Role of the Homeobox Gene Hesx1 in forebrain and pituitary formation in mouse and human

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Our lab is focussed on the study of Hesx1 with the overall aim of a better understanding of the molecular and cellular mechanisms required for

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normal forebrain formation in mouse and humans. The homeobox gene Hesx1 is essential for normal forebrain and pituitary gland formation in mouse and humans. Hesx1 deficient embryos show variable degrees of deletion of the anterior forebrain at 9.5 dpc. Unlike Otx2, Hnf3beta and Lim1 mutants, the forebrain primordium is properly specified at 7.5 dpc in the Hesx1 mutants. Subsequently, however, there is less forebrain tissue at 8.5 dpc. In spite of these early forebrain defects, most Hesx1K/K mutants develop a morphologically recognisable, but abnormal, forebrain at late gestation. The forebrain is smaller than in wild-type littermates and shows defects in dorsal midline structures (septum pellucidum, corpus callosum, and anterior and hippocampal commissures). Hesx1K/K mutants also show pituitary dysplasia, anophthalmia or microphthalmia and defects in the olfactory bulbs. In humans, mutations in HESX1 are associated with familial cases of septo-optic dysplasia (SOD) and other forms of hypopituitarism.

We have used a genetic approach to answer specific questions about the function of Hesx1 in forebrain and pituitary formation. Combining lack and gain of function experiments in mouse embryos, we are analysing the role of Hesx1 in cell fate specification. The association of HESX1 mutations and human diseases is being studied by the introduction of specific mutations in the mouse locus using the Cre-loxp system. Details of this research will be presented.