Evolution of GWAS results through ADNI cohorts

Belen Marin*, Carlos Alquezar-Baeta*, Monica Hernandez, Elvira Mayordomo, and ADNI (*equal contribution)

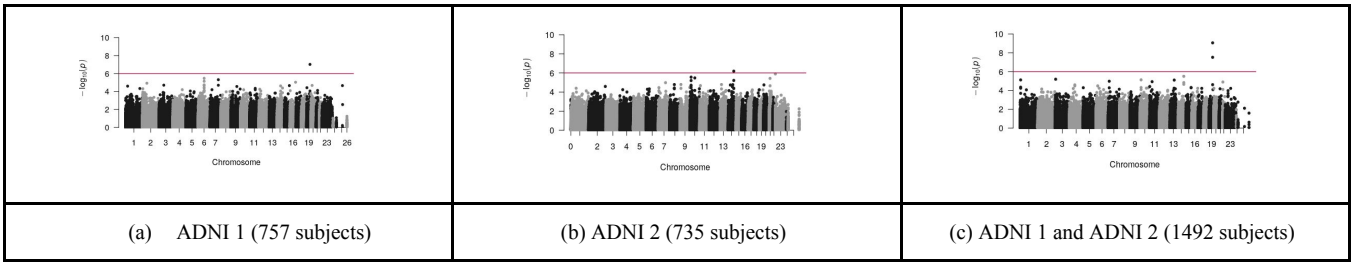
I. Introduction.

The identification of susceptibility genes for Alzheimer's disease represents a valuable source of knowledge about the genetic mechanisms underlying the onset and progression of the disease. Genome Wide Association Studies (GWAS) of Alzheimer's with quantitative phenotype is an active field of research that has pointed out a number of SNPs potentially related to the disease. In particular, extensive research has been performed on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, where different variants of GWAS analysis have confirmed the association of some genes like APOE with the atrophy of cerebral structures such as the hippocampus [1]. In 2009, Potkin et al. published the first GWAS based in quantitative traits rather than case-control study [2]. The authors used a subset of ADNI1 cohort and obtained a number of relevant SNPs with the hippocampus volume as quantitative phenotype. In the last decade, ADNI database has been progressively augmented yielding to the subsequent projects ADNIGO and ADNI2. To the best of our knowledge, the work of Potkin et al. has not been replicated with the whole ADNI1 or the subsequent databases, perhaps because the arise of meta-studies has opened the opportunity to deal with augmented cohort sizes [3]. However, we believe that it is also important to obtain GWAS results on more homogenous data before attempting more sophisticated meta-analysis. In this work, we intend to study which SNPs are consistently preserved through ADNI cohorts in GWAS.

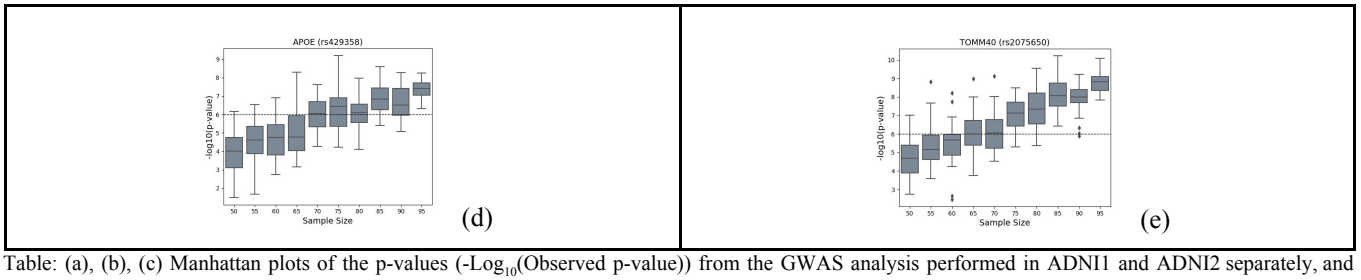
II. Materials and Methods

The GWASs were performed in the ADNI cohorts publicly available in 2018: ADNI1, ADNIGO and ADNI2 (http://www.adni.org). The GWAS included all the SNPs available in both ADNI1 and ADNIGO2 and the hippocampus volume was obtained from the *ADNIMERGE* table provided by ADNI. The hippocampus was segmented from the MRI images acquired in the baseline visit. PLINK software was used in the computation of the GWAS results (http://zzz.bwh.harvard.edu/plink/) with a standard check of quality-control. We performed two different GWAS including the subjects from ADNI1 and ADNI2 separately, and a single GWAS including all the subject in both phases. In addition, we performed an exhaustive randomized analysis of the patients in order to assess the consistency of the results with different selections of patients. The randomized analysis selected p% patients of the whole ADNI cohort where p ranged from 50 to 100% in steps of 5%. For each p, we performed 25 different GWAS.

III. Results



(a) ADNI 1 (757 subjects) (b) ADNI 2 (735 subjects) (c) ADNI 1 and ADNI 2 (1492 subjects)



(d) (e)

Table: (a), (b), (c) Manhattan plots of the p-values ($-Log_{10}$(Observed p-value)) from the GWAS analysis performed in ADNI1 and ADNI2 separately, and both cohorts jointly. (d), (e) Statistical distribution of the p-values ($-Log_{10}$(Observed p-value)) obtained in the randomized analysis. Left, results for APOE SNP. Right, results for TOMM40 SNP.

IV. CONCLUSIONS AND FUTURE WORK

Surprisingly, our GWAS analysis through the different ADNI cohorts reported a positive association for APOE and TOMM40 SNPs only in ADNI1. The analysis in the whole cohort of patients reported the expected association for APOE and TOMM40 according to current knowledge. From the exhaustive randomized analysis the association was consistent with the results in the whole ADNI cohort from a percentage of 75%. In future work, we will study the association of alternative SNPs and brain structures.

BIBLIOGRAPHY

[1] Stein et al., Identification of common variants associated with human hippocampal and intracranial volumes, Nat. Genet., 44(5), pp: 552-61, 2012.

[2] Potkin at al., Hippocampal Atrophy as a Quantitative Trait in a Genome-Wide Association Study Identifying Novel Susceptibility Genes for Alzheimer's Disease, Plos One, 4(8), e6501, 2009.

[3] Lambert et al., Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease, Nat. Genet., 45(12), pp:1452-1458, 2013.