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.

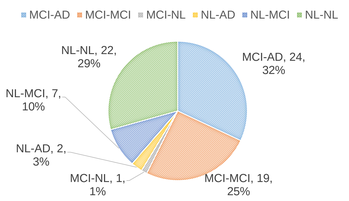


Figure 1. The number of subjects in each category of diagnosis transitions in the sample space. NL denotes Normal. MCI denotes mild cognitive impairment.

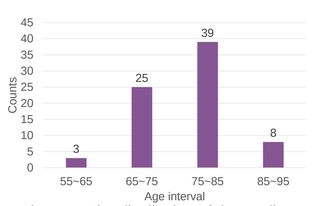


Figure 2. The distribution of the median age for each sample's records in the sample space.

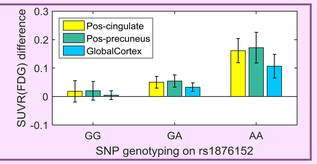
The PLINK toolkit [2] was used for data processing and analysis. 539,803 genotypes were selected from ADNI genetic dataset were used for analysis. All preprocessed PET images with structural MRIs were downloaded from ADNI database. All PET images were spatially normalized to MNI space using MRI and SPM8 with VBM8 toolbox. 35 regions of interest (ROI) were manually drawing in a high-resolution MRI template. Standard uptake values ratios (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 SUVRs. The SUVR(Tracer) denotes the SUVR for a tracer at one region. We use β_0, β_1, and α_i, where i=1…n, to denote coefficients. There are n types of allele in one SNP. The Freq(A_i) is 0 or 1 to denote a subject has allele i or not. The formula for the linear model is presented as:

$$\mathrm{SUVR(Tracer)} = \beta_0 + \beta_1 \cdot \mathrm{Age} + \sum_{i=1}^{n} \alpha_i \cdot Freq(A_i)$$

Results

Figure 3: The Y-axis denotes the mean difference of changing in 7 years FDG measures before and after diagnoses transition. The error bar denotes the 95% confidence interval of means' difference. The SNP genotype rs1876152 has 3 variations, w.r.t. GG, GA and AA on X-axis. The subjects have GG alleles relate to the lowest difference FDG measurements between two transitions. The higher difference in AA alleles shows the greatest decrease in FDG SUVR after the transition.
For the 3 typical subjects with 3 variations in the SNP rs1876152, their FDG images for the first and last visit are shown from Figure 4 to Figure 6.



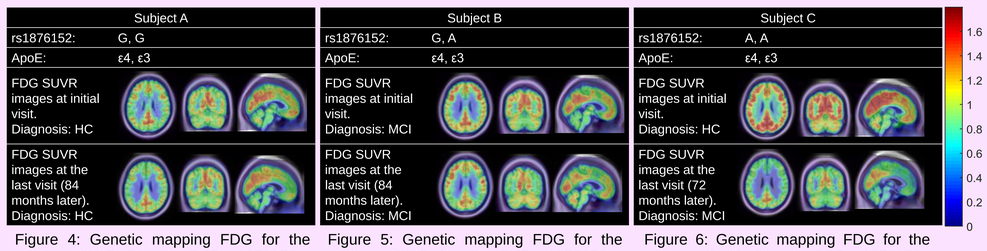


Figure 4: Genetic mapping FDG for the subject with (G, G) at the SNP rs1876152.

Figure 5: Genetic mapping FDG for the subject with (G, A) at the SNP rs1876152.

Figure 6: Genetic mapping FDG for the subject with (A, A) at the SNP rs1876152.

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(FDG) image in cortexes, including pos-cingulate and pos-precuneus, 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, ε3). Therefore, the different decreasing speed is not related to the variation of ApoE in the case.

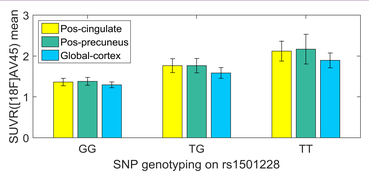


Figure 7: The SNP genotype rs1501228 has 3 variations. The GG and TG alleles correlate to the low and the medium level of SUVR([18F]AV45) measurements, respectively. The subjects of TT alleles have higher SUVRs in the 3 ROIs. The error bar denotes the 95% confidence interval of the mean.

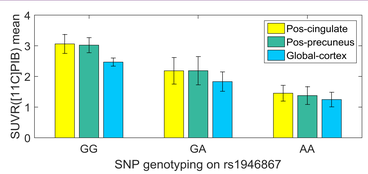


Figure 8: The SNP genotype rs1946867 has 3 variations. The GA and AA alleles correlate with the medium and the low level of SUVR([11C]PIB) measurements, respectively. The subjects have GG alleles have higher SUVRs in the 3 ROIs. The error bar denotes the 95% confidence interval of the mean.

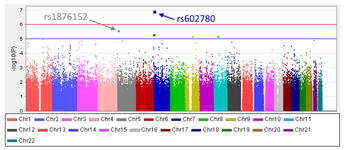


Figure 9: The Manhattan plot shows the p-values of correlations between FDG quantitative traits of Global-Cortex and SNPs.

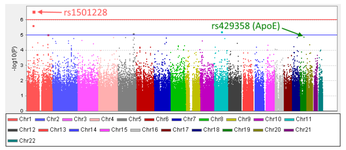


Figure 10: The Manhattan plot shows that rs1501228 has smaller p-value than rs429358 in correlation with SUVR[18F]AV45. The SNP rs429358 is one of two SNPs for ApoE.

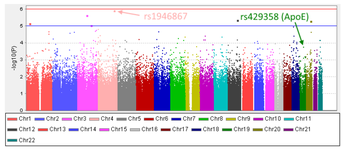


Figure 11: The Manhattan plot presents the p-value evaluation for all 539,803 SNPs in analyzing SUVR([11C]PIB). The identified SNP rs1946867 gets the smallest p-value.

In Figure 9, rs602780 gives better correlation in Global-cortex than rs1876152. However, by considering all selected ROIs, the SNP rs1876152 has more significant correlation with QT of FDG in all ROIs than rs602780, as shown in Table 1. In Figure 10, SNP rs1501228 has smaller p-value than SNP rs429358 which is a key SNP in ApoE gene.

Results

Table 1. The p-value of association analyses of SNPs with quantitative trait (QT).

Tracer	SNP	Pos-cingulate	Pos-precuneus	Global-cortex
FDG	rs429358	1.409×10^{-1}	1.409×10^{-1}	4.630×10^{-2}
	rs1876152	8.283×10^{-6}	4.420×10^{-6}	2.801×10^{-6}
[18F]AV45	rs429358	2.774×10^{-5}	4.420×10^{-6}	4.420×10^{-6}
	rs1501228	1.228×10^{-7}	3.857×10^{-7}	2.594×10^{-7}
[11C]PIB	rs429358	3.034×10^{-4}	2.428×10^{-4}	1.807×10^{-4}
	rs1946867	1.641×10^{-6}	2.573×10^{-6}	1.221×10^{-6}

In Table 1, p-values for the proposed SNPs and SNP rs429358 from ApoE are compared. The result shows that the proposed SNPs have stronger correlations with QTs than the SNP from ApoE gene.

Table 2: The top 5 SNPs that have the best fit with QT of FDG in the linear regression model.

Pos-cingulate	rs10746995	rs794237	rs1416410	rs773824	rs1876152
Pos-precuneus	rs6503342	rs9350532	rs9430069	rs773824	rs1876152
Global-cortex	rs602780	rs1876152	rs669028	rs10746995	rs11601331

Table 3: The top 5 SNPs that have the best fit with QT of [18F]AV45 in the linear regression model.

Pos-cingulate	rs1501228	rs12408850	rs8093490	rs2027701	rs12565755
Pos-precuneus	rs12408850	rs1501228	rs12286785	rs12565755	rs2240792
Global-cortex	rs1501228	rs12565755	rs602003	rs2796254	rs2240792

Table 4: The top 5 SNPs that have the best fit with QT of [11C]PIB in the linear regression model.

Pos-cingulate	rs1946867	rs3905886	rs9951577	rs11917038	rs6508522
Pos-precuneus	rs11917038	rs1946867	rs3905886	rs1293448	rs12330203
Global-cortex	rs1946867	rs3905886	rs12371097	rs2278361	rs1293448

The genotype rs1876152 on chromosome 5, genotype rs1501228 on chromosome 1, and genotype rs1946867 on chromosome 4 have significantly linear correlation with the measurements from FDG, [18F]AV45, [11C]PIB, respectively ($p < 1\times10^{-5}$).

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 genotype.
- The evaluation of the 3 genotypes in monitoring AD progression will be followed with the ongoing ADNI study.

References

[1] Saykin et al. "Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans." In: Alzheimer's & dementia: the journal of the Alzheimer's Association 6.3 (May 2010), pp. 265–73.
[2] Purcell et al. "PLINK: a tool set for whole-genome association and population-based linkage analyses." In: American journal of human genetics 81.3 (Sept. 2007), pp. 559–75.
[3] Potkin et al. "Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease." In: PLoS one 4.8 (Jan. 2009).