Frequency of APOE in Hispanic Populations' Effect on Alzheimer's Disease and Inheritance

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Introduction

- **Alzheimer's Disease** (AD) is a Neurodegenerative disease (4) and is a terminal illness.
  - Common symptoms are memory loss, cognitive impairment (7), and loss of independence. Typical age of onset (AOO) is ±65 and has no cure.
- Risk factors are genetics, familial links, and environmental factors (Ex. education, diet, region) (6,7)
- **Tau** or MAPT is a common molecule associated with AD (7)
  - Found in microtubules
  - Stabilize cell/organelles
  - Creates NFTs by hyperphosphorylation
- **Amyloid-beta** associated with AD (6,7)
  - Forms from Amyloid Precursor Protein (APP)
  - Fatty membrane
  - Found in neurons
- **Apolipoprotein** (APOE) is a protein that is associated with cardiovascular health in the brain. The gene encodes for APOE protein which binds with lipids to form lipoproteins and regulate cholesterol (5)
  - Produced by microglia/astroglia
  - Macrophages/Liver
- Three alleles of APOE: ε2, ε3, ε4 (1)
  - ε4 cannot degrade Aβ well (causing plaques) and correlates with greater risk of AD (3)
  - ε3 is deemed neutral (1)
  - ε2 has protective values (1)
- APOE frequency differs based on ethnic group (3)
  - Hispanic populations have high chance of AD
  - Unknown frequency

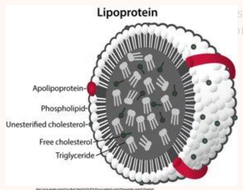
Purpose of Research

- Understand AD in Hispanic communities
  - How does APOE and its alleles affect inheritance?
- Understand implications of APOE alleles in AD
- How does APOE and other mutations of genes contributed to AD and other diseases?

Literature Review

- Amyloid Beta and Amyloid Precursor Protein (APP) form plaques
  - Liu et al, 2012
- Tau protein forms neurofibrillary tangles (NFTs) because of kinase and molecular zipper and kinks
  - Liu et al, 2012
- APOE E4 genetic risk factor for AD and obscures other loci
  - Jun et al, 2016
- Patients with E4 allele had greatest diagnosis of AD
  - Berlau et al, 2009
- APOE E4 and TMEM106B interact to further progress AD
  - Jun et al, 2016
- Hispanic communities face high risk of AD and dementia
  - Blue et al, 2019

https://neurosciencenews.com/neuroscience-terms/tau-tangles/



- E4 allele is weaker in Caribbean Hispanics, implicating genetic variation in AD risk
  - Blue et al, 2019
- Variants of p.Gly206AlA, GRN, PSEN1, PSEN 2, MAPT genes exist influencing AD and FTD
  - Lee et al, 2014

Gap in Research

- Cause of AD is unknown
- Hispanic populations are under researched in studies and primary participants are of Northern European descent
- APOE alleles and specific variants are not well understood with AD and the specific implications they have on disease progression

Hypothesis

Hispanic populations will have a lower frequency of APOE and the alleles will not have a massive impact on AD progression.

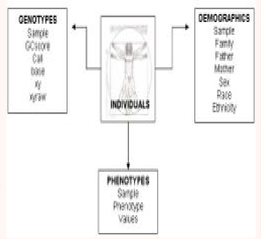
Purpose
- Understand APOE in Hispanic communities
- Identify risk APOE poses to ethnic group

Goals
- Measure frequency of APOE in CU Hispanics and NIALOAD Europeans
- Measure effect of APOE in both ethnic groups

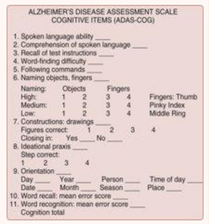
Limitation
- Sample size
- Lack of uniformity in AD symptoms

Methods

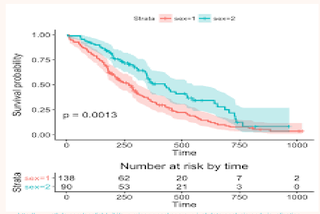
- Database of Genotypes and Phenotypes for genomic data is needed(12)
  - Columbia University Study of Caribbean Hispanics with Familial and Sporadic Late-Onset AD (CU Hispanics)
  - National Institute on Aging's Late-Onset Alzheimer's Disease Europeans (NIALOAD Europeans)
  - Controls (Provided by NIALOAD/CU databases)



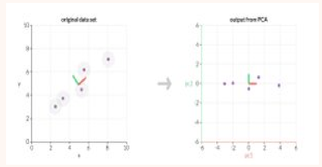
- Consent form distributed for use of personal data (1-16)
- Select individuals based on criteria for AD (13)
- Neurological/Neuropsychological exams (14)
- Chosen based on type of AD (16)
  - Sporadic: Occurred without familial relation
  - Familial: Runs throughout family
- Individuals' AOO ≥65 (4)
  - Any age lower is Early-Onset AD
- Filter based on essential fields (2,7,8,14)
  - Ex: Education, Region,
- Past research used at least 800 participants



https://www.sciencedirect.com/topics/medicine-and-dentistry/alzheimer-disease-assessment-scale



http://www.sthda.com/english/wiki/survminer-r-package-survival-data-analysis-and-visualization



- Cox proportional hazard regression analysis (6, 7, 15)
  - Models adjusted to alleles
  - Survival Package R
- Kaplan-Meier Curve (7,12)
  - Estimates effects of alleles
  - Survival Package R
- Estimate ancestry proportions (5,6,14)
  - Softwares necessary; Ex. Shapeit2, RFMix
  - Requires reference data
  - Around 19th Chromosome
- Case control analyses (16)
  - GENESIS package
- Principal component analysis (7,15)
  - Looks for relation amongst participants

Anticipated Results

Based off of analyses of CU Hispanics and NIALOAD Europeans, frequency of APOE was measured.

Frequency of APOE

NIALOAD EUROPEANS

Table 1
Description of the data

Summary statistic	NIALOAD Europeans
N_{total}	3028
$N_{affected}$	1238
$N_{markers}$	592,126
$Age_{affected}$	73.28 (48-96)
$Age_{at\text{-}risk}$	69.37 (42-103)
%Female	62%
APOE E2 freq	5%
APOE E3 freq	62%
APOE E4 freq	32%

Lee et al., 2008

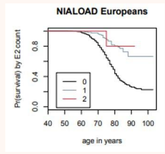
CU HISPANICS

Table 1
Description of the data

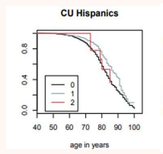
Summary statistic	CU Hispanics
N_{total}	3067
$N_{affected}$	1329
$N_{markers}$	904,966
$Age_{affected}$	74.84 (30-100)
$Age_{at\text{-}risk}$	73.17 (35-100)
%Female	66%
APOE E2 freq	6%
APOE E3 freq	74%
APOE E4 freq	21%

Lee et al., 2008

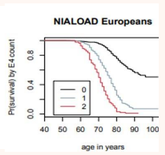
Using Kaplan-Meier Curves, the effects of the alleles were also measured.



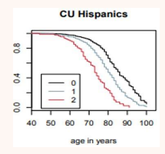
Lee et al., 2008



Lee et al., 2008



Lee et al., 2008



Lee et al., 2008

Discussion

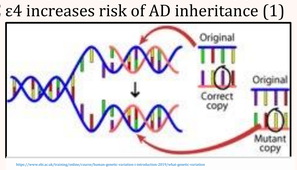
CU Hispanics had less APOE frequency

NIALOAD Europeans had greater APOE frequency

APOE ε2 increase AOO for both ethnic groups

APOE ε4 reduced AOO for both ethnic groups

- APOE has weaker effect in Hispanic populations based on the lower frequency of the alleles measured by the analyses. (9)
  - Indicates potential variants of other genes may be an underlying cause of AD and APOE does not have strong effects on Hispanic populations.
- Variants can be genes, ancestry, etc. There are several other factors that can be implicated in the development of AD in such communities (5)
  - Local ancestry and where one may have grown up, along with the environment plays a role
  - Missense variants or the replacement of a nucleotide, changing the codon, and thus, the amino acid coded for
  - MAPT, GRN, PSEN1, p.Gly206Ala, etc. are all examples of other genes and variants implicated with AD in past research
- Environmental Factors (11)
  - Education: Higher education is linked to lessen chance of inheriting AD
  - Diet: Depending on habits and if nutrient-rich foods are included in diet consistently influences chances.
  - Region: Local ancestry is correlated with region and development of AD.
- Implicates additional coding/variation for AD risk factors (6)
- Supports past research with European participants (4)
- Supports APOE ε2 may have protective values (1)
- Supports APOE ε4 increases risk of AD inheritance (1)



https://www.ebi.ac.uk/training/online/course/human-genetic-variation-i-introduction-2019/what-genetic-variation

Significance

- This research is impactful on research in AD specifically in Hispanic communities
  - Surges in AD are occurring in Hispanic populations(5)
  - Research gives insight on specific alleles' effect on AD
  - Identifies new areas of focus for AD research
  - Opens up discussion on other ethnic groups risk of AD

Conclusion

Hypothesis
Hispanic populations will have a lower frequency of APOE and the alleles will not have a massive impact on AD progression.

Purpose
Investigate the impact and frequency of APOE alleles in Hispanic populations compared to European populations

Results
CU Hispanics has lower APOE frequency than Europeans; APOE alleles differ in AOO

Significance
APOE alleles do not play significant role in AD inheritance for Hispanics; variants may be underlying cause

Future Research

- Research into variants that may have effects on AD development
- Investigate environmental factors further and understand which creates a higher risk of AD
- Research other "at-risk" ethnic groups and understand if APOE affects risk
- Further knowledge of APOE alleles effects and functions in the brain and AD


https://www.ucsfmemoryandaging.org/news-updates/advances-in-neurodegenerative-disorders-for-neurological-conditions

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