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DNA METHYLATION ANALYSIS OF BICUSPID AORTIC VALVE IN TURNER SYNDROME

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Abstract

Turner Syndrome (TS) is a rare cytogenetic disorder caused by the partial or complete loss of a second sex chromosome, which occurs in 1 in 2,000 female live births. The most common cause of early mortality in TS is due to congenital heart defects. Bicuspid Aortic Valve (BAV) is the most common congenital heart defect in the general population with a prevalence of 0.5-2%. TS patients have the highest burden of BAV with a prevalence around 30% with near complete penetrance of aortic disease. It is unknown why there is such a large increase of BAV in TS. TS is associated with genome wide hypomethylation when compared to karyotypically normal female and male controls. Epigenetic alterations in BAV have been found with changes identified in circulating miRNAs and the DNA methylation profiles of patient derived aortic tissue. We hypothesize that BAV is associated with DNA methylation alterations in TS.

The purpose of this study is to investigate DNA methylation alterations when comparing 1) BAV to non-BAV in TS and 2) TS BAV to 46,XX Non-Syndromic BAV. Illumina TruSeq-Methyl Capture EPIC methylation sequencing (Methyl Capture Seq) will be performed on whole blood genomic DNA samples from 45,X TS BAV (n = 15), 45,X TS non-BAV (n = 22), and 46,XX Non-Syndromic BAV (n = 11). Capture region enrichment of these Methyl Capture Seq libraries will be performed as a quality control step. Differential methylation will be assessed using logistic regression on the whole genome tiled into 1kb regions adjusting for cell type composition using Surrogate Variable Analysis. These regions will be annotated and assessed for biological inference using transcription factor motif enrichment and resources such as DAVID, GREAT, and STRING. We anticipate that DNA methylation alterations will correlate to previously found changes in BAV and in TS.