A STUDY ON THE FUNCTION OF *ahi1*, A HOMOLOG OF THE JOUBERT SYNDROME GENE *AHI1*, DURING ZEBRAFISH DEVELOPMENT

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ABSTRACT

Joubert syndrome (JBTS) is a rare autosomal recessive neurodevelopmental disorder, characterized by developmental delay, clumsiness, irregular breathing, mental retardation, abnormal eye movements, some autistic behaviors and midline defects in the midbrain and the hindbrain, especially the cerebellum. Mutations in *AHI1* were identified as being one of the causes of JBTS.

To investigate the function of *ahi1*, we knocked down *ahi1* expression in zebrafish and observed touch insensitivity, smaller eyes, cerebellar midline defects, and neuroanatomical defects in the hindbrain, comparable to those of individuals with JBTS. We also identified defects during early development in *ahi1*-knockdown embryos, including defects at the midline of the cerebellar primordium, defects during convergence-extension movements, and defects in neurulation. The defect of convergence-extension movements resembles that of mutants with mutations in members of the non-canonical Wnt signaling pathway. To test the hypothesis that *ahi1* may be involved in non-canonical Wnt signaling, we show that *ahi1* genetically interacts with *wnt5b*. Further support for this hypothesis comes from the observation that inhibition of *ahi1* expression results in loss of the spindle morphology of cells in the neural tube.

In summary, this work establishes zebrafish as a model for investigating JBTS, and provides evidence for a function of *ahi1* in regulating cell morphology, potentially through the interaction with non-canonical Wnt signaling, during early morphogenesis of zebrafish.