Genetics of Cognition in Down Syndrome Postdoctoral Training Fellow

This is a full-time, 4-year position on Crick terms and conditions of employment funded by a Wellcome Trust Collaborative Award.

The Tybulewicz Lab

We seek a talented and motivated postdoc to join a Research Group led by Victor Tybulewicz at the Francis Crick Institute. The Group currently consists of 12 scientists, including 6 postdocs and 4 PhD students. One of the two main research interests of the Group is the study of the genetics underlying Down Syndrome (DS). DS is a human condition caused by trisomy of human chromosome 21 (Hsa21) resulting in a large number of different phenotypes including cognitive impairment, congenital heart defects and craniofacial abnormalities. The overall aim of our research is to identify the genes on human chromosome 21 (Hsa21) that are required in three copies to cause specific DS phenotypes and to establish the molecular and cellular mechanisms by which increased dosage of these genes causes pathology.

The Group has previously generated a series of mouse models of DS that can be used to map the location of dosage-sensitive genes that cause Down Syndrome phenotypes (Figure 1), and has used these to study congenital heart defects, locomotor dysfunction, craniofacial abnormalities and neural oscillations (Lana-Elola et al 2016, Watson-Scales et al 2018, Toussaint et al 2019, Chang et al 2019).

More information about the Tybulewicz Lab.
Lana-Elola et al (2016) eLife pii:e11614. doi:10.7554/eLife.11614.001. Pubmed
Watson-Scales et al (2018) PLoS Genetics **14**:e1007383. Pubmed
Toussaint et al (2019) bioRxiv doi:10.1101/711259
Chang et al (2019) bioRxiv doi:10.1101/644849

Project summary

The Dp1Tyb mouse strain has three copies of 148 Hsa21-orthologous genes and models many DS phenotypes (Figure 1). We have recently discovered that these mice have learning and memory deficits and, in collaboration with Prof Trevor Smart (UCL), have shown that they have increased production of the inhibitory GABA neurotransmitter in the hippocampus, potentially accounting for defective spatial memory in these animals. Analysis of all the strains in the mapping panel (Figure 1) has shown that this GABA phenotype maps to two regions: a 33-gene region and a 39-gene region duplicated in Dp2Tyb and Dp3Tyb mice respectively.

The aim of the proposed project will be to identify the causative genes that are required in three copies to cause the overproduction of GABA, and to establish the mechanisms by which increased dosage of these genes causes pathology, including the cell type(s) the genes are acting in. The work will involve the use of mouse genetics, lineage-selective gene ablation, transcriptomics (bulk and single cell), proteomics, cell biology and electrophysiology.

This study is part of a collaboration between our group and 4 other research groups funded by a Wellcome Trust Collaborative Award, whose overall aim is to understand the GABA

dysfunction in DS at the molecular, cellular, synaptic, network and behavioural levels. These 4 other groups are led by:

- Prof Elizabeth Fisher (UCL) – mouse neurogenetics
- Prof Trevor Smart (UCL) – ex vivo electrophysiology of GABA signalling
- Prof John O'Keefe (UCL) – in vivo analysis of neuronal circuits in animals carrying out learning tasks
- Prof Dean Nizetic (QMUL) – analysis of neuronal excitation and inhibition using human induced pluripotent stem cells from people with DS.

We expect that there will be 6 postdocs working on this programme across the 5 groups. The new postdoc in the Tybulewicz Group will work closely with this team and with other members of these groups.

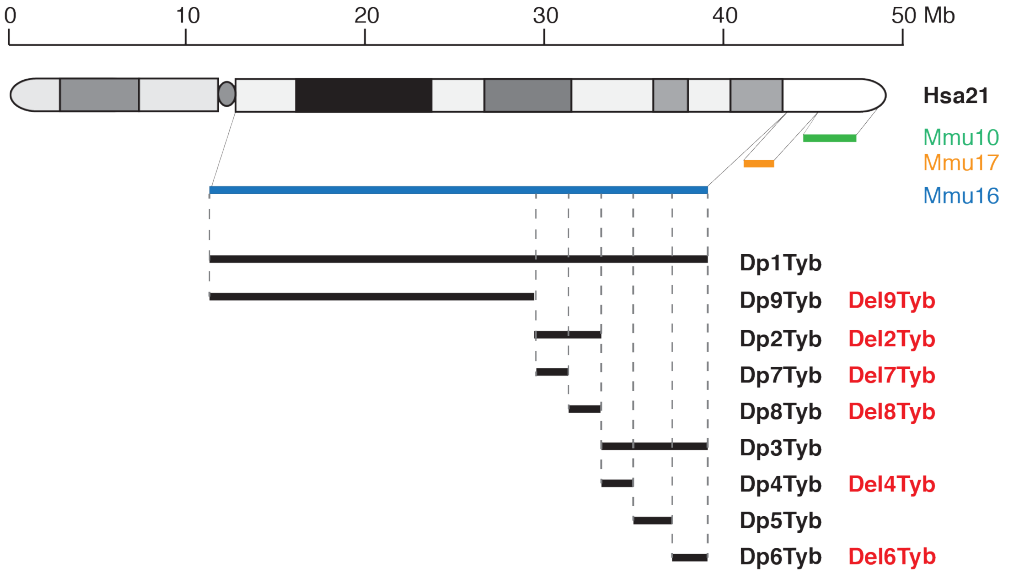

Figure 1. Mouse mapping panel for Down Syndrome. Human chromosome 21 (Hsa21) is orthologous to regions on mouse chromosomes 10, 16 and 17 (Mmu10, Mmu16, Mmu17). We have generated the Dp1Tyb mouse strain with a 23Mb tandem duplication of the entire region of Mmu16 that is orthologous to Hsa21. Furthermore, we have generated a series of strains (Dp2Tyb – Dp9Tyb) with nested duplications that can be used to map the location of genes required in three copies to causes Down Syndrome phenotypes. We have also generated a number of strains with deletions (Del2Tyb – Del9Tyb) of the equivalent regions to further aid genetic mapping.

Key experience and competencies

The post holder should possess the following characteristics:

Essential

- PhD in a relevant area, e.g. neurobiology, developmental biology, mammalian genetics, or be in the final stages of PhD submission
- Good knowledge and experience of neurobiology or mammalian genetics
- Track record of writing papers as evidenced by publications or submitted manuscripts in refereed journals

- Evidence of data presentation at scientific meetings
- Ability to work independently and also capable of interacting within a group

Desirable

One or more of the following would be desirable:

- Expertise in developmental neurobiology
- Expertise in neuronal cell biology
- Expertise in electro-physiology
- Expertise in histology and/or imaging of the brain
- Expertise in transcriptomics or proteomics
- Expertise in use of induced pluripotent stem cells

Postdoctoral Training Fellows are expected to lead their own projects, contribute to other projects on a collaborative basis (both in the lab and with external collaborators) and guide PhD students in their research. The ability to work in a team is essential.