Genetic Association Between Alzheimer's Disease and Cardiovascular Risk Factors

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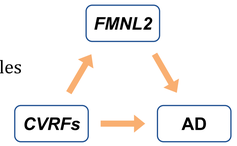
BACKGROUND

- Cardiovascular disease and dementia are major health problems for **African American** (AA) and **Caribbean Hispanic** (CH) individuals
- Alzheimer's Disease (AD) is **neurodegenerative** and 30-50% of patient deaths are accompanied by **cerebrovascular pathology**
- Four cardiovascular risk factors (CVRFs) frequently associated with AD are **hypertension, diabetes, heart disease, and body mass index** [1]
  - The interaction of genes and CVRFs is not fully known
    → No effective prevention or treatment
- Formin-like protein 2 (***FMNL2***)
  - important in regulating actin and microtubules
  - highly expressed in astrocytes
  - associated with CVRFs [1]
  - implicated in cerebrovascular pathology [2]



OBJECTIVES

- To understand the genetic association between cardiovascular risk factors and Alzheimer's Disease in African Americans and Caribbean Hispanics
- To identify **single nucleotide polymorphisms** (SNPs) in the ***FMNL2* gene** that interact with cardiovascular risk factors on Alzheimer's Disease

METHODS

- **CVRF score** was defined by the first principal component of the 4 CVRFs using Principal Component Analysis
  - Cumulative burden of the 4 CVRFs > single risk factor burden
- **Logistic regression** was fitted using the model:
  AD ~ SNP x CVRF Score + SNP + CVRF Score + Age + Sex + PC1 + PC2 + PC3

DATA

Table 1. Participant demographics included.

	African American	Caribbean Hispanic
N	978	3404
% AD	33%	51%
% Women	72%	68%
% Heart Disease	38%	23%
% Hypertension	82%	76%
% Diabetes	29%	31%
Mean BMI (s.d.)	28.21 (6.16)	26.89 (5.26)
Mean Age (s.d.)	79.76 (7.24)	75.27 (7.94)

Data from the Washington Heights–Inwood Columbia Aging Project (WHICAP).

RESULTS

Figure 1. Correlation matrix for heart disease, hypertension, diabetes, body mass index, age, and sex at last visit of African American and Caribbean Hispanic cohorts.

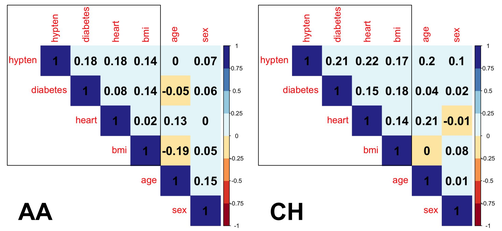


Table 2. Odds Ratios for SNP x CVRF interactions in *FMNL2* for African American and Caribbean Hispanic cohorts.

	OR	2.5%	97.5%	p-value	sig
CH rs7580023 (2:153334971)					
(Intercept)	0.014	0.00669	0.0281	<0.0001	***
SNP	0.993	0.855	1.152	0.922	
CVRF Score	0.881	0.826	0.940	1.38e-04	***
Age	1.056	1.046	1.066	<0.0001	***
Sex	1.183	1.067	1.312	0.00148	**
PC1	0.004	4.19e-05	0.445	0.0215	*
PC2	3.241	0.0331	322.9	0.615	
PC3	7.9e-06	9.76e-08	6.09e-04	1.00e-07	***
SNP:CVRF Score	**1.291**	**1.143**	**1.462**	**4.80e-05**	***
AA rs12693405 (2:153430606)					
(Intercept)	0.001	2.353e-04	0.00771	<0.0001	***
SNP	1.094	0.847	1.408	0.489	
CVRF Score	0.840	0.716	0.985	0.0320	*
Age	1.079	1.056	1.103	<0.0001	***
Sex	0.647	0.466	0.898	0.00930	**
PC1	2076.1	14.711	3.481e+05	0.00293	**
PC2	0.037	2.27e-04	5.242	0.198	
PC3	0.277	0.00142	45.847	0.628	
SNP:CVRF Score	**1.380**	**1.108**	**1.730**	**0.00452**	**

Significant result at α < (*) 0.05, (**) 0.01, (***) 0.001
OR = Odds Ratio, 95% Confidence Interval

Figure 2. Principal component plot for history of heart disease, hypertension, diabetes, and BMI at last visit of African American and Caribbean Hispanic cohorts.

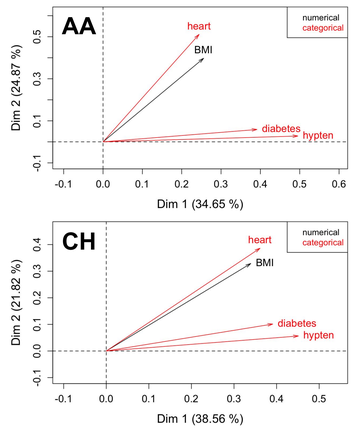
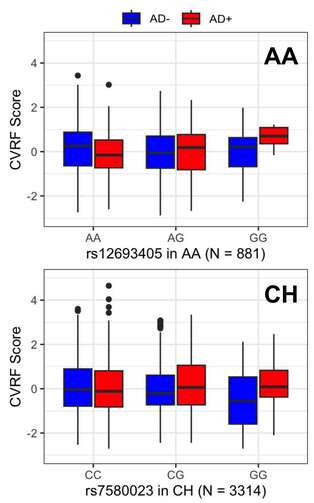


Figure 3. Boxplots of CVRF score by SNP in *FMNL2* and AD status.



DISCUSSION

- Figure 1 shows correlation among the CVRFs ranges from **0.02 to 0.18 in AA and 0.14 to 0.22 in CH.**
- Figure 2 shows the **principal component plot** for the 4 CVRFs.
  - Cumulatively, PC1 and PC2 explain approximately 60% of the variance.
  - For **PC1**, **hypertension** and **diabetes** had the highest contribution.
  - For **PC2**, **heart disease** and **BMI** had the highest contribution.
- Figure 3 shows that for each additional SNP allele, the **CVRF score significantly increases for AD cases** and **decreases for controls**.
- The `rs12693405` and `rs7580023` SNPs of the *FMNL2* gene have significant interactions with CVRF scores to modify AD risk. The association between CVRF scores and AD differed based on the *FMNL2* SNP genotypes.
  - AA `rs12693405` ↑ **major** allele (G instead of A), ↑ AD risk
  - CH `rs7580023` ↑ **minor** allele (G instead of C), ↑ AD risk
- Table 2 shows that `rs12693405` in AA and `rs7580023` in CH interacted with the CVRF score on AD.

CONCLUSION

- There is a genetic association between AD and CVRF.
- Understanding how genes and CVRFs interplay to influence AD risk will help to identify potential therapeutic targets to prevent or treat AD.
- More studies can be conducted to determine how other SNPs play a role on CVRF and the development of AD.

REFERENCES

1. Lee, A.J., Raghavan, N.S., Bhattarai, P. et al. (2022). FMNL2 regulates gliovascular interactions and is associated with vascular risk factors and cerebrovascular pathology in Alzheimer's disease. *Acta neuropathologica*, *144*(1), 59–79. doi.org:10.1007/s00401-022-02431-6
2. Hohman, T. J., Cooke-Bailey, J. N., Reitz, C. et al. (2016). Global and local ancestry in African-Americans: Implications for Alzheimer's disease risk. *Alzheimer's & Dementia*, *12*(3), 233–243. doi:10.1016/j.jalz.2015.02.012

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