Open position for the LSM call of applications

Department/Institute: LMU Faculty of Biology, Neuroscience

Subject areas/Research fields: Neuroscience

Keywords: Organoids, Neurodevelopmental Disease, Microtubules

Name of supervisor: Professor David Keays

Project title: Modelling Human Neurodevelopmental Disease with Cerebral Organoids

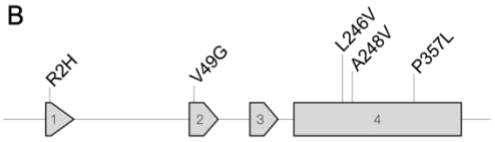
Project description:

Background. The human brain is arguably the most complex structure in biology. It's construction is dependent on a complex cascade of cellular events that include mitotic division, relocation of migrating neurons, and the extension of dendrites and axons. These processes are reliant on a dynamic and functionally diverse microtubule cytoskeleton. Microtubules form the mitotic spindle enabling the separation of sister chromatids, they facilitate translocation of the nucleus and extension of the leading process during neuronal migration, and microtubule polymers extend and maintain large and longstanding axons in mature neurons. Reflecting their importance mutations in genes encoding for tubulin subunits and microtubule associated proteins cause severe neurodevelopmental disorders. For instance, variants in TUBA1A are known to cause lissencephaly and cerebral palsy, mutations in TUBB2A cause cortical malformations, and substitutions in MAST1 cause microcephaly, autism and corpus callosum phenotypes. To study the underlying molecular and cellular mechanisms of these diseases the Keays laboratory is exploiting iPSCs and advanced 2D and 3D neuronal cultures. This project will utilise our recently created biobank of patient derived iPSCs (http://www.tubulinbiobank.org), coupled with CRISPR-cas9 genome engineering to generate isogenic controls. This project with focus on TUBB2A which is known to cause abnormal cortical gyration, microcephaly, and/or autism. Following the generation of cerebral organoids the student will study how disease causing mutations influence the properties of the microtubule cytoskeleton, and the cellular events necessary for brain formation.

A

Line	*TUBB2A* Mutation	Nucleotide Change	Cortical Malformation
1	p.R2H	c.5G>A	Microcephaly
2	p.V49G	c.146T>G	Severe dysgyria
3	p.L246V	c.736C>G	Severe dysgyria
4	p.A248V	c.743C>T	Pachygyria
5	p.P357L	c.1070C>T	Severe Dysgyria

B



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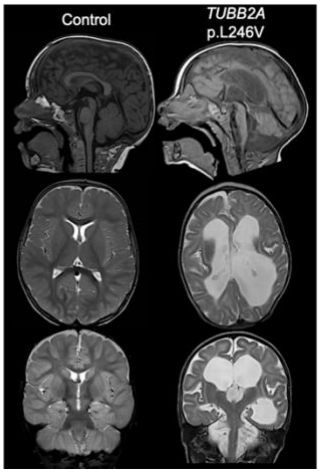

Figure 2. *TUBB2A* patient lines acquired for this study. **(A)** Table outlining the patient lines ascertained, the residue and nucleotide change carried by each individual and major cortical malformation diagnosed upon neuroimaging. **(B)** The position of each variant across the *TUBB2A* gene. **(C)** Representative neuroimaging of an individual harbouring a *TUBB2A* L246V variant.

Hypothesis.

1) Mutations in *TUBB2A* act by altering the assembly, stability and/or dynamics of microtubules.
2) Microtubule dysfunction perturbs the generation and/or the migration of neurons causing neurodevelopmental disease.

Methods

Cerebral Organoid Generation, iPSC culturing, CRISPR-Cas9 genome engineering, histological analysis, single cell sequencing, imaging.

References:

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