Alzheimer's Disease Risk Variant within the CLU Gene Affects White Matter Microstructure and Function in Nondemented Subjects

Lihua Qiu[1,2], Yong He[3], Yi Zhou[3], Hehan Tang[1], Qiuju Huang[1], Ling Zou[1], Lanlan Wang[3], and Qiyong Gong[1]

[1]Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China, [2]Radiology, The second people's hospital of Yibin, Yibin, Sichuan, China, [3]Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Target audience: Neurologist, Neuro-radiologist, fMRI researcher

Purpose

Alzheimer's disease (AD) is the most common form of dementia and is highly heritable. Although genetically complex, the C allele of the clusterin (CLU) gene variant rs11136000 has been identified to associate with risk for late onset AD.(1, 2) Fractional anisotropy (FA) reduction has been reported in AD patients (3) and healthy young humans with genetic risk allele C of the clusterin (CLU) gene variant rs11136000.(4) However, few studies have reported the brain microstructure and function changes in nondemented elderly subjects with AD risk gene of C allele in clusterin. The imaging phenotype of the risk genetic allele has not been clarified so far. In our study we investigate the microstructural and functional change of AD genetic risk variants in nondemented elderly subjects, which may help to better understand disease development and further interventions for those at risk.

Methods

Fifty-one nondemented subjects (age range 51-84 years, female: male=23: 28) were recruited in our present study. Thirty-six subjects with (CC) genotype compared with 15 subjects with (TT+TC) genotype. There was no significant difference in age, sex and handedness between the two groups. Verbal fluency scores and Mini Mental State Examination (MMSE) scores were also available for all 51 subjects. Each subject was scanned on a 3T Siemens Trio system (Erlangen, German) by using single-shot echo planar imaging (EPI) sequence to acquire Diffusion-weighted (DW) image. SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/), Matlab 2010 (The MathWorks, Natick, MA) and FSL4.1 (http://www.fmrib.ox.ac.uk/fsl/) were used to analyze the data. First, the raw DW images were converted into a single multivolume NIFTI file and "eddy current correction" was used to correct the distortions induced by the eddy current and head motion in the dataset. Then, nonbrain regions were automatically extracted using FSL BET and the FA maps were calculated with FSL DTIFit. A whole brain voxel-wise analysis was performed using SPM 8 and the threshold of statistical maps were set at $p<0.001$ (uncorrected) with a minimum cluster size of 10 contiguous voxels to exclude small random clusters. FA values in each region that revealed group difference were extracted and partial correlations were computed to examine relationships between the FA changes and clinical measures using age and sex as covariates.

Results

The CC genotype group revealed lower FA in left anterior cingulate gyrus and left extra-nuclear and increased FA in bilateral frontal, right subcallosal and left temporal lobe (see figure 1). The negative correlation were found between the FA in left middle frontal gyrus and the verbal fluency scores ($r = -0.377$, $p = 0.028$), the positive correlation of FA discrepancy in left extra-nuclear with MMSE scores were also identified ($r = 0.382$, $p = 0.026$) in CC genotype group.

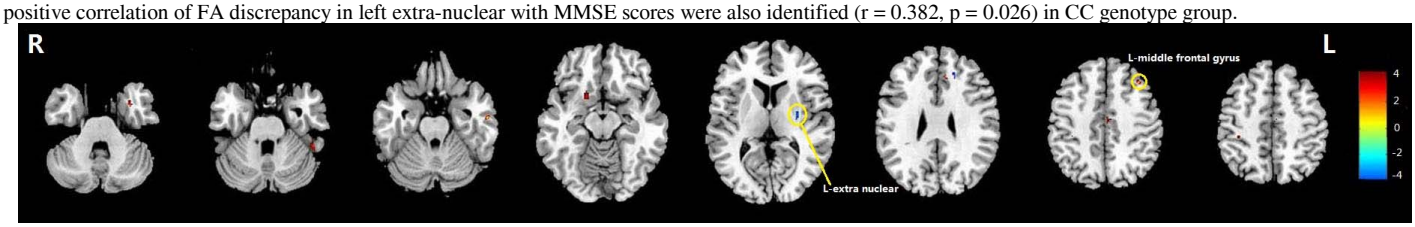

Figure 1. The CC genotype group revealed decreased FA (cool color) in left anterior cingulate and left extra-nuclear and increased FA (warm color) in bilateral frontal, right subcallosal gyrus and left temporal lobe. The highlighted areas are those which reveal significant correlations with clinic measurements.

Discussion

Both increased and decreased FA were found in genetic risk subjects, when compared with non-risk genetic allele T carrier. As lower FA value usually indicates reduced myelin integrity or axonal damage, (5) the lower FA found in left anterior cingulate and extra-nuclear may indicate white matter microstructural abnormalities within the region in genetic risk group. The positive correlation of FA in left extra-nuclear with MMSE scores indicate the myelin integrity of left extra-nuclear which is important to remain cognitive function in genetic risk group. Measurement FA value in this area may help to predict the possibility of AD development. Some areas with increased FA in our study are parts of the memory and cognitive network which may associate with impaired memory and cognitive function when later developed AD. Although increased FA is not an usual finding in neurodegenerative diseases, higher FA in some brain regions with abnormal function is found in neurogenetic syndromes.(6) Consistent with above study, higher FA in left middle frontal gyrus correlate negatively with verbal fluency scores in our study suggests higher FA in left middle frontal gyrus may affects verbal function. Those findings, together with the increased FA in nondemented genetic risk healthy subjects in our study, still need further exploration to clarify whether they are early compensatory response or results of development abnormality in white matter.

Conclusion

Nondemented healthy carriers of the CLU gene risk variant showed complex FA discrepancy when compared with T allele carriers, some of which related with cognitive measures. These changes can be considered as abnormal imaging phenotypes for the risk genetic type. But future longitudinal studies and comparison with dementia group are needed to identify the dynamic FA change associated with genotype over the course of developing AD.

Reference

1. Lambert, J.C., S. Heath, G. Even, et al., *Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease.* Nat Genet, 2009. **41**(10). 1094-9.
2. Harold, D., R. Abraham, P. Hollingworth, et al., *Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease.* Nat Genet, 2009. **41**(10). 1088-93.
3. Medina, D., L. DeToledo-Morrell, F. Urresta, et al., *White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study.* Neurobiol Aging, 2006. **27**(5). 663-72.
4. Braskie, M.N., N. Jahanshad, J.L. Stein, et al., *Common Alzheimer's disease risk variant within the CLU gene affects white matter microstructure in young adults.* J Neurosci, 2011. **31**(18). 6764-70.
5. Nucifora, P.G., R. Verma, S.K. Lee, et al., *Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity.* Radiology, 2007. **245**(2). 367-84.
6. Hoeft, F., N. Barnea-Goraly, B.W. Haas, et al., *More is not always better: increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome.* J Neurosci, 2007. **27**(44). 11960-5.