'Big Data' hub helps prioritize novel therapeutic targets for seizure disorders

Introduction

Several loss-of-function mutations have been described at **KCNJ10,** a gene which encodes the inward-rectifying potassium channel **Kir4.1**, in patients with **EAST syndrome** (epilepsy, ataxia, sensorineural deafness, and tubulopathy). The Acute Neurology Research Unit (ANRU) is therefore interested targeting Kir4.1 for the treatment of epilepsy. However, common variants at potassium ion genes like **KCNJ10** have not previously been linked with risk of sporadic epilepsy. Additionally, one paper reported a link between a gain-of-function mutation at **KCNJ10** (**p.R18Q**) and risk of epilepsy, complicating the ANRU's goal to develop a KCNJ10 activator.

Methods

Translational Biology combined three resources - (1) UK Biobank, (2) ProteinPaint, and (3) ChembioDB, to help prioritize novel potassium channel targets for seizure disorders.

Results

Using **ProteinPaint**, we mapped the previously-described gain-of-function mutation at KCNJ10 (p.R18Q) to a region likely to have little or no effect on Kir4.1 function. By contrast, most loss-of-function mutations affected the main inward-rectifying domain (**Fig. 1**). A GWAS meta-analysis of 9,671 generalized epilepsies & 381,447 controls identified novel signals at a gene encoding the potassium channel, **KCNN2**. Using **ChembioDB**, we mapped this gene to an existing BIIB compound - **BIO-0556089**.

Conclusions

Biogen's **bigdata.biogen.com** hub is a useful resource for drug target validation and drug repurposing. We used the tool to help validate the link between loss-of-function mutations in potassium ion genes and risk of epilepsy, and identified potential tool compounds for further i**n-vivo** and **in-vitro** investigations.

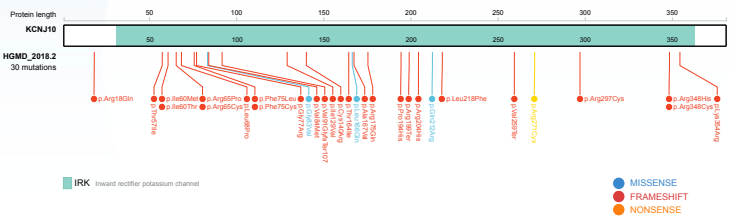

FIGURE 1: p.R18Q does not affect the inward-rectifying channel of Kir4.1 protein.

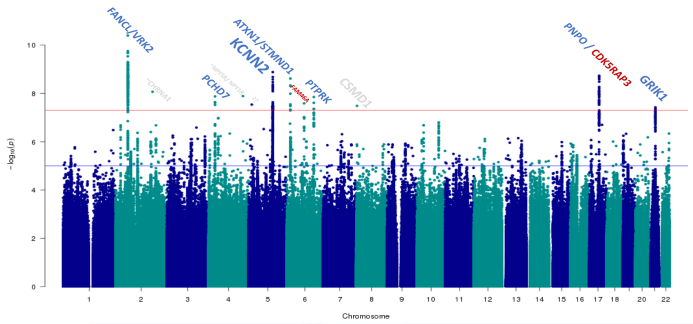

FIGURE 2: Generalized epilepsies GWAS Manhattan plot