Alzheimer’s disease (AD) is the most common cause of dementia in elderly individuals, affecting 44 million people worldwide. AD is highly multifactorial, with established genetic and environmental risk factors. While previous studies have identified AD risk genes, there has been limited research regarding another potentially important factor: drug-gene interactions (DGIs). We hypothesized that AD progression and biomarkers are influenced by DGIs involving both AD and non-AD medications, and this study’s aim was to identify them.

For each medication that we examined, we performed genome-wide association studies (GWAS) for two outcomes in AD cases in the Alzheimer’s Disease Neuroimaging Initiative (ADNI): a longitudinal composite cognitive score measuring rate of decline and hippocampal volume loss. We used a linear regression model that included covariates for age, sex, race, and principal components. This model tested the interaction between each individual’s medication and SNP dosage in order to find genome-wide significant variants ($P < 5 \times 10^{-8}$) that modified the effect of the medication. We applied genomic control to the results and created Manhattan plots and regional association plots to visualize the results. Of the several DGIs that we found, the most statistically and biologically significant are ASA-KHDBR3, atorvastatin-COLEC12, atorvastatin-RAP1GAP, and memantine-KLHL29. These results are the first, to our knowledge, to identify specific DGIs contributing to the progression of AD.

Results

We performed GWAS on 460 participants categorized as E3MCL, L3MCL, or AD in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study. GWAS tests variants across the genome to find associations between single-nucleotide polymorphisms (SNPs) and a trait. For the gene we used, we genotyped and imputed SNPs. We analyzed two longitudinal outcomes to represent AD progression change in composite cognitive decline score (CGPS) and change in hippocampal atrophy. Both indicators of AD progression. The hippocampal volume data was found in UCSF—SN1 Hippocampal Volumes in ADNI, and the composite cognitive data was prepared by Gross et al. To perform the GWAS, we used the Universal Genome Analyzer (UGA) pipeline. For each GWAS, we used a linear regression model that included covariates for age, sex, race, principal components, and the medication and SNP dosage. The $P$-value for the association between the medication and SNP is calculated using the test statistic $t$, where $t$ is the observed and expected $P$-values by plotting their quantiles against each other. We observed that significant $P$-values should be $< 5 \times 10^{-8}$.

Conclusions

We discovered four drug-gene interactions that are associated with longitudinal changes in composite cognitive score and hippocampal volume, two parameters that act as a proxy for understanding the progression of Alzheimer’s disease. The biological roles of the ASA-KHDBR3 DGI in forming synaptic connections, as well as the important biological roles of RAP1GAP and memantine-KLHL29, are promising and justify further investigation.

References

Acknowledgements

To our knowledge, this is the first GWAS of longitudinal AD phenotypes that tested for DGIs. We identified several drug-gene interactions implicated in the progression of AD and highlight four DGIs that are especially significant both statistically and biologically ($P < 5 \times 10^{-8}$). KHDBR3 encodes the T-STAR protein, which is a splicing repressor of the alternatively spliced segment 4 exons from each of the Neuroligin-3 genes and is highly concentrated in the hippocampus. Neuroligin-3 encodes neuromedin, which are involved in forming synaptic connections and are involved in neurotransmission. Each copy of the C allele was associated with a 1.5212 decrease in slope of composite cognitive score in individuals taking ASA.

COLEC12 is expressed in astrocytes and microglia and may play a role in the clearance of Aβ. Aβ accumulation is a hallmark of AD. In addition, COLEC12 is involved in the degradation of oxidatively modified low density lipoproteins, which is important in AD. Each copy of the G allele was associated with a 292.06 units increase in hippocampal atrophy in individuals taking atorvastatin.

RAPIGAP is highly expressed in the brain. It controls Rap1 signaling, which regulates processes involved in synaptic plasticity and thereby learning and memory. Rap1 is an intracellular GTPase, which directly impacts synaptic function. Synaptic failure is a central to AD pathology. Each copy of the G allele was associated with a 322.92 units increase in hippocampal atrophy in individuals taking atorvastatin.

KLHL29 may also have biological relevance to AD progression. A paralogue of KLHL29 reduces kainate receptor-mediated currents in hippocampal neurons by modifying channel properties. Each copy of the C allele was associated with a 212.33 unit increase in hippocampal atrophy in individuals taking memantine.