

# KAT6A Syndrome

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Arboleda-Tham Syndrome (ARTHS) is a rare genetic disorder caused by heterozygous, de novo mutations in Lysine(K) acetyltransferase 6A (KAT6A). ARTHS is clinically heterogeneous and characterized by several common features, including intellectual disability, developmental and speech delay, and hypotonia, and affects multiple organ systems. KAT6A is the enzymatic core of a histone-acetylation protein complex; however, the direct histone targets and gene regulatory effects remain unknown. In this study, we use ARTHS patient (n = 8) and control (n = 14) dermal fibroblasts and perform comprehensive profiling of the epigenome and transcriptome caused by KAT6A mutations. We identified differential chromatin accessibility within the promoter or gene body of 23% (14/60) of genes that were differentially expressed between ARTHS and controls. Within fibroblasts, we show a distinct set of genes from the posterior HOXC gene cluster (HOXC10, HOXC11, HOXC-AS3, HOXC-AS2, and HOTAIR) that are overexpressed in ARTHS and are transcription factors critical for early development body segment patterning. The genomic loci harboring HOXC genes are epigenetically regulated with increased chromatin accessibility, high levels of H3K23ac, and increased gene-body DNA methylation compared to controls, all of which are consistent with transcriptomic overexpression. Finally, we used unbiased proteomic mass spectrometry and identified two new histone post-translational modifications (PTMs) that are disrupted in ARTHS: H2A and H3K56 acetylation. Our multi-omics assays have identified novel histone and gene regulatory roles of KAT6A in a large group of ARTHS patients harboring diverse pathogenic mutations. This work provides insight into the role of KAT6A on the epigenomic regulation in somatic cell types.