Title – Genomic Etiologies of CHARGE Syndrome, Related Conditions and Structural Anomalies

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Abstract
Identification of the genetic basis of developmental disorders can provide a better understanding of the underlying pathogenesis and help in the design of effective therapies. CHARGE Syndrome (Coloboma of the eye, Heart Defects, Atresia of the choanae, Retardation of growth and development, Genital abnormalities including pubertal delay and infertility, Ear abnormalities with deafness and vestibular disorders) is a multiple anomaly condition that affects a wide variety of organ systems and is caused by autosomal dominant pathogenic variants in *CHD7*, the gene encoding Chromodomain Helicase DNA binding protein 7 (CHD7). CHD7 is an ATP-dependent remodeling protein with pleiotropic effects in developing tissues. Pathogenic variants in *CHD7* are identified in ~90% of individuals with features of CHARGE, suggesting that additional genetic or environmental mechanisms may be present in those individuals with CHARGE features but no known genetic etiology. Our initial studies identified pathogenic variants in genes associated with other Mendelian disorders (Kabuki, Rubinstein-Taybi, and Verheij Syndromes) in individuals with CHARGE-like phenotypes. Individuals with CHARGE Syndrome often exhibit variable expressivity and reduced penetrance of clinical features. We hypothesize that genetic evaluation of individuals with CHARGE and CHARGE-like features will help identify non-coding regions and copy number variants that contribute to CHARGE. To test this hypothesis, we have generated a cohort of deeply phenotyped individuals with CHARGE Syndrome and related structural anomalies whose genetic testing (chromosomal microarray, single gene sequencing, next generation panel sequencing, or exome sequencing) was negative. Our cohort includes affected and unaffected family members who consented to clinical and research genetic testing and donated blood samples for DNA and RNA isolation and sequencing. Identification of novel alleles that contribute to the CHARGE-related genetics will provide important insights toward understanding the developmental mechanisms of CHARGE and related structural birth defects.