# LOSS OF HISTONE METHYLTRANSFERASE ASH1L IN THE DEVELOPING MOUSE BRAIN CAUSES AUTISTIC-LIKE BEHAVIORS

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## INTRODUCTION

*Autism spectrum disorder (ASD) is one of the most prevalent neurodevelopmental disorders (NDDs) that have a strong genetic basis. Recent genetic and clinical studies report that mutations of the epigenetic gene ASH1L are highly associated with human ASD and intellectual disability (ID). However, the causality and underlying molecular mechanisms linking ASH1L mutations to genesis of ASD/ID remain undetermined. Here the researchers show loss of ASH1L in the developing mouse brain is sufficient to cause multiple developmental defects, core autistic-like behaviors, and impaired cognitive memory. This study establishes an ASD/ID mouse model (Ash1L knockout mouse model) revealing the critical function of an epigenetic factor ASH1L in normal brain development, a causality between Ash1L mutations and ASD/ID-like behaviors in mice, and potential molecular mechanisms linking Ash1L mutations to brain functional abnormalities.*

## RESULTS

### GENERATION AND CHARACTERIZATION OF ASH1L KNOCKOUT MICE

*Ash1L was dispensable for mouse embryonic development. Ash1L might be critical for establishing and maintaining a stable physiological condition for neonatal survival. . Similar to the craniofacial deformity observed in patients, mice displayed an abnormal craniofacial appearance with a reduced eye-to-mouth distance.*

### LOSS OF ASH1L DELAYS EMBRYONIC AND POSTNATAL BRAIN DEVELOPMENT

*Ash1L deletion in the developing mouse brain resulted in the delayed lamination of neuronal cells during embryonic cortical layer formation. Ash1L deletion in the developing brain led to delayed myelination during early postnatal brain development.*

## LOSS OF ASH1L IN THE DEVELOPING MOUSE BRAIN CAUSES ASD/IDLIKE BEHAVIORS

*The loss of Ash1L in the developing mouse brain resulted in both autistic-like behaviors and ID-like defects, which were featured by reduced sociability, loss of interest in social novelty, repetitive and compulsive behaviors, impaired recognition memory, and increased anxiety-like behaviors.*

## LOSS OF ASH1L IMPAIRS EXPRESSION OF GENES CRITICAL FOR BRAIN DEVELOPMENT

*. Ash1L is highly expressed in the embryonic and adult mouse brain, suggesting its possible role in brain development and function. Multiple genes downregulated in the Ash1L-KO cells, such as Emx2, Dbx2, Pcdh10, Sall3, and Foxg1, were previously reported to be involved in normal brain development and NDDs.*

## DISCUSSION

*Disruptive ASH1L gene mutations found in patients are likely to be the causative drivers leading to clinical ASD/ID. Ash1L might also play important roles in establishing neural circuits in the developing hypothalamus, which is critical for normal feeding behaviors and early postnatal growth. The loss of Ash1L in NPCs leads to delayed brain development in both neuronal and glial lineages. Multiple genes critical for normal brain development and highly related to human ASD/ID were found to have reduced expression in the differentiating Ash1L-KO NPCs, suggesting that impaired expression of neurodevelopmental genes is likely to be a main molecular mechanism linking ASH1L mutations to abnormal brain development. ASH1L might function as a master epigenetic regulator to facilitate the expression of FOXG1 and other critical genes for normal brain development, while mutations of ASH1L lead to mis-regulation of gene expression, disturbance of the normal brain developmental program, and brain functional abnormalities of ASD/ID.*

**It is time to consider ASH1L as a serious driver gene for causing ASD and other NDDs.**