1. Introduction to AUTS2 and AUTS2 syndrome (AUTS2 variants-point back to mouse model develops)-Hevner lab
2. Functions of AUTS2 during neurodevelopment-Hevner lab
3. Knowledge gaps in understanding mechanisms AUTS2 syndrome using current model systems-Hevner lab
4. Description of previous mouse model systems (Hori, Reinberg, Hevner, compare and contrast) to understand AUTS2 function, then describe Castanza et al publication emphasizing hippocampal deficits (Table, suggestion)-Hevner lab

**Introduction to AUTS2 and AUTS2 syndrome**

**Functions of AUTS2 during neurodevelopment**

Auts2 has been proposed to function in neurodevelopment by three distinct mechanisms. The first proposed by Gao et al. and based primarily upon CHIP-seq studies, describes an interaction with a novel polycomb complex to convert a repressive histone modification into an activating one thereby activating the transcription of targeted neurodevelopmental genes. The second mechanism proposed by Hori et al. describes cytoplasmic interactions between AUTS2 and Rac1 to induce pro-migratory cytoskeletal changes through the induction of lamellipodia suppression of filopodia. The third mechanism, proposed more recently by Castanza et al. posits that, like the mechanism proposed by Gao, Auts2’s function is primarily nuclear but rather than acting at the level of histone modification, Auts2 exerts a transcriptome regulatory effect through interactions with splicing factors to modify RNA abundances, including of members of the novel polycomb complex proposed by Gao, chiefly p300, and Prex1, a key member of the Hori et al. model. An additional study by Monderer-Rothkoff et al. provides further support for a spliceosome interacting Auts2 model, identifying that a key splicing factor, SF3B1, interacted with both short and long isoforms of Auts2 in yeast two-hybrid screens, but that polycomb factors only interacted with the long isoform of Auts2. Likewise, Hori et al determined that the cytoplasmic functions of Auts2 were confined to N-terminal regions. This is a critical distinction as it is the c-terminal “short” isoform of Auts2 that is primarily expressed in developing neocortex (Castanza et al.) and it is therefore c-terminal isoforms of Auts2 which must contain it’s essential developmental functions.

Additional recent studies by Liu et al, attempted to further elucidate the mechanism by which Auts2’s polycomb interacting function regulates neurodevelopment. They found that an HX motif recruits the Auts2-Polycomb complex to the transcripton factor NRF1 to activate transcripton of neurodevelopmental genes. However, this study omitting the dominant c-terminal isoform expressed from a transcription start site in Exon 9 and instead misstated that minor isoform expressed from Exon 7 comprises the c-terminal short isoform. This distinction is important because while the minor isoform expressed from exon 7 contains the HX motif, the major short isoform expressed from exon 9 does not. Furthermore, this study focused primarily on the mechanism of Auts2 in the development of cerebellum. Differential expression patterns of N-terminal and C-terminal Auts2 were observed between developing cortex and cerebellum (unpublished data), due to this difference in isoform expression, and the confinement of the necessary motif to the N-terminal isoform, it is likely that Auts2 performs different functions in development of the cerebellum and development of the cortex.

D**escription of previous mouse model systems**