in 16%. Dental anomalies, which include micrognathia, crowding of teeth, absent teeth, poor oral hygiene and periodontal disease, regard 60% of our patients. Hearing loss is found in 50% of the cohort. It consists primarily of conductive hearing loss (40%); sensorineural hearing loss concerns 27% of our patients and mixed hearing loss was found in 20% of the cohort. Moreover, renal hypo-dysplasia with a lack in cortical-medullary differentiation is evident in 17% of our patients. Behavioral issues such as self-injury, anxiety and obsessive-compulsive behavior are often present and worsen with age.

Our findings, consistent with what is described by Kline et al., confirm the importance of a multidisciplinary clinical follow-up in young-adult patients affected by CdLS.

The Role of *NIPBL* in Cornelia de Lange Syndrome

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Cornelia de Lange Syndrome (CdLS) is a severe developmental disorder frequently associated with heterozygous loss-of-function *NIPBL* mutations. *NIPBL* loads cohesin onto chromatin. Cohesin mediates sister chromatid cohesion important for mitosis, but is also increasingly being recognized as a regulator of gene expression. In CdLS patient cells and animal models, the presence of multiple gene expression changes with little or no cohesin defect suggests that disruption of gene regulation underlies this disorder. However, the effect of *NIPBL* haploinsufficiency on cohesin binding, and how this relates to the clinical presentation of CdLS, has not been fully investigated. We examined genome-wide cohesin binding and its relationship to gene expression using mouse embryonic fibroblasts (MEFs) from *Nipbl* +/− mice that recapitulate the CdLS phenotype. We found a global decrease in cohesin binding, including those at CTCF sites and repeat regions. Cohesin-bound genes are enriched for H3K4me3 at the promoters and are mostly downregulated in *Nipbl* mutant MEFs with evidence for reduced promoter-enhancer interaction, suggesting that gene activation is the primary cohesin function sensitive to *Nipbl* reduction. Over 50% of genes affected in mutant MEFs are cohesin target genes, including those involved in adipogenesis, indicating their direct contributions to the *Nipbl* haploinsufficiency-induced CdLS phenotype. Interestingly, mutations in several cohesin subunit genes exhibit mild and somewhat distinct phenotypes compared to that of *NIPBL* haploinsufficiency, raising the possibility that *NIPBL* may have unique functions independent of cohesin. We will discuss our recent findings that support the notion that the cohesin-independent role of *NIPBL* also contributes to the CdLS pathogenesis. *This work was supported in part by NIH grants P01-HD052860 and R21 HD062951.*

High Resolution (Using Digital Droplet PCR) *NIPBL* Expression Levels in CdLS Probands as a Predictor of Mutation Type and Phenotypic Severity

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Cornelia de Lange syndrome is a rare multisystem developmental disorder characterized by growth retardation, intellectual disability, dysmorphic facial features, multisystem malformations, and limb reduction defects. Mutations in genes encoding either regulators (*NIPBL*, *HDAC8*) or subunits (*SMC1A*, *SMC3*, *RAD21*) of the cohesin complex, are found in at least 65% of CdLS patients. Cohesin plays many roles including its canonical role in sister chromatid cohesion during cell division and non-canonical roles in DNA repair, stem cell maintenance and differentiation, chromatin looping and regulation of gene expression. Disruption of this latter role seems to be a major contributor to the underlying molecular

pathogenesis of CdLS. *NIPBL* is required for loading and unloading the cohesin complex onto chromosomes and mutations in this gene account for the majority of cases of CdLS. We, and others, have shown that the levels of *NIPBL* expression is tightly regulated across species and even in CdLS probands haploinsufficient for *NIPBL*, they are able to maintain expression levels above 65–70%. From a cohort of 45 total probands (*NIPBL*, *SMC1A*, *SMC3*, *HDAC8*, and *RAD21* mutation positive and negative), *NIPBL* RNA expression levels were determined using digital droplet PCR (DD-PCR) with two different *NIPBL* Taqman probes. Gene expression levels for all samples were analyzed and correlated in relation to the phenotypic severity and specific gene and mutation type. Probands with severe forms of CdLS were found to have lower levels of *NIPBL* in comparison with milder patients and controls. Corroborating this data, patients with more severe mutation types (e.g., stop, frameshift) also had lower *NIPBL* levels. Levels of *NIPBL* also correlated with the presence of mutations in different CdLS-causing genes. The genetic data suggests that *NIPBL* levels influence the severity of CdLS, and these levels are correlated with specific genes and types of mutations. DD-PCR may provide a tool to assist in diagnostic approaches to CdLS, for genetic counseling and prognosis as well as for monitoring potential therapeutic modalities in the future.

The Cohesin Loader *Scs2* Promotes rRNA Biogenesis and Translational Fidelity

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The *Scs2*-*Scs4* complex is essential for loading the cohesin complex onto DNA. Cohesin generates cohesion between sister chromatids, which is critical for chromosome segregation. *Scs2*/*NIPBL* is mutated in patients with Cornelia de Lange syndrome, a multi-organ disease characterized by developmental defects in head, limb, cognition, heart, and the gastrointestinal tract. How mutations in *Scs2* lead to developmental defects in patients is yet to be elucidated. One hypothesis is that the binding of *Scs2*/cohesin to different regions of the genome will affect transcription. In budding yeast, *Scs2* has been shown to bind to RNA Pol III transcribed genes, as well as RNA Pol II-transcribed genes encoding small nuclear and nucleolar RNAs (snRNAs and snoRNAs) and ribosomal protein genes. In order to understand how *Scs2* mutations might cause human disease, we examine the transcriptional signature of a *scs2* mutant in budding yeast using RNA seq. We found that H/ACA snoRNA genes were consistently downregulated in an *scs2* mutant. Further examination by ChIP-seq showed reduced enrichment of mutant *scs2* at H/ACA snoRNAs. Consistent with reduced transcription of H/ACA snoRNAs, Pol II recruitment to H/ACA snoRNAs was significantly decreased in the *scs2* mutant, indicating that *Scs2* is required for normal occupancy of Pol II at H/ACA snoRNAs promoters. These RNAs are important for the pseudouridylation of ribosomal RNAs and the U6 RNA of the spliceosome. Consistently, the *scs2* mutant was associated with defects in ribosome biogenesis and splicing. Mutations that affect the protein component of the pseudouridylation machinery have previously

been shown to cause an increase in frameshifting and a reduction in the use of internal ribosome entry sites (IRES)/cap independent translation. While the *scc2* mutant does not show a general defect in translation initiation, it has increased frameshifting and reduced IRES usage in reporter assays. These findings suggest *Scc2* normally promotes translational fidelity. We hypothesize that translational dysfunction may contribute to Cornelia de Lange syndrome.

Semi *In Vitro* Reconstitution System for the Analysis of Transcriptional Regulation by Cohesin and Its Loader

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Sister chromatid cohesion (SCC) is crucial to ensure accurate chromosome segregation during mitosis. The cohesin complex mediates SCC, and recent studies show cohesin and the *NIPBL/Mau2* complex, a loader protein required for the loading of cohesin onto chromatin, as important players in transcriptional regulation and chromatin architecture. Discoveries of mutations in subunits of cohesin and *NIPBL* in human developmental disorders, so-called cohesinopathies, reveal crucial roles for cohesin in development, cellular growth, and differentiation. However, it is still unclear how cohesin and its loader work in the transcriptional regulation.

To reveal the complicated mechanisms played by cohesin and its loader in transcriptional regulation, we applied *in vitro* Pre-initiation complex (PIC) and Early Elongation Complex (EEC) assembly systems. In this system, we used the biotin-labeled DNA template, which contained 5xGAL4 DNA binding motifs, adenovirus late promoter sequence and a part of luciferase gene. After binding of activator protein, GAL4-VP16 recombinant protein, to this DNA, PIC, and EEC assembly were induced by addition of the nuclear extract from HeLa cells. Each component of protein complex formed on template DNA was monitored by Western blotting. We showed that PIC factors, mediator, general transcriptional factor and RNA polII, were recruited to the template, which depended on the activator-binding. Further, we observed cohesin- and *NIPBL/Mau2*-binding to the template, and their recruitments also depend on the activator binding. Interestingly, cohesin seemed to get more stably bound after addition of activator. Furthermore, when we treated lysate with 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole (DRB), a CDK9 inhibitor, we found that DNA binding of *NIPBL* and *Mau2* is dramatically enhanced. Taken together, we propose that cohesin-loader and cohesin together regulates step that controls activation of paused RNA polIII nearby promoter.

Origins of Congenital Heart Defects in Mouse Models of CdLS

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Structural defects of the heart, skeleton, and nervous system are common features of Cornelia de Lange syndrome (CdLS). To understand the origins of these abnormalities in CdLS, and poten-

tially also the origins of similar birth defects in nonsyndromic settings, we have developed mouse models of haploinsufficiency for *NIPBL*, the most common genetic cause of CdLS. Mice with a single null copy of this gene (*Nipbl*^{+/-} mice)—which encodes a highly-conserved protein with roles in cohesin loading and transcriptional regulation—display cardiac, neurological, and skeletal defects characteristic of CdLS, as well as widespread changes in gene expression. Our group's recent work on *nipbl*-deficient zebrafish, which also display abnormalities of heart and visceral organ development, led to the hypothesis that structural defects in CdLS arise through the combinatorial effects of small changes in gene expression in multiple tissues. To address this question in mice, we have developed animals with conditional/invertible alleles of *Nipbl*, which may be toggled in either direction between genetically wild-type and genetically null states: *Nipbl*^{FLEX/+} mice are haploinsufficient, but regain normal *Nipbl* expression in tissues that express or have expressed Cre recombinase; whereas *Nipbl*^{Flox/+} mice (derived from *Nipbl*^{FLEX/+} mice) express *Nipbl* normally, but become haploinsufficient in tissues that express or have expressed Cre recombinase.

Focusing initially on the most obvious heart abnormality in *Nipbl* haploinsufficient mice (*Nipbl*^{+/-} and *Nipbl*^{FLEX/+})—large atrial septal defects (ASDs) at the time of birth in about one third of animals—we found that a similar frequency of ASDs could be produced in *Nipbl*^{Flox/+} mice crossed to mice expressing a cardiomyocyte lineage-specific Cre recombinase. Conversely, the occurrence of ASDs was suppressed in *Nipbl*^{FLEX/+} mice crossed to mice expressing the same Cre recombinase. These results imply that deficiency for *Nipbl* in the cardiomyocyte lineage is both necessary and sufficient to produce ASDs. Yet, surprisingly, we also found that ASDs could be produced, at similar frequency, in *Nipbl*^{Flox/+} mice by crossing them to mice expressing Cre recombinase specifically in endodermal lineages. This result mirrors our earlier findings in zebrafish, which suggested that both mesoderm and endoderm abnormalities underlie the origins of heart defects, and supports the view that abnormalities in multiple cell lineages contribute to individual structural defects.

Interestingly, we also found that reduction in *Nipbl* expression specifically in the cardiomyocyte mesoderm lineage, when combined with haploinsufficiency for the homeobox gene *Nkx2.5*, produces more severe structural abnormalities; these include ventricular septal defects (VSDs), which are characteristic of CdLS but had not been observed by us in *Nipbl*-deficient mice. *Nkx2.5* is known to be genetically associated with septal defects in man, and we find that its expression is significantly reduced in *Nipbl*^{+/-} mice. These results raise the possibility that individual variation in *NKX2.5* expression might predispose individuals with *NIPBL* haploinsufficiency toward more severe congenital heart defects. Supported by NIH grant P01-HD052860.

Modeling Cornelia de Lange Syndrome Using Induced Pluripotent Stem Cells

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The cohesin complex, and accessory regulatory proteins, plays a critical role in several basic cellular processes including its canonical role in sister chromatid cohesion and recently described roles including DNA repair, long-range chromosomal architectural integrity, stem cell maintenance and pluripotency and regulation of gene expression. The interest in cohesin's role in transcriptional regulation was heightened after mutations were identified in the human *NIPBL* gene in Cornelia de Lange syndrome (CdLS), a multisystem developmental disorder. *NIPBL* (*Scs2* in yeast) is a cohesin regulatory protein that plays a critical role in the loading and unloading of the cohesin complex onto chromosomes. Mutations in additional cohesin structural (*SMC1*, *SMC3*, *Rad21*) and regulatory (*HDAC8*) subunits were also found to cause CdLS. Subsequently mutations in other cohesin related proteins have been identified in other developmental disorders collectively termed "cohesinopathies." Clinical manifestations of CdLS include intellectual disability, growth retardation, craniofacial abnormalities including cleft palate, limb defects, gastrointestinal defects, cardiac and hematopoietic abnormalities. In order to study this multiorgan diagnosis on a developmental level using human cells, we have generated patient specific human cell lines called induced pluripotent stem cells (iPSCs). iPSCs resemble embryonic stem cells (ESCs) in their capacity to be maintained *in vitro* and differentiate into all cell types present in the body and hold great promise for biomedical research and the treatment of human diseases. These iPSCs generated in our lab carry mutations in the *NIPBL*, *HDAC8*, *SMC1A*, or *SMC3* genes. All iPSCs have been generated using technologies that result in transgene-negative cell lines, and have been characterized using standard pluripotency evaluations. Our research will investigate: (1) The mechanism by which cohesin controls global gene expression in undifferentiated iPSCs and during developmental-specific stages of cardiac and neuronal patterning, and (2) Determine if we can characterize the CdLS-related cardiac and neurological developmental differences, through analysis of genome-wide gene expression and cohesin binding at various stages of cell differentiation, in patient-derived iPSCs. We will perform these studies using *in vitro* and *in vivo* assays, which model early stages of embryonic development. We hope this *in vitro* system can serve as the framework to develop an infrastructure where our methodologies can be applied to other cohesin genes and the related cohesinopathies, in order to develop and assess effectiveness of therapeutics for treatment of CdLS.

Modulation of *Scs2* Function by Phosphorylation

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Although a clinical description of Cornelia de Lange syndrome (CdLS) has been developed, much less is known regarding its molecular origins. While genetic analyses reveal that the majority of CdLS patients exhibit mutations in the cohesin deposition factor *NIPBL*, very little is known about how these mutations actually disrupt *NIPBL* function. *NIPBL* is required for cohesin's association with chromosomes and when cohesin is unable to associate with its specific chromosomal locations, genes that must be pre-

cisely regulated during development lose their ability to coordinate expression. In addition, *NIPBL* can also directly affect gene expression at promoter regions independently of its role in cohesin deposition. It is therefore proposed that proper *NIPBL* function is required to avoid the severe developmental delays observed in CdLS patients. Key to understanding the complex etiology of CdLS is the elucidation of precisely *how NIPBL* function is regulated.

In this study, we investigated how the budding yeast *NIPBL* ortholog, *Scs2*, is regulated throughout the cell cycle. We find that *Scs2* is subject to cell cycle specific cleavage that regulates its cohesin deposition activity and that this specific cleavage is further regulated by the phosphorylation status of *Scs2*. We have mapped several phosphorylation sites throughout *Scs2* and have determined the importance of phosphorylation for *Scs2* activity with a series of mutants that either mimic or abolish the modification(s). Our findings suggest that *Scs2* phosphorylation mutants affect *Scs2*'s ability to co-immunoprecipitate with its binding partner, *Scs4* and we note changes in *Scs2*'s chromatin binding capacity as well as its cohesin deposition activity when phosphorylation is altered. Furthermore, we provide evidence that the modulation of *Scs2* phosphorylation affects its stability. Collectively, these results provide a mechanistic view detailing the regulation of *Scs2* function through phosphorylation.

Identifying Functional Domains of the Budding Yeast Orthologs of the Cohesin Deposition Subunits, *NIPBL* and *MAU2*

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Approximately 60% of Cornelia de Lange syndrome (CdLS) patients have mutations in the *NIPBL* gene, which encodes one of two subunits of a heterodimeric cohesin deposition complex. Cohesins promote chromosome biorientation on spindle microtubules, efficient DNA repair, and chromatin looping. Altered gene expression resulting from defective cohesin-mediated chromatin looping is likely responsible for the pathogenesis of CdLS. Furthermore, recent evidence suggests that *NIPBL* has cohesin-independent functions that are adversely affected by mutation in CdLS patients. While *NIPBL* and its partner protein *Mau2* are required for cohesin deposition, the molecular roles of these proteins in deposition remain enigmatic.

We have taken advantage of facile genetics in the budding yeast model system to identify functional domains within the well-conserved budding yeast orthologs of *NIPBL* (*Scs2*) and *MAU2* (*Scs4*) in cohesin deposition. Currently, a single conditional allele of each gene is available, with one of these (*scc4-4*) having seven amino acid substitutions throughout the open reading frame, making it impractical to determine which single substitution or combination of substitutions is responsible for defects observed in this mutant. Therefore, we have undertaken a screen of pools of random 15 base pair insertion mutants of *SCC2* and *SCC4*, generated by saturating *in vitro* transposon mutagenesis, to identify novel conditional dominant negative and temperature sensitive mutant alleles, as well as lethal insertions that will inform as to key functional domains of the proteins. Dominant negative *SCC2* insertion

mutants are enriched within the carboxyl terminal two-thirds of the protein, and map near conserved residues shown previously to be mutated in CdLS patients. Interestingly, these regions contain HEAT repeat motifs that are thought to mediate protein-protein interactions. Conditional temperature sensitive *scc4* insertion mutants cluster within the amino-terminal region of the protein, but are also found at a number of other locations. We have also identified several lethal *scc4* insertion mutants that impact *Scs2-Scs4* interactions, and interestingly, affect *Scs2* stability. The effects of these mutants on *Scs2/Scs4* chromatin association and *Scs2/Scs4* interactions with cohesins will be presented. Thus, this approach had identified novel mutants whose characterization is likely to identify key functional domains of *Scs2* and *Scs4* proteins, and may inform as to the etiology of CdLS.

An Overview of Behavioral Symptomatology in a Cohort of Individuals Diagnosed with Cornelia de Lange Syndrome

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Parental intake evaluations of multiple individuals with Cornelia de Lange syndrome (CdLS) include detailed behavioral history and completion of the Aberrant Behavior Checklist (ABC). This information was gathered at regional and national meetings for individuals referred for behavior concerns by their caregivers. This report includes a summary of 30 cases, 30% male and 70% female. All individuals had a clinical diagnosis of CdLS confirmed and were seen for reports of challenging behaviors. The age range was from 4 years to 48 years of age with a mean age of 17 years old. 33.3% were under the age of 10, while 40% were over the age of 20.

Results of data from the ABC will be highlighted. Scores on the ABC suggest that a full 50% scored in the elevated or clinically significant range on the Irritability subscale of the ABC. In addition, 46.67% of the scores for the Inappropriate Speech were in the elevated or clinically significant range. On the Hyperactivity subscale, 36.67% of the individuals scored in the elevated or clinically significant range. Additionally, 26.67% of the sample scored in the elevated or clinically significant range on the lethargy scale, which has been utilized as an index of depression. However, on the Stereotypy subscale, only 16.67% scored in the elevated or clinically significant range.

A case example of the assessment and treatment with an 11-year-old female referred for evaluation of self-injurious behavior (head hitting, head banging, self-scratching, and self-biting) will be used to highlight the behavior challenges for this subset of individuals with Cornelia de Lange syndrome.

Repetitive Compulsive Features in Children with Cornelia de Lange Syndrome

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Purpose: Cornelia de Lange syndrome (CdLS) is a cohesinopathy causing delayed growth, craniofacial abnormalities, limb trunca-

tion defects, and mild to profound intellectual disability. Affected children can also exhibit a range of maladaptive features, including repetitive compulsive behaviors. This study characterizes the phenotype of repetitive and compulsive behaviors in children with CdLS.

Methods: Children with CdLS (5–18 years) were administered normed instruments to characterize repetitive behaviors (Aberrant Behavior Checklist, ABC), compulsions (Children's Yale-Brown Obsessive-Compulsive Scale, CY-BOCS), and adaptive skills (Vineland Adaptive Behaviors Scales, VABS).

Results: Forty-one children with CdLS (23 females, 18 males) were included in the analysis. The mean CY-BOCS compulsions severity total was 11.9 ± 4.0 (severe-extreme). These individuals exhibited various kinds of compulsions: washing/water play ($n = 18$; 43%), checking ($n = 13$; 31%), repeating ($n = 34$; 83%), ordering ($n = 11$; 27%), hoarding ($n = 11$; 27%), and miscellaneous ($n = 26$; 63%). The mean ABC Stereotypy subscale score was 0.52 ± 0.62 (between "not at all a problem" and "slight in degree"). Within the ABC Stereotypy measure, the highest endorsed question pertained to abnormal repetitive movements (0.76 ± 0.92). There was a statistically significant correlation between increasing ABC Stereotypy subscale scores and decreasing VABS Composite, Socialization, Communication, and Activities of Daily Living standard scores ($p \leq 0.004$).

Conclusions: Compulsions, in particular repeating and washing/water play behaviors, are a common feature of CdLS and occur with significant severity. When present, repetitive behaviors are correlated with worsening adaptive function. More research is needed to explore the biological mechanisms surrounding this phenotype.

Quality of Life for Families with a Child with CdLS: Differences Between Families Based on the Child's Primary Residence Location

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As individuals with Cornelia de Lange syndrome (CdLS) age, family discussions may start to include questions about long-term care. While some individuals with CdLS live independently, many require lifelong care that is fulfilled by either family at home, or an out-of-home residential placement. Family Quality of Life (FQOL) is a recently emerging concept in intellectual disability research used to assess the effects of specific interventions, such as out-of-home residential placements, on the whole family. Little is known about the effects of placement on a family or the factors affecting overall FQOL for the family with a child with CdLS. This study aimed to assess differences in FQOL between families based on the primary residence of the child with CdLS and to examine the effect of demographic and biographic factors on overall FQOL. Seventy-three parent members of the CdLS Foundation, with a child with CdLS over age 13, completed a survey, adapted from *FQOL-2006 Survey* (Surrey Place Centre, Canada) that elicited family demo-

graphics, clinical characteristics of the child with CdLS, and subjective FQOL responses. Kruskal–Wallis, Mann–Whitney, and Spearman correlation tests, and thematic analysis of the data were performed. No statistically significant difference in FQOL existed between families based on the child's primary residence. However, the study found that an increase in the child's behavior problems, specifically aggression, correlated to a decrease in overall FQOL. Furthermore, thematic analysis revealed additional factors that may contribute to the FQOL of families with a child with CdLS. For example, it is important for families to have support from immediate family members in addition to support from friends, and the effect of parental aging on the care of the child with CdLS is a common concern of families. Providing anticipatory guidance for CdLS families, this study suggests that although there are no statistical FQOL differences based on the child's primary residence, interventions for behavioral problems, resources for aging parents, and increased family support are needed to improve the FQOL for families who have a child with CdLS.

The Multidisciplinary Clinic for Individualized Management of Cornelia de Lange Syndrome at The Children's Hospital of Philadelphia: Successes and Challenges

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Cornelia de Lange syndrome (CdLS) is a multisystem developmental diagnosis with variable growth, cognitive, craniofacial, limb, intestinal, cardiac, and other systemic abnormalities. Many patients with CdLS need continued assistance and care throughout their life due to the cognitive and behavioral impairment, physical limitations, and multi-systemic involvement associated with the diagnosis. Given the clinical complexities of CdLS and the need for multispecialty care, the Center for Cornelia de Lange Syndrome and Related Diagnoses was established at The Children's Hospital of Philadelphia (CHOP) in 2009 to develop a comprehensive and integrated approach to clinical management and research into issues relevant to individuals with CdLS.

The multidisciplinary clinic of the Center functions under the hypothesis that by understanding the clinical issues and training experts in relevant specialties to develop expertise in CdLS they will be able to proactively manage these issues, and as a result improve the quality of life and cognitive outcomes of our patients. The clinic, as it exists now, is a monthly clinic that consists of four core specialists as well as a consulting team of clinicians selected from various divisions within CHOP. To provide the best medical care, we work together, across many specialties to develop an individualized plan of care for every patient. The clinic's collaboration with the National CdLS Foundation, with representatives attending the clinics, has allowed for additional support and education serving as a valuable resource for the families attending the Center.

The multidisciplinary clinic also serves as an interface with the Center's research goals. Our clinical and laboratory research aims to improve medical management and scientific understanding of

CdLS. Understanding the molecular etiologies is a key step in translating knowledge into novel diagnostic, management and eventually therapeutic tools.

Overall, our Center provides a setting in which individuals with CdLS and related diagnoses can receive coordinated care, comprehensive services, family support, and the opportunity to participate in translational research. The integrated investigative arm is working to translate clinical and laboratory research into the development of improved management and therapeutic modalities. This presentation will provide an overview of the Center structure at CHOP and present our experience over the past 4 years of the successes and challenges of applying a multidisciplinary integrated clinical and research approach to the management of over 75 patients with CdLS as this models applicability to other multisystem developmental diagnoses.

Meeting the Unique and Specialized Needs of Children and Youth Who Have Combined Hearing and Vision Loss

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Deaf-blindness is a complex disability that can challenge the most knowledgeable and experienced educators. Individuals who are deaf-blind have unique and highly specialized needs, and present a set of educational needs that impact service delivery at virtually all levels of students' educational programs. When vision and hearing are reduced, distorted, or missing, this combined sensory loss can have a profound impact on how these individuals communicate, learn, and access their world.

Deaf-blindness is, at its core, a disability of access—to other people, to learning, to social relationships, and to the development of basic concepts. For many children who are deaf-blind, it is said that their lives can be spent in a state of near constant surprise and confusion. Routines and predictability are critical if we are to help these individuals make sense of what they must often perceive as a chaotic and random world.

Trust is a critical component of the relationship between students and teachers, but the importance of relationships built on trust is magnified for students who are deaf-blind. Children who are deaf-blind must place a significant level of trust in others and this can be difficult to repair if these relationships built on trust are ever broken or at risk of breaking down. This level of trust is a component of almost all educational domains.

Many skills that non-disabled children develop are learned incidentally and not through direct teaching. Children with typical hearing and vision gain information by continually watching and listening to their environment in order to support the development of language, cognition, motor skills, and social skills. Children who are deaf-blind typically do not have the vision and hearing necessary for incidental learning. These children must be actively engaged in all activities in order to develop the same knowledge and skills that might otherwise be acquired through incidental learning. Full participation with real materials in real environments and with natural consequences is an essential component of educational programs for children who are deaf-blind, and requires a high level of energy and creativity from all members of educational teams.

Because students who are deaf-blind have complex needs, they are often served by large teams that may include special and general education teachers, therapists, medical and nursing staff, and others. Team members must share information, including assessment findings and educational strategies so that team members can integrate goals and strategies from other disciplines. Many children who are deaf-blind are also served by interveners (i.e., one-on-one paraeducators who have specialized knowledge and skills specific to deaf-blindness). Interveners or other teaching assistants are integral members of student teams and educational systems may need to be adapted to ensure their full participation in program planning and evaluation.

This session will include foundational information about deaf-blindness and include evidence-based strategies for meeting the needs of children and youth who are deaf-blind. This will be an interactive session with ample opportunities for questions, sharing of strategies, and linkages to resources.

Speech-Language Pathology Treatment Guidelines and Procedures for Communication Delays in CdLS

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As early as the 1960's, speech and voice involvement were documented in Cornelia de Lange syndrome (CdLS). Over the past 30 years, this researcher has performed speech and language evaluations on over 900 individuals with CdLS, and has noted trends in abilities, relationships between other factors and speech and language delays, and differences in communication development and disorders when compared to other populations with developmental delays and/or autism spectrum disorder.

This presentation will provide treatment guidelines and specific procedures for behaviors exhibited by each of the four "communication subgroups" identified during assessment and intervention for individuals with CdLS. Specific intervention procedures used with individuals with CdLS who are nonverbal, who exhibit expressive language delay, and who evidence apraxia of speech will be discussed and demonstrated. General comments will be made about other concerns, such as the relatively high rate of selective mutism in this syndrome. In addition, misunderstandings about communication and CdLS will be clarified. Brief video clips will also be presented. This information should be useful for parents and caretakers as well as speech pathologists addressing these needs.

Selective Mutism and Social Anxiety Characteristics in Cornelia de Lange and Fragile X Syndromes

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Background: Selective mutism is a disorder that typically emerges in childhood that is characterized by the persistent failure to speak in contexts when speaking is typically expected (e.g., school and social settings). Although selective mutism has a low rate of occurrence in the general population, selective mutism is reported to have elevated rate of occurrence in individuals with Cornelia de Lange syndrome (CdLS) and Fragile X syndrome (FXS). Selective mutism has a strong association with social anxiety in the general population. The present study evaluated the severity of selective

mutism and social anxiety symptoms in individuals with CdLS and FXS. We also examined the relationship and comorbidity between selective mutism and social phobia in these populations.

Method: 41 individuals with CdLS (48.8% male, mean age 11.4 years (SD = 4.1)), 30 individuals with FXS (83.3% male, mean age 12.2 years (SD = 5.0)), and a comparison group of 21 children and adolescents with Down Syndrome (DS) (46.7% male, mean age 11.1 years (SD = 4.5)) were assessed by parental report on two behavioral measures. The Selective Mutism Questionnaire (SMQ) and the Spence Children's Anxiety Scale (SCAS) were completed.

Results: The groups differed on the SMQ total score ($F = 6.9$, $p < 0.001$) school subscale ($F = 3.1$, $p < 0.01$), social subscale ($F = 5.4$, $p < 0.001$), and home subscale ($F = 9.8$, $p < 0.000$). The groups differed on the SCAS total score ($F = 6.2$, $p < 0.001$) and the social phobia subscale ($F = 6.8$, $p < 0.001$). Individuals whose scores fell within a standard deviation of a clinical sample on the SMQ were 14.3% in the CdLS group, 36.7% in the FXS group, and 5.5% in the DS group. The percentage of participants who met cutoff scores that indicated social phobia in the sample was 19.0% for the CdLS group, 33.3% in the FXS group, and 5.5% for the DS group. A moderate correlation between the total anxiety rating and selective mutism severity was moderate ($r = 0.4$). Individuals whose selective mutism severity fell within the clinical standard deviation met cutoff for social phobia 33.3% of the time, indicating some comorbidity of the two anxiety disorders.

Conclusions: These results demonstrate that severity and prevalence of selective mutism and social anxiety characteristics differ across three intellectual disability-associated syndromes. Further research on assessment and treatment of selective mutism and social anxiety in individuals with CdLS and FXS is warranted.

SBAR for Patients: Improving Communication with Parents/Caregivers of Children with CdLS

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SBAR is a standard structured communication tool used by healthcare providers across North America and the world to improve patient outcomes through improved communication. Health care team members use this tool to communicate important information in a clear and concise manner. However, it has not been shared with the key member of the healthcare team, the patient and their family. The *SBAR-4-Patients* project used an existing SBAR tool created by the Empowered Patient Coalition for use by patients. This project aimed to empower families by teaching them SBAR as a standard communication tool that they could use with their child's healthcare providers and to study the effect of the *SBAR-4-Patients* on the knowledge and confidence of communication of the target population: the parents and caregivers of children with Cornelia de Lange syndrome (CdLS) who are members of a closed discussion and support group in a popular social networking site.

A pre- and post-survey design with an on-line educational presentation was used. The education was used to identify the impact on parents' and caregivers' communication by

teaching them about how to use the *SBAR-4-Patients* tool and the importance of clear, concise and to the point communication in healthcare settings.

Thirty respondents completed the baseline survey. Of those, half were 30–39 years of age and an additional 33.33% 40–49 years. The majority of individuals with CdLS were in the 6–10 year old range (43.33%). Most respondents had an average of 1–5 healthcare encounters per month ($n = 13$; 43.33%), followed by 6–10 encounters ($n = 8$; 26.67%). Seventeen respondents completed the post-survey. When asked whether the SBAR tool will make them better prepared to communicate with healthcare providers, the majority of respondents chose “Strongly Agree” ($n = 13$; 76.47%). Comparison of five baseline and post-survey questions highlighted that most ($n = 14$; 46.67%) were not aware of the use of SBAR as a communication tool used by healthcare professionals. Most indicated an increased confidence, knowledge and skill in their ability to communicate after they had been introduced to the tool with most of the baseline respondents choosing “Agree” ($n = 12$; 40%) and on the post-survey “Strongly agree” ($n = 11$). Participants were also given open-ended questions that provided more interesting responses. When asked to provide their opinions about the SBAR method, they felt that using it would allow them some equal footing with health care providers and be more able to provide information in a clear, concise, direct and organized manner. Reservations reported by respondents included whether or not their health care provider would be willing to consider their opinions, they would be able to remember the steps to the tool, and whether it would be too restrictive in scope.

Overall however, results showed that the respondents considered the SBAR tool to be beneficial when speaking with health care providers. The future implications of this project demonstrate the need to include patients and family as true partners in care by providing them with tools to be active members of the healthcare team. It alerts us to broaden our research of individuals with CdLS and their families to other important aspects in their experience of care. This presentation will aim to discuss the results of the study and more broadly the necessary shift required in the role and direction of healthcare providers and researchers working with families and caregivers of individuals with CdLS to improve health outcomes.

RNA Polymerase II Activity Is Affected at the Promoter Regions in *SMC1A*-Mutated Cornelia de Lange Syndrome Cells

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Mutations in genes encoding cohesin subunits or regulators, namely *NIPBL*, *SMC1A*, *SMC3*, *HDAC8*, and *RAD21*, have been linked to Cornelia de Lange syndrome (CdLS). It has been hy-

pothesized that the dysregulation of gene expression by chromatin remodeling likely represents the underlying pathogenesis of CdLS, however the exact mechanism by which this is effected is unknown. To gain a better understanding of this process we investigated whether the gene transcription machinery was somehow affected by *SMC1A* mutations. We used chromatin immunoprecipitation coupled with massively parallel DNA sequencing (ChIP-seq) to identify genomic regions co-occupied by cohesin, NIPBL and RNA pol II in normal human lymphoblastoid cells. Genes co-localizing cohesin, NIPBL and RNA pol II have been compared to gene expression data from CdLS cell lines. Finally, we investigated the recruitment of RNA pol II onto genes differentially expressed in CdLS mutated cells. Our results indicate that *SMC1A* mutations reduce the recruitment of Pol II at promoter regions and also affect the activity of the Pol II elongating form. These findings highlight the pivotal role of cohesin in transcriptional regulation and the effect on Pol II occupancy may explain the typical gene dysregulation observed in CdLS cell lines.

A Novel Genetic Disorder of Cognitive Impairment, Heart Defects, Obesity, Pulmonary Involvement and Short Stature with Skeletal Dysplasia

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Three probands, who had been collectively followed over a period of 12 years, were all referred for initial evaluation due to a suspected diagnosis of Cornelia de Lange syndrome (CdLS). All probands had strikingly similar clinical manifestations and were felt to represent a common unknown diagnosis phenotypically overlapping CdLS. The shared clinical features with CdLS include developmental delay/intellectual disability (with language being most significantly delayed), short stature, failure to thrive and facial dysmorphisms (arched eyebrows, syndophrys, short nose, posterior rotated ears, long philtrum, micrognathia), small hands and feet. However, these probands have additional clinical features including obesity and severe respiratory manifestations (subglottic stenosis, laryngo-tracheomalacia, tracheal stenosis, chronic lung disease) that distinguished them from CdLS. Their facial features were not typical of CdLS and appeared coarser with age and the skeletal manifestations (brachydactyly, vertebral abnormalities) were different from those seen in CdLS. All probands had been extensively screened for underlying genetic diagnoses by high-resolution SNP arrays, multiple gene analyses and evaluation for biochemical disorders (including mucopolysaccharidoses). Due to the previously undescribed constellation of physical and medical features that were highly conserved among all three probands, we hypothesized that this condition represents a novel genetic disorder and was likely

caused by *de novo* mutations (lack of involvement of any other family members) in a single causative gene.

Using whole exome sequencing, we identified missense mutations in all three probands in a novel disease gene that plays an important role in regulating transcriptional elongation. Transcription elongation is a critical mechanism by which gene expression is regulated during development and has been extensively studied. Somatic mutations in genes that control transcriptional elongation have been described in cancers but to our knowledge this is the first human developmental disorder caused by germline disruption of this process. To evaluate the effect of these missense mutations, whole genome expression arrays were performed on patient-derived skin fibroblast cell lines identifying many developmentally important misexpressed genes. Since the role of cohesin in transcriptional elongation has recently been proposed, this newly identified diagnosis may provide valuable insights into how cohesin functions in transcriptional elongation.

Circadian Rhythm Disorders in Cornelia De Lange Syndrome

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Objective: Sleep disturbance occurs in up to 55% of patients with Cornelia de Lange syndrome (CdLS). In children with a similar degree of self-injurious behavior and intellectual disability, but not CdLS, research suggests that melatonin disturbance and circadian issues may explain similar sleep disturbances.

Study Design: Prospective cohort study.

Methods: Caregivers of 37 patients with CdLS completed a sleep history questionnaire and surveys specific for circadian rhythm disorders, sleep apnea and insomnia including the children's chronotype questionnaire (CCTQ).

Results: The mean/median age of participants was 13.0/8.0 years (range 0.7–56.1 years, SD 12.0); 23 were <12 years. The overall chronotype score was unsure in 13.5% (5/37). For the remainder, 6.3% were classified as definitely morning, 31.3% rather morning, 34.4% neither, 15.6% rather evening, and 12.5% as definitely evening. There were significantly fewer definite morning types than in the validation study where 46% classified as morning, 15% as neither and 37% as evening ($p = 0.0041$). Mean morningness/eveningness scores were similar to the validation study at 28.6 ± 6.8 versus 28.2 ± 6 ($p = 0.724$). Midsleep point on free-days was 3:02 am versus 2:32 am in the validation group. Major difficulty in falling asleep (33% pediatric, 30% adult) was noted and time to sleep onset was 33.7 ± 38.8 minutes. Family members reported a possible circadian rhythm disorder in 51%.

Conclusion: Symptoms suggestive of circadian rhythm disorder are prevalent in this cohort of children and adults with CdLS. Further studies with actigraphy and melatonin analysis may be helpful to further investigate circadian alternations in the CdLS population.

MRI of the Brain in Cornelia de Lange Syndrome and Correlation with Behavior

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The central nervous system findings on brain MRI have not been evaluated previously in comparison to clinical findings in Cornelia de Lange syndrome (CdLS). Neurobehavioral and developmental issues are prominent features, including intellectual disability, autism spectrum disorder, self-injury, obsessive-compulsive disorder, seizures and sleep disturbance. Neurologic exams are typically normal or with hyperreflexia. Several autopsies have included brain findings such as hypoplasia of cerebellum, corpus callosum, septum pellucidum and brainstem, and some brain CT scans or MRIs have shown enlarged ventricles, thinning of white matter and brainstem and cerebellar hypoplasia. Findings on MRI of the brain should be able to be correlated with phenotypic findings, particularly specific behavioral diagnoses and intellectual abilities, with molecular changes if available. Similar studies have been carried out in other developmental disorders including Down syndrome, fragile X syndrome and Bardet-Biedl syndrome. This study assessed retrospectively previously obtained MRI scans of the brain compared to behavior at the time of the scan, and other clinical features and physical exam findings.

We obtained MRI scans on individuals with CdLS age 2 years and higher and reviewed them (TL, MK), collected medical records and confirmed the diagnosis (AK, ADK). The Aberrant Behavior Checklist (ABC) was completed by telephone (TR) for behavior at the time at which the MRI was obtained and scored (JO), with results compared statistically (JA). Behavior and MRI findings have been compared on 14 individuals. Half of the MRI scans were abnormal, including 30% with cerebral atrophy, 15% with white matter changes and 15% with cerebellar hypoplasia. Acquired findings included 15% with pituitary tumors, several patients with cysts, and one patient with Chiari I malformation. Abnormal behavioral scores included 64% with inappropriate speech, 57% with irritability and agitation, 50% with lethargy and social withdrawal, 43% with hyperactivity and noncompliance and 14% with stereotypic behavior. Normal ABC scores were noted in 57% of the patients with abnormal MRI changes. All of the patients with normal MRI's had abnormal ABC scores. This project is still ongoing.

There are a number of limitations: retrospective nature of the study, the numbers are too small to attain statistical significance, the occasional long period of time between obtaining the MRI scan and obtaining the ABC scores, and no evaluation of anxiety and other psychiatric disorders. There are several broad conclusions, however. There may not be an indication to obtain an MRI of the brain in CdLS unless the individual presents with an underlying neurologic condition. Also, abnormal behaviors seem to occur in patients with normal MRI's of the brain. Further investigation is needed to assess

whether clinical findings support that these are more mildly affected individuals. A prospective study for this would be ideal.

Establishment of Workable Database and Anonymous Registry for the Cornelia de Lange Syndrome Foundation

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Historically, there have been databases for the Cornelia de Lange syndrome (CdLS) Foundation since its inception to utilize for communicating with families, maintaining information on affected individuals, monitoring clinical trends, and assessing demographics for the planning of services and long-term plans. Other sites have had research-based databases which have been kept separate and strictly used for that institution's work. In 2008, the idea of establishing a more global database was raised (LGJ) in conjunction with a company that could provide the software and maintenance, and it was brought to the Board of Directors by the Research Committee in 2009. That same year an intake questionnaire for medical, developmental and behavioral aspects of individuals with CdLS was circulated to the Clinical Advisory Board for each member to provide questions if relevant. In 2010 a final form of the questionnaire received IRB approval through a hospital IRB (ADK), and through the Research Committee of the Board of Directors (DD). The paper-based questionnaire was distributed at the CdLS National Conference in Dallas, TX that summer. Eighty-two questionnaires were obtained and clinicians and researchers could have access to them if they

had families sign a consent form specifically for their project. These questionnaires have continued to be collected, at the National Conference in Chicago, IL in 2012 and sporadically elsewhere. The data could be transferred to a database if personnel were available.

Also in 2010, the Offices of Rare Diseases Research and the National Institutes of Health began discussing forming a de-identified registry of registries for rare diseases that could also be tied eventually to a registry of biologic samples. In 2011 a pilot project was launched to establish the Global Rare Diseases Patient Registry and Data Repository, and the CdLS Foundation was one of 20 groups chosen to help formulate common disease elements for the registry, format syndrome-specific elements, load the data, and begin the de-identified registry. The same company approached by the Foundation in 2008 won the bid to help manage this new registry. Over the next 2 years the common disease and syndrome-specific elements were formulated (LMC-M, ADK), template completed and all approved by the Research Committee (REH). Only three additional parent support organizations also completed their pilot registries and only one registry was started. Plans were in place for the rest to "go live" when the 2-year NIH funding ran out and the project was terminated without formulation of additional registries.

Currently the Foundation is assessing costs and possibilities for a registry to be maintained at the Foundation.

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