**Dissecting the causes of frontal cortex abnormalities in a mouse model for CHARGE syndrome**

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Difficulties in executive functioning are characteristic of many neurodevelopmental disorders, including schizophrenia and Autism Spectrum Disorder (ASD). Individuals with CHARGE (Coloboma, Heart defects, Atresia of the choanae, Retarded growth, Genital anomalies and Ear defects) syndrome share certain behavioural characteristics with ASD, in particular those related to executive functioning. These problems manifest themselves in CHARGE patients as difficulties in shifting focus and attention, monitoring their work and effects of their actions on others and impulse control.

The neuroanatomical basis of these and other behavioural and neurological issues associated with CHARGE syndrome and other neurodevelopmental disorders are not known. Executive functions are controlled by the prefrontal cortex, and we therefore hypothesise that the development, structure and function of the prefrontal cortex is affected in CHARGE syndrome. We have produced mouse models for CHARGE syndrome in which one copy of the causative *Chd7* gene has been inactivated, which provides us with the necessary tools to test this hypothesis in a model system.

The objectives of this project will be to use the *Chd7+/-* mouse to investigate the role of *Chd7* in cortical development. Specifically, we will 1) characterise anterior-posterior neocortical regionalisation and prefrontal cortex growth in the *Chd7+/-* mouse model, 2) investigate the interaction of *Chd7* with the FGF signalling pathway in prefrontal cortex development, and 3) determine the effects of *Chd7* haploinsufficiency on neuronal micro-architecture and excitatory:inhibitory balance in the prefrontal cortex.

This project will provide significant insights into the role of *Chd7* in neocortical development, its interaction with signalling molecules that pattern the developing cortex, and identify specific cortical defects that might underlie executive dysfunction. These findings will also have significant implications for CHARGE syndrome. We expect that the successful completion of these aims will be followed by further analysis of frontal cortical defects in patients with CHARGE syndrome, the assessment of executive functioning deficits in conditional mouse mutants where *Chd7* is deleted specifically in the early FGF8-producing signalling centre in the forebrain and electrophysiological studies.



*Etv5 (Erm)* gene expression visualised by in situ hybridisation on an E9.5 mouse embryonic head as a read-out of FGF signalling activity. Note the FGF signalling gradients emanating from two seconday organisers, the isthmus organiser (IsO) at the mid-hindbrain junction and the anterior neural ridge (ANR) that directs patterning of the frontal cortex.