

**STRONG CHILDREN'S RESEARCH CENTER**

**Summer 2015 Research Scholar**

**Name:** Samah Hoque

**School:** Cornell University

**Mentor:** Kate Ackerman, MD

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**ABSTRACT**

**Title:** Genetics of Congenital Heart Disease: Are Genes Deleted or Duplicated in Patients with Clinically Interpreted "Findings of Unknown Significance" Associated with Cardiac Development and Disease?

**Background:** One of the most common forms of birth defects, congenital heart defects (CHD), consists of abnormal heart and great vessel development and affects approximately 1 in 100 newborns. Genetic testing to identify potential causes of congenital heart disease has become a standard of care for syndromic patients and is now increasingly done for patients with isolated disease. A common approach to testing involves a genome wide analysis for copy number variations using microarray comparative genome hybridization (aCGH). The American College of Medical Genetics and Genomics recommends that data be stored for at least 2 years to allow for future re-analysis of data, however there are no strict standards for re-reviewing and/or re-interpreting data from patients who had previous testing.

**Objective:** To identify whether patients with congenital heart disease and prior array CGH testing have findings that may be interpreted differently now after years have passed since the time of original testing. To identify whether the use of mouse genetic data strengthens hypotheses about genotype-phenotype association in these patients.

**Design/methods:** Patients were identified with congenital heart disease and microarray CGH testing. Patients with deletions or duplications of unclear significance were investigated. Genes in the deleted/duplicated regions were identified using Ensembl genome browser, and individual genes were studied for functional data and disease associations using a variety of publically available resources including the Mouse Genome Informatics (MGI) annotated databases, and NCBI databases.

**Results:** 62 patients with congenital heart disease had aCGH testing performed between 2009 and 2013 at ages that ranged from day of birth to 20 years. 27 of 62 had abnormal results: 4 had 22q11.21 deletions (DiGeorge Syndrome), and 2 had trisomy (1 with trisomy 18, 1 with trisomy 21) and 19 had other deletions and/or duplications. All patients with deletions of unknown significance had deleted regions that contained genes associated with cardiac diseases as well as some other non-cardiac diseases. Of the 14 patients with duplications of unknown significance, 7 patients had duplication regions that contained genes associated with human diseases. Further investigation is required to understand whether these potentially damaging chromosomal variants caused the phenotypes observed in these patients. Several genes within the deletions/duplications of our cohort (GJA5, IRX4, DNAH5, TXNIP, and GATA4) cause abnormal heart development in mouse models while other identified genes are associated with non-cardiac related pediatric and/or adult onset diseases.

**Conclusion:** In our cohort of congenital heart disease patients, a large number (44%) had abnormal array CGH findings. While some findings were previously described and easy to assign as being causal of disease, many required further investigation. A review of deleted and duplicated genes in the cohort

with findings of unclear significance reveals many interesting potential causes of disease. Many of the gene-phenotype associations identified have been made only very recently and were not known at the time of original genetic data interpretation. It is important for clinicians to consider the value of “old” genetic testing data that may be more informative now than it was at the time of the original data analysis. These data may be interpreted with a variety of techniques and levels of stringency depending on the clinical question and the interest of the patient, family, or investigator.