A novel approach to unravelling the pathophysiology of CHM using iPSC-derived RPE from patients

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We reached a milestone in CHM research when *CHM* gene replacement clinical trials began. However, these trials did not signal the end of CHM research as many questions still needed to addressed. For example, although the causative *CHM* gene has been identified, and the function of its encoded REP1 protein elucidated, we do not know how a REP1 deficiency leads to the clinical signs associated with CHM. It is likely that the primary defect of the disease lies in the retinal pigment epithelium, which is the supporting tissue of the light-sensing photoreceptors. We have a bank of retinal pigment epithelium derived patients carrying different *CHM* mutations. To generate such tissue, we take a small skin sample from CHM volunteers and treat the cells in the sample to lose their skin identity and become stem cells or rather "induced pluripotent stem cells" (or iPSCs). These iPSCs then have the potential to become any cell type in the body and we differentiate them into retinal pigment epithelium. Our project funded by the CRF aims to provide comprehensive analyses of the functionality of the CHM retinal pigment epithelium in comparison to healthy tissue.

The retinal pigment epithelium has diverse roles that are vital for the support and survival of the neighbouring photoreceptors and choroid. These functions are closely regulated by a series of ion channels. Our functional analysis of the iPSC-derived retinal pigment epithelium of two CHM patients suggests a deregulation of a subtype of ion channels. This deregulation disrupts some of the key functions of the epithelium, which would in turn have implications for both the photoreceptors and the choroid. We complemented this work by a transcriptomic study (i.e. a study of the expression profile of all the genes expressed in the cell), which confirmed that the expression of the genes coding for these channels is indeed altered in the CHM retinal pigment epithelium compared to controls. The next step of this work is to study the activity of other channel subtypes and to assay the retinal pigment epithelium of additional patients in order to consolidate our observations. Overall our study, which represents a first insight into the functional alterations of CHM retinal pigment epithelium, aims to better understand the disease and to identify novel targets for alternative therapeutic approaches.

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