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

Anne L. Calof, Akihiko Muto, Martha E. Lopez-Burks, Thomas Schilling, Arthur D. Lander

1Departments of Anatomy & Neurobiology, 2Developmental & Cell Biology, and the 3Center for Complex Biological Systems, University of California, Irvine, CA, USA; 4Department of Biological Science, Graduate School of Science, Hiroshima University, Hiroshima, Japan

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 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

Clair Francomano1, Amy Kimball1, Lisa Krantz2, Yana Sandlers2, Richard Kelley2, Antonie D. Kline1

1Harvey Institute for Human Genetics, Greater Baltimore Medical Center, 2Biochemical Genetics and Neurogenetics, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD

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 SMC1A

How to Cite this Article: