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Novel Genetic Etiologies of CHARGE Syndrome Identified with Whole Genome Sequencing

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Presenter Information

Research in the Bielas lab focuses on discovering the genetic basis of for human neurodevelopmental disorders, including CHARGE syndrome. Neurogenetic findings provide a platform from which to investigate the molecular pathology of disease and novel features of normal development using mammalian models of neural development.

Presentation Abstract

Solving the genetic basis of developmental disorders is a powerful approach to gain a better understanding of the underlying pathogenesis, as evident from the discovery of the role of CHD7 variants in CHARGE syndrome. However, pathogenic CHD7 variants are not detected in all individuals with clinical features of CHARGE. These findings suggest additional genetic etiologies for CHARGE lie within the non-coding regions of CHD7 and of the genome. Our initial studies demonstrate that pathogenic variants in genes associated with other Mendelian disorders account for a portion of this missing genetic etiology, but not its entirety. Non-coding regions of the genome show promise for this missing heritability. Here, we evaluate proximal and distal cis-regulatory elements of CHD7 and other developmentally related genes to identify novel genetic etiologies of CHARGE. Screening these regions has led to identification of candidate variants. Functional validation using CRISPR/Cas9 to introduce variants or deletions in human pluripotent stem cells will be critical to model the pathogenicity of these variants. This approach will lead to a better understanding of the molecular and developmental mechanisms of CHARGE syndrome.

Learning Objectives

- Describe the known genetic basis for clinical features of CHARGE syndrome.
- Outline rationale for prioritizing non-coding variant as pathogenic for CHARGE syndrome
- Describe choice of developmental stage and cell-type to functionally validate pathgenicity of non-coding variants.