LARGE-SCALE BIOBANK APPROACH TO IDENTIFY NOVEL GENETIC FACTORS UNDERLYING CONCUSSION RISK AND RECOVERY

Joseph Holmes[1], Neven Maksemous[2], Robert Smith[2], Heidi Sutherland[1], Lyn Griffiths[1]

[1]*Queensland University of Technology, Faculty of Health, School of Biomedical Sciences, 60 Musk Ave, Kelvin Grove QLD 4059, Australia.*

[2]*Queensland University of Technology, Faculty of Sciences, Research Infrastructure, 60 Musk Ave, Kelvin Grove QLD 4059, Australia.*

Concussion is a complex neurological disorder, that remains incompletely understood. In most cases of concussion, acute symptoms are typically resolved within 2-3 days, with any lasting symptoms resolved after a week, however, some cases can persist for months or years with no discernible cause. It is estimated that risk factors such as injury severity, sex or health condition only explain a portion of the inter-individual variability seen among concussion cases, which suggests that genetic factors play a role. It is known that mutations within the calcium channel gene *CACNA1A* can cause catastrophic brain oedema and death following trivial head injuries. Yet beyond isolated findings such as this, genetic research is unable to adequately explain the variability in concussion outcomes. Until recently investigation has been performed primarily through candidate gene studies which are limited in scope, and often fall prey to underpowered results, ill-defined cohorts and variable findings. This present study aims to utilise the large-scale genotype and phenotype information provided by modern biobanks to overcome these limitations and investigate novel genetic factors that can be implicated in poor concussion outcomes.

Whole genome sequencing (WGS) data was extracted for individuals who suffer from post-concussive symptoms or have suffered from multiple concussive injuries (>3), to build a disease group (n=3,087) of individuals who suffer from worse concussion outcomes. WGS data was also extracted for a neurologically healthy control group (n=11,844). Common variants (minor allele frequency > 1%) underwent a genome-wide association study (GWAS), while rare variants (minor allele frequency <1%) underwent filtering to identify a subset of potentially pathogenic exonic rare variants, which then underwent further gene-based and pathway-based burden testing.

A preliminary GWAS investigation into a subset of this cohort (n=396) has revealed several loci which have reached suggestive significance in neurologically related genes. Through a full, comprehensive investigation of this cohort, further novel loci and genes are expected to be uncovered, which not only improves our understanding of the more severe cases of concussion, but promote the use of large biobanks to enhance the discovery of genetic factors in complex disease.