Massively Parallel Reporter Assays (MPRAs) can be used to experimentally evaluate the impact of genetic variants on gene expression. In this study, our objective was to systematically evaluate the functional activity of 3'-UTR SNPs associated with neurological disorders and use those results to help understand their contributions to disease etiology.

To choose variants to evaluate with the MPRA, we first gathered SNPs from the GWAS Catalog that were associated with any neurological disorder trait with p-value < 10^{-5}. For each SNP, we identified the region that was in linkage disequilibrium ($r^2 > 0.8$) and retrieved all the common 3'-UTR SNPs (allele-frequency > 0.05) within that region. We used an MPRA that we developed (PASSPORT-seq; PMIDs: 31477794, 33119910) to measure the impact of these 3'-UTR variants in SH-SY5Y neuroblastoma cells and a microglial cell line.

Of the 13,515 3'-UTR SNPs tested, 400 and 657 significantly impacted gene expression in SH-SY5Y and microglia, respectively. Of the 1,170 tested SNPs associated with a substance use disorder, 47 and 60 were significant in SH-SY5Y and microglia residing on 34 and 36 different genes. Of these, 10 SNPs were significant in both cell lines and were on genes including $ADH1C$ and $ADH4$, among others.

This study demonstrates that MPRAs can be used to evaluate the functional effect of non-coding variants on gene expression to help identify causal variants and further understand the etiology of diseases.