Ancestral functions of genes regulated by imprinting in mammals

Supervisory team:
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Project description:

Around 100 mammalian genes are subject to regulation by genomic imprinting such that only one of the two parental alleles is expressed. This form of epigenetic regulation is unique to mammals and the evolution of imprinting has been hotly debated since its discovery. The most widely accepted theory for evolution of imprinting predicts a critical role for imprinted genes in regulating growth during development. However, while it is clear some imprinted genes are important regulators of growth, there are many with other functions. Much of what we know about imprinted genes comes from mouse genetic studies and relatively little is known about the functions of the analogous genes in animal species in which imprinting does not exist. For each gene with imprinted expression in mammals this project will identify orthologues in non-mammalian vertebrate and invertebrate species. By comparing gene function in different species, the aim is to test the hypothesis that imprinting first evolved to act on genes with established roles in growth regulation. Alternative hypotheses will be considered. The PhD project will combine two main approaches to be carried out in parallel: First, through careful evaluation of the literature and genome databases, evidence of gene function in both mammalian and non-mammalian species will be gathered and evaluated. It is anticipated that functional information from studies of non-mammalian models will be scarce relative to a wealth of information for mammalian genes, particularly from mouse genetic studies. This exercise will go some way to addressing the hypothesis, and will identify a short-list of imprinted gene orthologues for functional testing in zebrafish. The second approach will involve genetic testing of gene function in zebrafish and will begin with zebrafish orthologues of Grb10, which is expressed from the maternally-inherited allele in mouse and is an important regulator of fetal growth that acts independently of IGF signaling. Mutant grb10 zebrafish strains are available and will be used to identify whether growth regulation, or other functions known from mouse genetic studies, are conserved in fish. This will involve studying morphology, histology and physiology of developing zebrafish. Additionally, the molecular phenotype will be addressed using antibody staining and mRNA in situ hybridisation to assess expression of marker genes and through the generation of an RNA-seq data set. The student will acquire both 'wet-lab' techniques in embryology, in vivo imaging, molecular biology, and a range of bioinformatic skills.