Influence of Genetic Variants in Cognitive Ability

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Introduction

- Early detection of risk factors for cognitive impairment could help inform interventions to delay or slow down disease progression thereby increasing quality of life and decreasing costs associated with dementia care.
- The human genome has an extensive amount of variations among individuals and these differences could contribute to adaptation, phenotypic variability, disease susceptibility and environmental interactions.
- In this preliminary study, we examined whether genetic variations due to mutations are associated with cognitive and clinical markers.

Methods

- A sample size of 31 healthy elderly participants were selected and processed through the following measurements given in the flowchart below.

Objective measure of memory

- Telephone Interview of Cognitive Status (TICS)- a brief screening measure to assess cognitive ability in several domain
- TICS total score: Participants asked 13 questions with sub questions, score based on correct answers provided for each question
- Immediate word recall score (sensitive to cognitive aging): participants are read list of 10 words and asked to recall, score based on total words recalled

Self-report measure of cognitive functioning

- Patient reported outcomes information system (PROMIS)-Applied Cognition (consist of 8 items)
- Participants respond to each question on a scale from 1(not at all)-5 (very much)
- Scores for 8 items summed to create a total score (higher score better cognitive functioning)

Clinical biomarkers

- Blood work done to measure : Lipid Profile test (LDL, HDL, Triglyceride, Total cholesterol), fasting glucose, C-reactive protein
- Blood pressure (BP) - measurements taken after 5 minute rest period and averaged.
- Pulse pressure (PP)- calculated subtracting mean systolic BP from diastolic BP (Predictor for cardiovascular diseases).

Blood drawn from these participants (n=31) and genomic DNA isolated → Processed on next generation sequencing system (next seq) → Data imported to Illumina Variant Seq program in variant calling format (.vcf) → Analyzed for missense mutation in coding region using SIFT score

- Although several genes have been associated with cognitive impairments, most notably APOE, BDNF val66Met, SORL1, CLU, PICALM, BIN1, ABCA7, for the present study we focused on SORL1 (sortilin-related receptor 1).
- SORL1 plays a key role in trafficking amyloid β precursor protein (APP), thereby reducing amyloidogenic processing of APP (reduces amyloid load). Missense variants in SORL1 reduces its ability to mediate APP reduction in brain.
- Accumulation of amyloid β peptides in the form of plaques depends on the rate of production and clearance. Studies suggests these deposits cause neurotoxicity leading to cognitive deficits like dementia. Therefore, mutations in SORL1 could be a strong risk factor for neurocognitive disorders.

- Demographic, neuropsychological and clinical testing data are summarized in Table 1 along with genetic marker SORL1 value (based on SIFT (sorting intolerant from tolerant) score which predicts altered protein function due to amino acid substitutions, SIFT score ≤ 0.05 are deleterious, mean value calculated as present in 17 samples out of 31).

Table 1. Sample Description

	M (SD) or %
SORL1(n=17)	54.8
Demographic Parameters	
Age	63.9 (10.2)
Sex (%female)	61.3
Education (years)	16.9 (2.3)
Neuropsychological Parameters	
Applied cognition (n = 24)	29.9 (7.0)
TICS total (n=30)	35.1 (3.7)
TICS (Immediate word recall) (n=30)	5.63 (1.93)
Clinical Parameters	
Total cholesterol (n=27)	191.9 (39.7)
HDL (n=27)	61.4 (22.3)
LDL(n=27)	110.9 (28.7)
Triglycerides(n=27)	99.1 (47.2)
Pulse pressure (n = 28)	53.1 (16.1)

Analyses:

- Hierarchical regression analyses were used to explore the association between presence of one or more non-synonymous mutations in SORL1 and parameters listed in Table 1. Age was entered in the first step of the equation as a covariate and SORL1 was entered into the second step of the regression.

Results

- There was a significant ($p < .05$) negative association between immediate word list recall from TICS and non-synonymous mutations in SORL1 (Table 2).
- A significant ($p < .05$) positive correlation was obtained between pulse pressure of the participants and total number of non-synonymous mutations in SORL1 (Table 3).
- A significant ($p < .05$) negative correlation was obtained between applied cognition and total number of non-synonymous mutations in SORL1 (Table 4).
- SORL1 was not significantly ($p > .05$) associated with TICS total score, LDL, HDL, Triglycerides, or total cholesterol.

Table 2. Hierarchical regression analysis for the presence of non-synonymous mutations in SORL1 predicting immediate word list recall (n = 30); *$p < .05$.

	β	t	p
Step 1			
Age	-.329	-1.85	.076
$\Delta R^2 = .108$ F = 3.40			
Step 2			
Age	-.282	-1.69	.102
SORL1 binary	-.391	-2.35	.027*
$\Delta R^2 = .151$; F = 5.51*			

Table 3. Hierarchical regression analysis for number of non-synonymous mutations in SORL1 predicting pulse pressure (n = 28); *$p < .05$.

	β	t	p
Step 1			
Age	.364	1.99	.057
$\Delta R^2 = .133$; $\Delta F = 3.98$			
Step 2			
Age	.269	1.64	.113
SORL1 count	.480	2.93	.007*
$\Delta R^2 = .222$; $\Delta F = 8.58$*			

Table 4. Hierarchical regression analysis for number of non-synonymous mutations in SORL1 predicting applied cognition (n = 24); *$p < .05$.

	β	t	p
Step 1			
Age	-.018	-.085	.933
$\Delta R^2 = .000$; $\Delta F = .007$			
Step 2			
Age	.059	.305	.764
SORL1 count	-.479	-2.46	.023*
$\Delta R^2 = .223$; $\Delta F = 6.03$*			

Discussion

- The present study is part of pilot work. Preliminary analysis revealed a significant association of SORL1 with cognitive abilities, including memory recall and self-reported cognition. Significant associations were also found with pulse pressure, these relations are in concordance with literature. However, no significant associations were obtained with TICS total score, LDL, HDL, Triglycerides, or total cholesterol although theory suggests SORL1 association with lipid panel.
- SORL1 plays a central role in cholesterol metabolism and amyloid clearance; findings associating SORL1 with PP also suggest a vascular risk pathway. The amyloid deposits in the blood vessels lead to cerebral micro bleeds (chronic brain hemorrhages) which seems to stem from clinical conditions like hypertension. This causes white matter lesion; prior studies indicate correlation with poor memory performance and executive functioning (Felsky et al. 2013, Schuur et al. 2011).
- Future work to increase the sample size is planned along with use of latest human genome reference and advanced bioinformatics software programs for more accurate results.

References

Felsky et al. 2014. Molecular Psychiatry 19, 1125–1132.
Schuur et al. 2011. J Neurol Neurosurg Psychiatry 82(1), 41-44.

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