Multi-functional PET imaging genetics in Alzheimer’s disease

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Introduction

Alzheimer’s disease (AD) is usually developing gradually and getting worse over time. The ApoE genotype in the form of ε4 is well-known considered as a genetic risk factor for AD. In addition, for the clinical diagnosis, PET/MRI is a comprehensive tool to identify AD by detecting the changing in brain. In the study, we examined single nucleotide polymorphisms (SNPs) based on the whole genome sequencing (WGS) data. We identified some SNPs that have significant association with quantitative traits (QTs) of PET imaging. The experiment demonstrates that the proposed SNPs can better map QTs of PET measurements than ApoE.

Objectives

The objective is to use longitudinal quantitative FDG and amyloid PET measurements to map genetic risk factors for Alzheimer’s disease based on WGS data.

Methods

75 subjects from ADNI GWAS dataset [1] with more than 7 years following up FDG PET and structural MRI. [18F]AV45 and [11C]PIB scans were collected. Some statistics of the samples are shown in Figure 1 and Figure 2.

The PLINK toolkit [3] was used for data processing and analysis. 539,803 genotypes were selected from ADNI genic dataset were used for analysis. All preprocessed PET images with structural MRIs were downloaded from ADNI database. All PET images were spatially normalized to MNI space using MRI and SPM8 toolbox. 35 regions of interest (ROI) were manually drawing in a high-resolution MRI template. Standard uptake values (SUVr) to the cerebellum were calculated. A general linear model [3] to include age as a covariate was used for the correlation between each SNP genotype and ROI SUVr. The SUVR(Tracer) denotes the SUVR for a tracer at one region. We use βA, βG, and βi, where i=1…n, to denote coefficients. There are n types of allele in one SNP. The Freq(A) is 0 or 1 to denote a subject has allele i or not. The formula for the linear model is presented as:

\[ \text{SUVR(Tracer)} = \beta_A + \beta_G \times \text{Age} + \sum_{i=1}^{n} \beta_i \times \text{Freq}(A) \]

Figure 1: The number of subjects in each category of diagnosis transitions in the sample space. NL denotes Normal. MCI denotes mild cognitive impairment.

Figure 2: The distribution of the median age for each sample’s records in the sample space.

The results were analyzed using the R statistical software (version 3.5.3). The SNPs of the SNPs of the SNPs of the SNPs were selected for further analysis. The error bar denotes the 95% confidence interval of the mean.

Figure 3: The Y-axis denotes the mean difference of changing in 7 years FDG measures before and after diagnosis is presented. The error bar denotes the 95% confidence interval of the mean.

Figure 4: The x-axis denotes the difference in 7 years FDG measures before and after diagnosis is presented. The error bar denotes the 95% confidence interval of the mean.

Figure 5: The x-axis denotes the difference in 7 years FDG measures before and after diagnosis is presented. The error bar denotes the 95% confidence interval of the mean.

Figure 6: The x-axis denotes the difference in 7 years FDG measures before and after diagnosis is presented. The error bar denotes the 95% confidence interval of the mean.

Figure 7: The SNP genotype rs1501228 has 3 variations. The GG and TG allele correlates to the low and 75% medium level of SUVR(18F)AV45 measurements, respectively. The subjects of TT allele have higher SUVr in the 3 ROIs. The error bar denotes the 95% confidence interval of the mean.

Figure 8: The SNP genotype rs61849667 has 3 variations. The GA and AA alleles correlate with the medium and the low level of SUVR(11C)PIB measurements, respectively. The subjects of GG allele have higher SUVr in the 3 ROIs. The error bar denotes the 95% confidence interval of the mean.

Figure 9: The Manhattan plot shows the p-values of correlations between FDG quantitative traits of Global-Cortex and SNPs.

Figure 10: The Manhattan plot shows rs1501228 has smaller p-value than rs429358 in FDG quantitative traits of Global-Cortex and SNPs. rs429358 is one of two SNPs for ApoE.

Figure 11: The Manhattan plot presents the p-value distribution for all 539,803 SNPs in cognitive phenotypes. The identified SNP rs6349967 gets the smallest p-value.

Results

As shown from Figure 4 to Figure 6, the rs1876152 is an SNP with 3 variations in the sample space, which are GG, GA, and AA. Three subjects with the three distinct variations were chosen to show their SUVR(18F)AV45 in cortexes, including posterior-occipital, post-cingulate, and post-precuneous, frontal, parietal, and occipital. By examining the allele of the SNP, the subject with GG in Figure 4 has the smallest changing of SUVR(FDG) measurement. The subject with AA in Figure 6 shows remarkable changing after 72 months. The presented results give consistent conclusion as described in Figure 3, i.e., the identified SNP can significantly impact the decreasing speed of FDG uptake. In particular, the ApoE genotype for the subjects are same, which is (ε4, ε4). Therefore, the different decreasing speed is not related to the variation of ApoE in the case.

Conclusion

- The identified genotypes rs1876152, rs1501228, and rs1946867 have significant correlation with FDG, [18F]AV45, [11C]PIB PET measurements, respectively.
- ApoE genotype is a coarser genetic risk factor for AD. To monitor the AD progress more accurately, our study identified the genes that have remarkable correlations with quantitative traits of three PET tracers than the ApoE.
- The evaluation of the 3 genotypes in monitoring AD progression will be followed by the ongoing ADNI study.

References