The Role of Haptoglobin Genotype on Cognition in African American Elderly with Type 2 Diabetes (T2D)

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Background

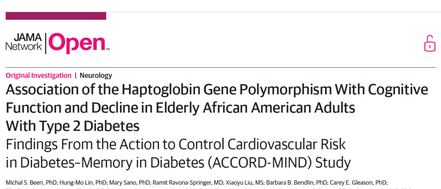
Type 2 Diabetes (T2D) is associated with ↑ risk of Dementia.
The prevalence for both conditions is alarmingly increasing.
The risk for both diseases is higher for African Americans.

Haptoglobin (Hp) is an antioxidant produced in the Liver. Its subtypes (1-1, 2-1, 2-2) have been linked to different health outcomes in the diabetic population: Hp1-1 is associated with increased risk of stroke and white matter hyper-intensities (WMH), Hp 2-2 with MI and greater mortality.

The longitudinal study Israel Diabetes & Cognitive Decline study (IDCD) on ~1000 T2D subjects found that:

- Hp1 carriers perform worse cognitively compared to the non-carriers[1]
- Among Hp1-1 diabetics, poor glycemic control (ie higher Hb-A1c) was associated with smaller hippocampal volume and worse cognitive function.[2]

Higher prevalence of Hp1-1 in people with **African American** descent (30% African American vs 14% in whites), raises the question whether Hp contributes to higher risk of dementia in African American population.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Association of the Haptoglobin Gene Polymorphism With Cognitive Function and Decline in Elderly African American Adults With Type 2 Diabetes
Findings From the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) Study

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Data on 466 African American/T2D patients from ACCORD-MIND study[3]

- Hp 1-1 subjects had worse cognition (MMSE) at baseline and declined faster.
- Hp 2-1m subtype (specific to African American subjects) was associated with better cognition at baseline and no decline.

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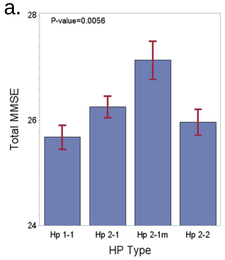
a.



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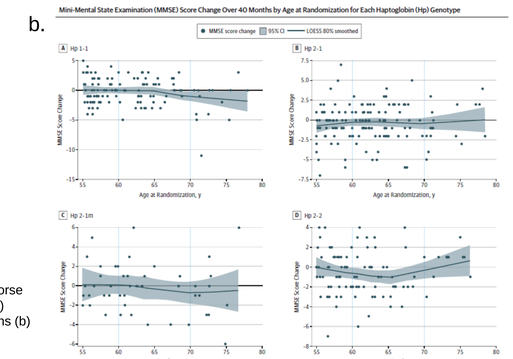

Figure 1. Hp1-1 subjects had worse cognitive function at baseline (a) and over the course of 40 months (b)

Objectives of the ADRC Pilot Study

1. Establish a directory of African American T2D patients
2. Explore the association between cognitive function and Hp subtypes among non-demented African American elderly with T2D. **Hypothesis**: Hp1-1 carriers will have poorer cognitive functioning compared to the other 2 genotypes (Hp 1-2, Hp 2-2).
3. Examine whether the association of Hp genotype with cognition is mediated by glycemic control. **Hypothesis**: Poor glycemic control will be more strongly associated with cognitive impairment among Hp 1-1 carriers than non carriers .
4. Explore the association of Hp and **Depressive symptoms**. **Hypothesis**: Hp1-1 genotype will be associated with higher reported Depressive symptoms

Methods

Participants (Target N= 60)

Diabetic African American, 65+, Exclude major neurological and psychiatric conditions

Assessments

- Assessment of 4 cognitive domains: Episodic Memory, Attention/Working Memory, Semantic Categorization/Language and Executive Function as well as a global composite of the 4 domains
- Blood Draws: Hp subtype, Apo E, Hb A1c
- Depression Assessment: Geriatric Depression Scale (GDS) and Hamilton Depression Rating Scale (HDRS)

Progress

Recruitment

- Clinic and community based approaches
- Data driven EMR search and pre-approval of PCPs
- Utilizing subjects from UDS and other studies
- Extending the study to the VA Health System
- **Updated census:** so far 17 have signed consent, 1 withdrew, and 2 were excluded

Obstacles

High exclusion rate due to stroke/ TIA
Low engagement of the Primary Physicians to approve out reach to the potential candidates
High rate of no shows

Discussion

Successful completion of the proposed study may contribute to identifying new targets for the intervention trials in dementia.
Determining the mechanism by which Hp 2-1m may confer a protective effect is particularly promising, as it could ultimately lead to therapies that protect against cognitive decline and dementia.

Future Directions

Haptoglobin

Compare the role of vascular function among different Hp subtypes (Doppler, MRI)
Comparing AD-related pathology among different Hp subtype
Longitudinal follow up of the subjects to assess trajectories of cognitive decline

Depression in diabetic patients

Subtypes of depression in T2D
Association of depression subtypes and apathy with cognitive function

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