



Genetic Mutations in Prokineticin2 Affect Grey Matter Volume in Alzheimer's disease

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Abstract

Objective: To investigate how genetic variation in the PROK2 gene affects clinical, cognitive and neurobiological outcomes in subjects with or without Alzheimer's disease (AD). **Methods:** PROK2 data was imputed from an Illumina Human610-Quad BeadChip. Linear mixed models and voxel wise regression assessed PROK2's influence on cognitive, metabolic and neurological outcomes. **Results:** Minor allele carriers at rs1512353 had grey matter (GM) volume in the anterior cingulate gyrus, decreased glucose metabolism in the left post central gyrus, and lower MMSE scores. **Conclusions:** Genetic variation in the PROK2 gene may influence grey matter volume and cognitive function among aged Caucasian adults.

Background and Objectives

Prokineticin (PROK2), a protein involved in hypothalamic-pituitary axis regulation, has been shown to stimulate neurons to produce more mitochondria¹ which could be protective during Alzheimer's disease². The effects of functional genetic mutations in PROK2 on clinical, and neurobiological indices have yet to be characterized in humans. The primary objectives of this study was to 1) identify if genetic mutations in PROK2 are associated with Alzheimer's disease risk and 2) Investigate how PROK2 genomic mutations affect clinical and neurobiological outcomes in aged adults across the AD spectrum.

Materials & Methods

Using data from 756 aged Caucasian subjects from the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort, rs1512353 located on chromosome 3 was extracted from imputed Illumina Human610-Quad BeadChip data using Plink 2.0. Linear mixed modelling in SPSS 24 tested main effects of rs1512353 on cognitive, metabolic and neurological outcomes. Voxel-wise regression on 404 subjects with imaging data gauged associations with baseline glucose metabolism and GM volume. Covariates included age, gender, education, and baseline Alzheimer's disease diagnosis. Heterozygous and homozygous subjects were grouped together for analyses. Alpha was .05 for non-imaging and for imaging .005 and .05 corrected at the voxel and cluster levels.

Results

PROK2 rs1512353 minor allele carriers versus common allele carriers had decreased grey matter in a small cluster of 1120 voxels spanning the right and left postcentral gyrus (**Figure 1**). Minor allele carriers also had decreased glucose metabolism in a small cluster of 1340 voxels spanning the right and left anterior cingulum (**Figure 2**). Similarly minor allele carriers demonstrated worse cognitive scores on the MMSE (F=3.519, P=0.046, **Figure 3**).

Figure 1

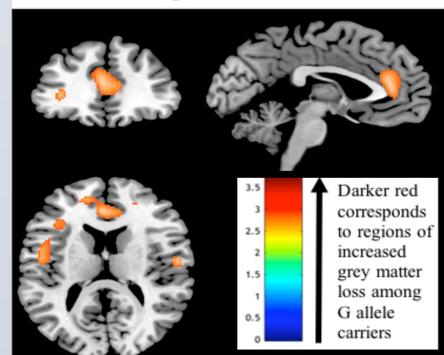


Figure 1: Brain regions where minor allele carriers had lower grey matter compared to non-carriers

Figure 2

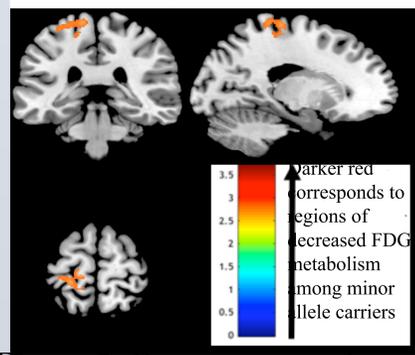


Figure 2: Brain regions where minor allele carriers had lower glucose metabolism compared to non-carriers

Figure 3

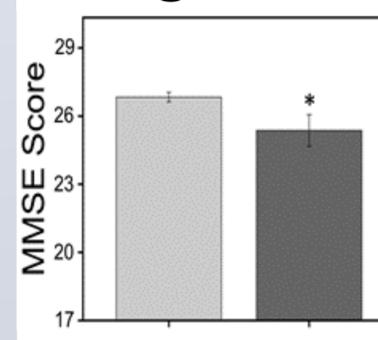


Figure 3: Difference in MMSE scores according to genotype
* = P < 0.05

Conclusions

This study demonstrates that common genetic variation in the PROK2 gene may influence brain structure but were not directly related to common clinical or biological markers commonly affected during Alzheimer's disease. These data indicate that PROK2 gene does significantly affect Alzheimer's disease risk, or affect classical biomarkers of Alzheimer's disease in the cerebrospinal fluid, but may affect cognitive function. Further in vitro investigation will further assess the role of PROK2 in regulating neuronal mitochondria that could potentially highlight novel pathways for therapeutic targets to treat age-related neurodegenerative diseases.

References

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2. Delrieu J, Ousset P, Voisin T, Vellas B. Amyloid beta peptide immunotherapy in Alzheimer disease. *Revue Neurologique*. 2014;170(12):739-748. doi:10.1016/j.neurol.2014.10.003.

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