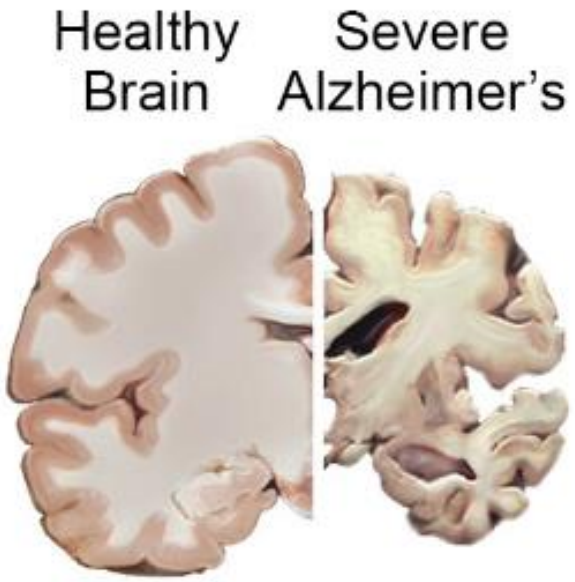
Frequency of APOE in Hispanic Populations' Effect on Alzheimer's Disease and Inheritance

Presentation and Research by: Ananya Govindarajan

Introduction:

Introduction:

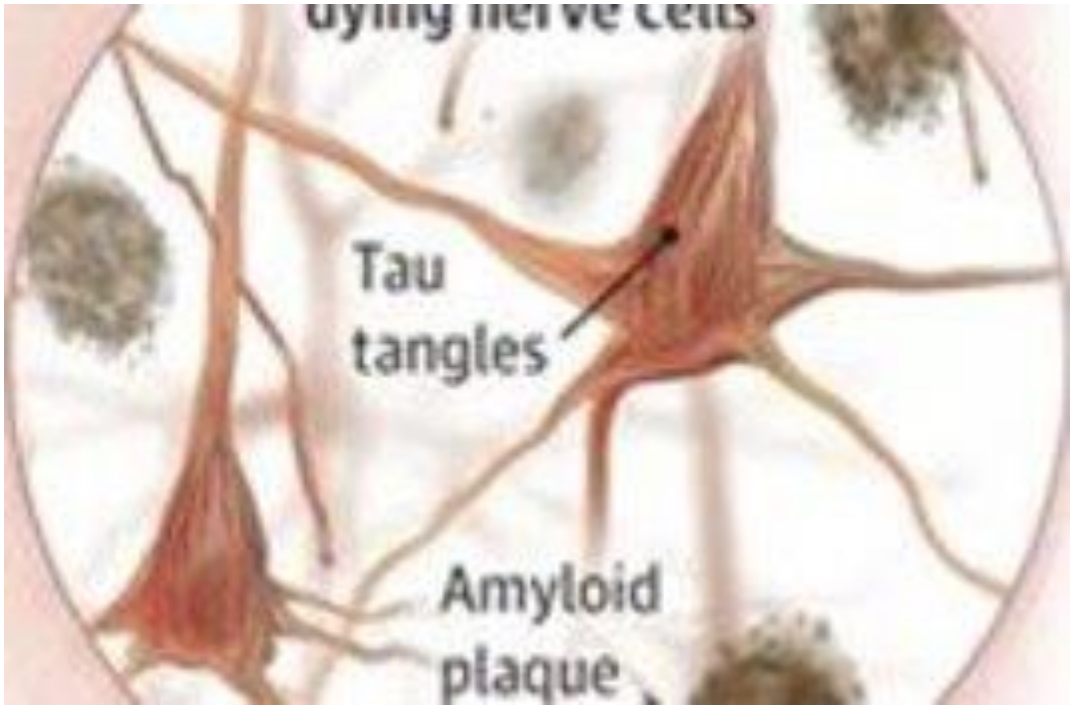
- Alzheimer's Disease (AD) (4)
  - Neurodegenerative disease
  - Terminal illness
  - Memory loss
  - Loss of independence
  - Cognitive impairment (7)
- Age of Onset: ±65
- No cure



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.nia.nih.gov%2Fhealth%2Falzheimers-disease-fact-sheet&psig=AOvVaw3EbKMlbDcUcig6qYv6RvWN&ust=1583736379493000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCJDlv_WjiugCFQAAAAAdAAAAABAD

Introduction:

- Risk factors (6)
  - Genetics
  - Familial links
  - Environmental
- Tau (MAPT) (6,7)
- Amyloid-Beta (Aβ) (6,7)



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

Introduction:

Roles of Aß (8)

- Forms from Amyloid Precursor Protein (APP)
- Fatty membrane
- Found in neurons

Roles of MAPT (8)

- Found in microtubules
- Stabilize cell/organelles
- Creates NFTs by hyperphosphorylation

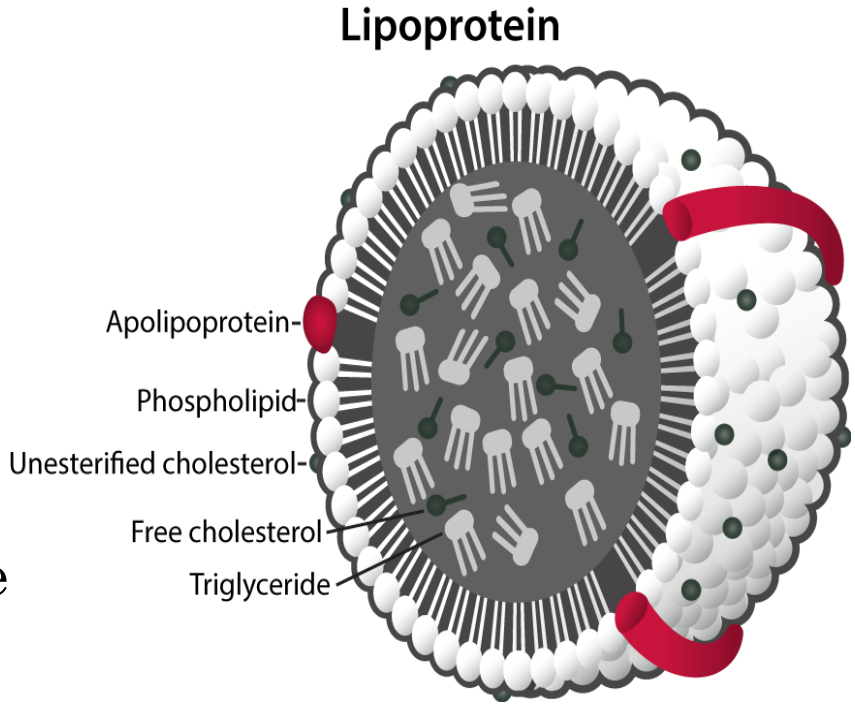
Introduction:

Genetic Risk:

- **Apolipoprotein E (APOE) (5)**

  Cardiovascular health

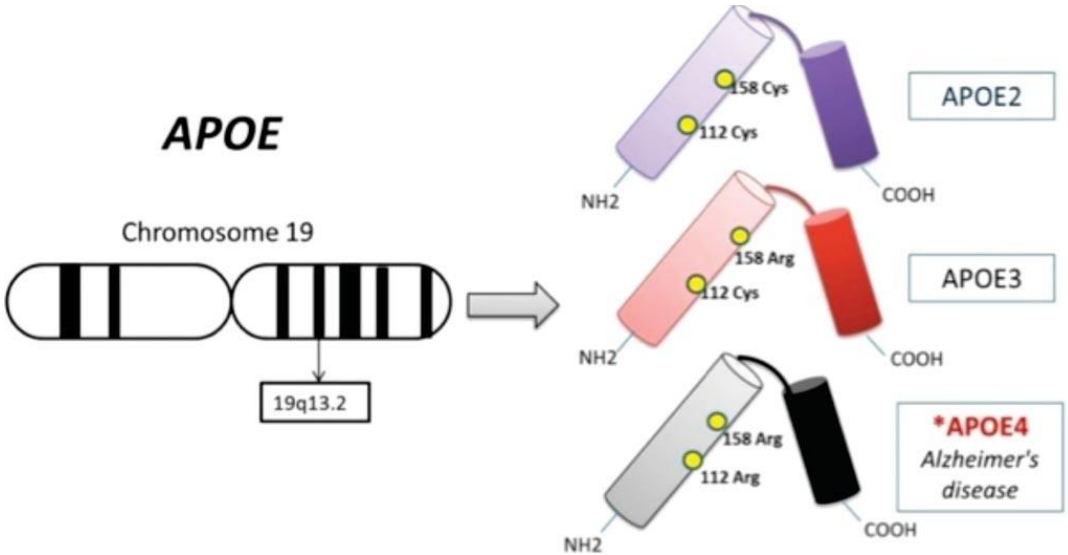
  - Encodes for APOE protein
  - Binds with lipids
  - Forms lipoproteins/regulate cholesterol
  - Produced by microglia/astroglia
  - Macrophages/Liver



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.mabtech.com%2Fknowledge-center%2Fapplied-research%2Fapolipoproteins&psig=AOvVaw2PG4PZ2oKsH6-GHlPiK69A&ust=1583765343722000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCNiG8-ePi-gCFQAAAAAdAAAAABAD

Introduction:

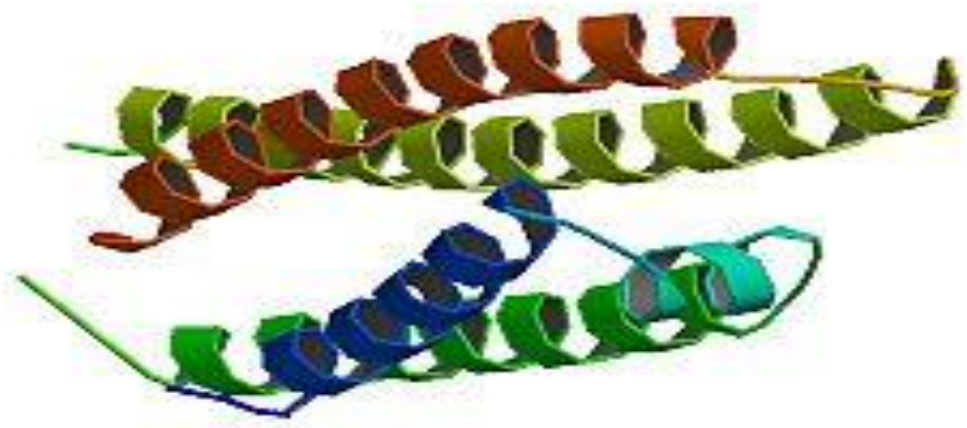
- Alleles: **ε2, ε3, ε4 (1)**
  - **ε4** is most researched
    - Greater risk for AD
    - No causitive relationship
  - **ε3** most common allele
  - **ε2** protective properties



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.labmedica.com%2Fmolecular-diagnostics%2Farticles%2F294778461%2Falzheimer-disease-stratified-by-apoe-genotype.html&psig=AOvVaw3V8N8gkL3frDZTS2TVZS4E&ust=1583766023234000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCKCX2KuSi-gCFQAAAAAdAAAAABAF

Introduction:

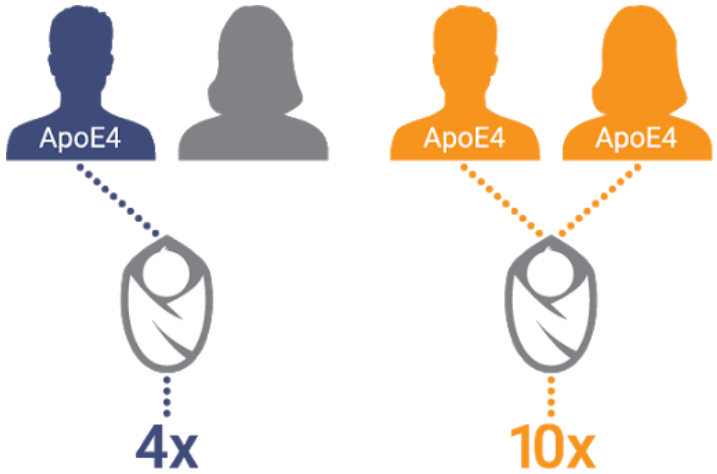
- APOE ε4 (3)
  - Greater risk for AD
  - Cannot degrade Aß well
  - ε2 and ε3 can degrade Aß
  - Linked to plaques



https://www.google.com/url?sa=i&url=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FApolipoprotein_E&psig=AOvVaw1MM_58zmhVQcP7EQ5VNrS4&ust=1583766330415000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCOjpxr6Ti-gCFQAAAAAdAAAAABBe

Introduction:

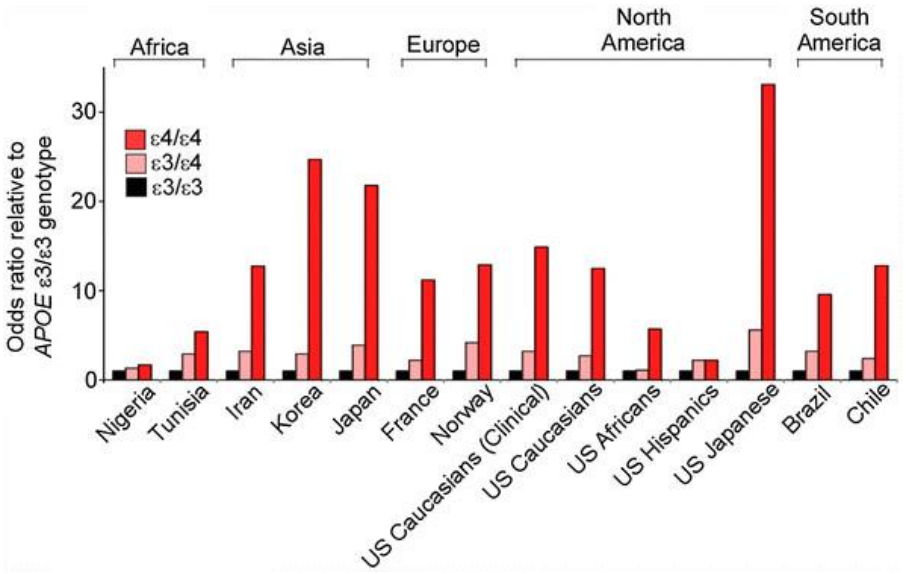
- APOE differs in ethnic groups (3)
- Nigerian/African groups report (3)
  - High APOE frequency
  - Low cholesterol
  - Low chance of AD



https://www.google.com/url?sa=i&url=http%3A%2F%2Fwww.myapoe.com%2Fapoe-and-alzheimers%2F&psig=AOvVaw1MM_58zmhVQcP7EQ5VNrS4&ust=1583766330415000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCOjpxr6Ti-gCFQAAAAAdAAAAABBl

Introduction:

- Caucasian and Japanese groups (3)
  - High cholesterol
  - Moderate frequency of APOE
- Hispanic groups (3)
  - Under researched
  - Estimate: low levels of APOE

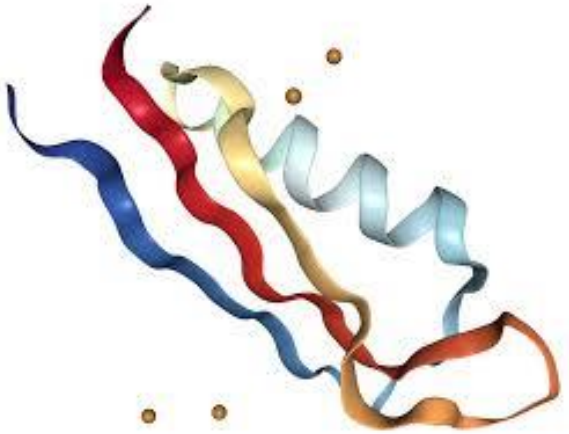


https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.researchgate.net%2Ffigure%2FThe-relative-odds-ratios-for-Alzheimers-disease-development-according-to-the-allelic_fig2_304324520&psig=AOvVaw1XJBZYprByizNi7kZBNQnh&ust=1583767216308000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCMC01OaWi-gCFQAAAAAdAAAAABAD

Literature Review:

Literature Review:

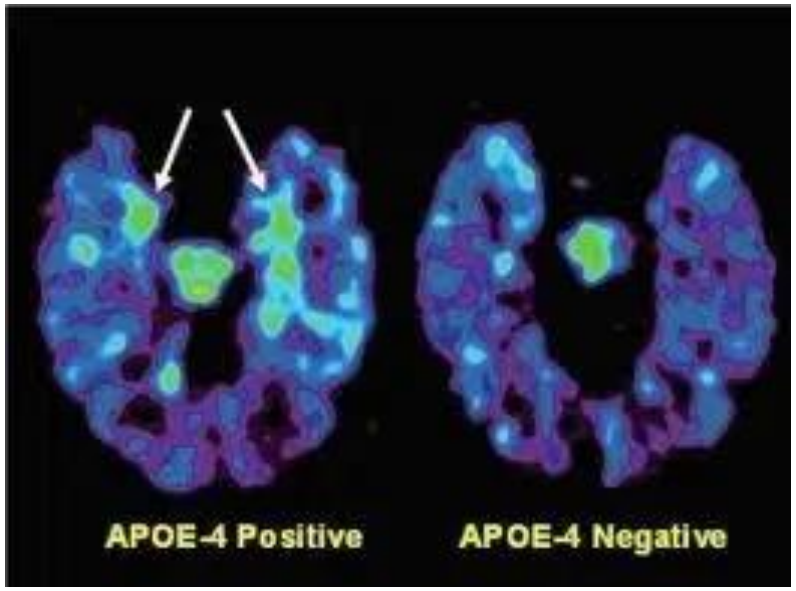
- Tau protein forms neurofibrillary tangles (NFTs) because of kinase and molecular zipper and kinks
  - Liu et al, 2012
- Amyloid Beta and Amyloid Precursor Protein (APP) form plaques
  - Liu et al, 2012
- Loci implicated in AD are ADAM10, WWOX, IQCK, ACE, APP
  - Kunkle et al, 2019



https://www.sinobiological.com/resource/app-protease-nexin-ii/proteins

Literature Review:

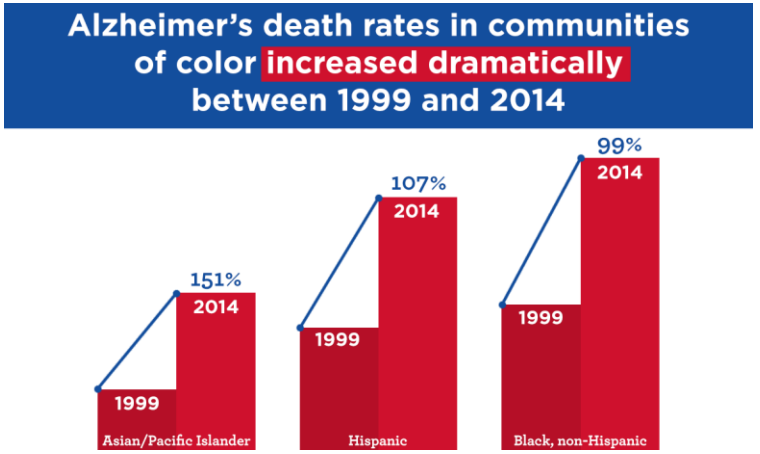
- APOE E4 genetic risk factor for AD and obscures other loci
  - Jun et al, 2016
- APOE E4 and TMEM106B interact to further progress AD
  - Jun et al, 2016
- Patients with E4 allele had greatest diagnosis of AD
  - Berlau et al, 2009



https://genesandinheritancr.wordpress.com/2011/09/20/inheriting-the-apoe-e4-gene-and-what-it-means/

Literature Review:

- Hispanic communities face high risk of AD and dementia
  - Blue et al, 2019
- 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



https://www.usagainstalzheimers.org/networks/latinos

Gap in the Research:

- Cause of AD is unknown
- Hispanic populations are underresearched in studies
- APOE alleles and specific variants are not well understood with AD

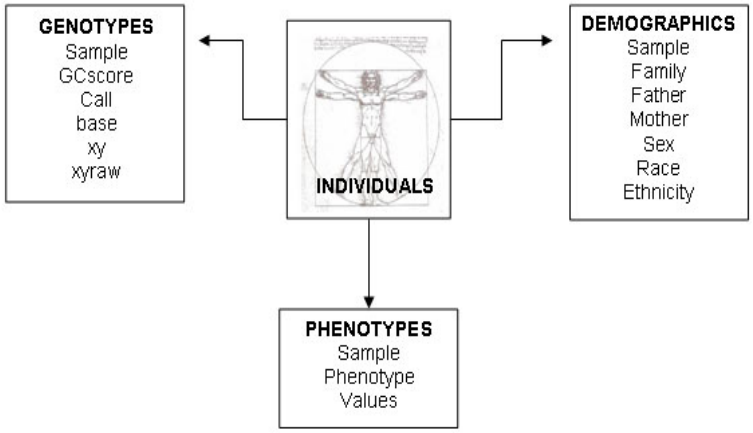
Goal of Research:

- 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?

Methodology:

Methodology:

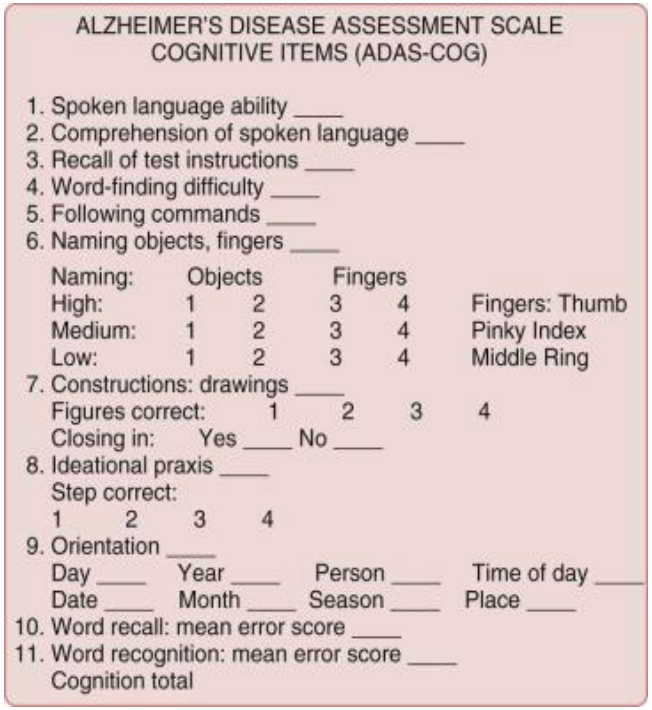
- Database of Genotypes and Phenotypes (12)
  - Columbia University Study of Caribbean Hispanics with Familial and Sporadic Late-Onset AD (CU Hispanics)
  - National Institute on Aging's Late-Onset Alzheimer's Disease Europeans (NIALOAD Europeans)
  - Controls (Provided by NIALOAD database)
- Consent form distributed (1-16)



https://www.researchgate.net/figure/Data-model-for-genotype-phenotype-and-demographic-data-Data-model-of-the-main-database_fig2_5465760

Methodology:

- Select individuals based on criteria for AD (13)
- Neurological/Neuropsychological exams (14)
- Chosen based on type of AD (16)
- Sporadic
  - Familial
- Individuals' AOO ≥65 (4)
- Filter based on essential fields (2,7,8,14)
  - Past research used at least 800 participants



ALZHEIMER'S DISEASE ASSESSMENT SCALE
COGNITIVE ITEMS (ADAS-COG)

1. Spoken language ability ____
2. Comprehension of spoken language ____
3. Recall of test instructions ____
4. Word-finding difficulty ____
5. Following commands ____
6. Naming objects, fingers ____

Naming:	Objects		Fingers		
High:	1	2	3	4	Fingers: Thumb
Medium:	1	2	3	4	Pinky Index
Low:	1	2	3	4	Middle Ring

7. Constructions: drawings ____
   Figures correct: 1 2 3 4
   Closing in: Yes ____ No ____
8. Ideational praxis ____
   Step correct:
   1 2 3 4
9. Orientation ____
   Day ____ Year ____ Person ____ Time of day ____
   Date ____ Month ____ Season ____ Place ____
10. Word recall: mean error score ____
11. Word recognition: mean error score ____
    Cognition total

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

Methodology:

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

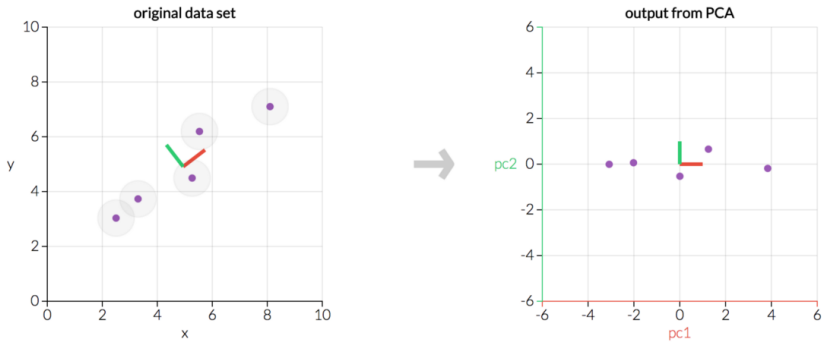
Methodology:

Case control analyses (16)

- GENESIS package

Principal component analyses (7,15)

- Looks for relation between participants



https://towardsdatascience.com/a-one-stop-shop-for-principal-component-analysis-5582fb7e0a9c?gi=9ea73f3016cc

Anticipated Data and Results:

Anticipated Data and Results:

Studies indicate lower frequencies of APOE ε2 and ε4 frequency in Hispanic participants (1)

ε2 increased AOO in both groups (9)

ε4 decreased AOO both groups (9)

ε4 increased risk substantially for Europeans (9)

Anticipated Data and Results:

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

APOE frequency is very prominent in European participants, indicating an effect on AD and inheritance

Anticipated Data and Results:

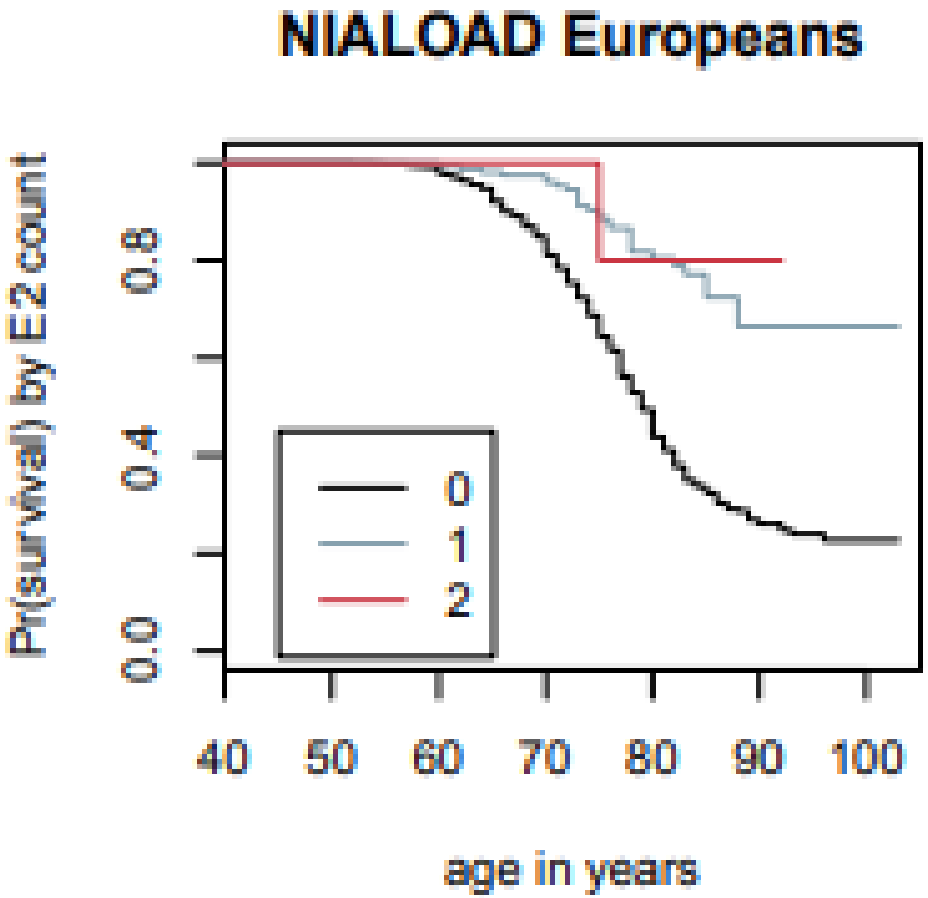
Table 1
Description of the data

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

Generally, lower numbers for frequency of APOE gene

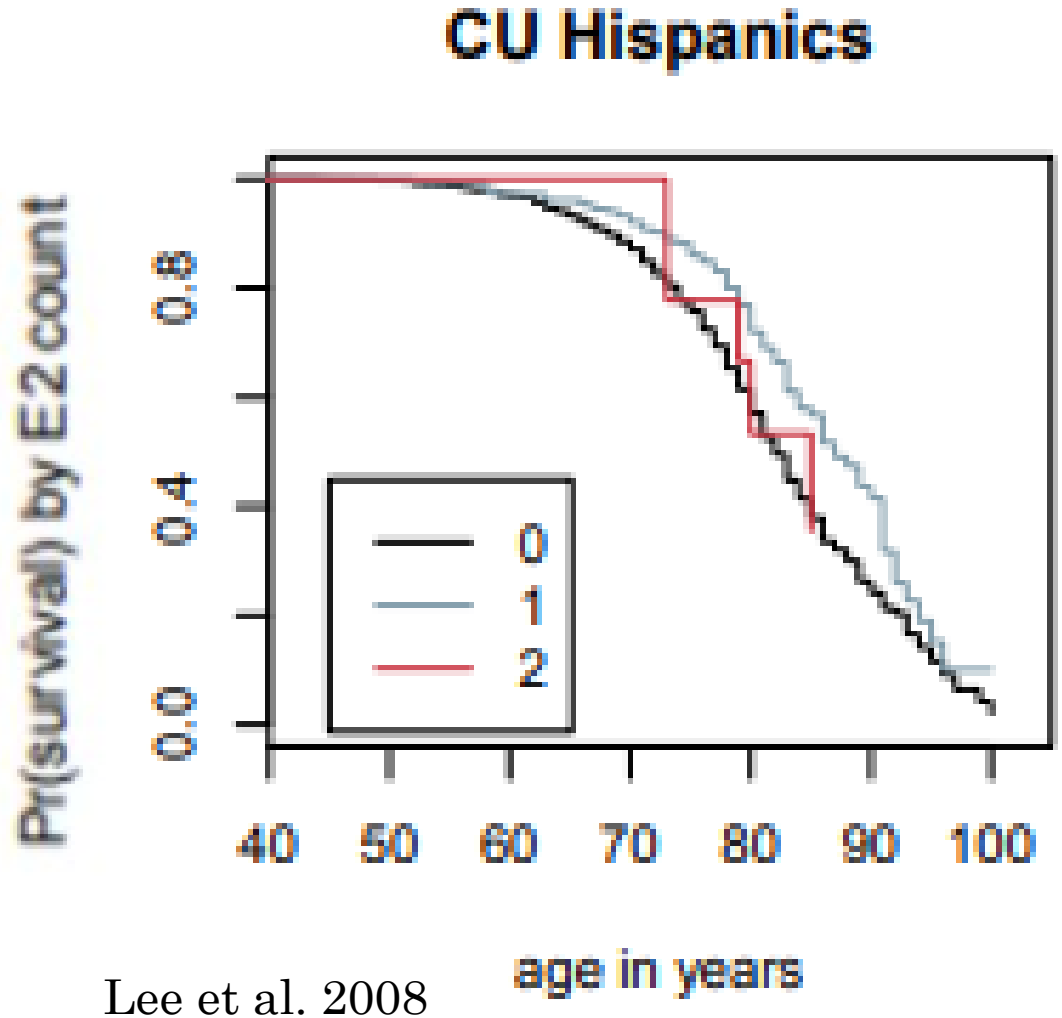
Anticipated Data and Results:



Kaplan-Meier survival curves used to assess the effect of gene on individual ethnic group and inheritance

Lee et al. 2008

Anticipated Data and Results:



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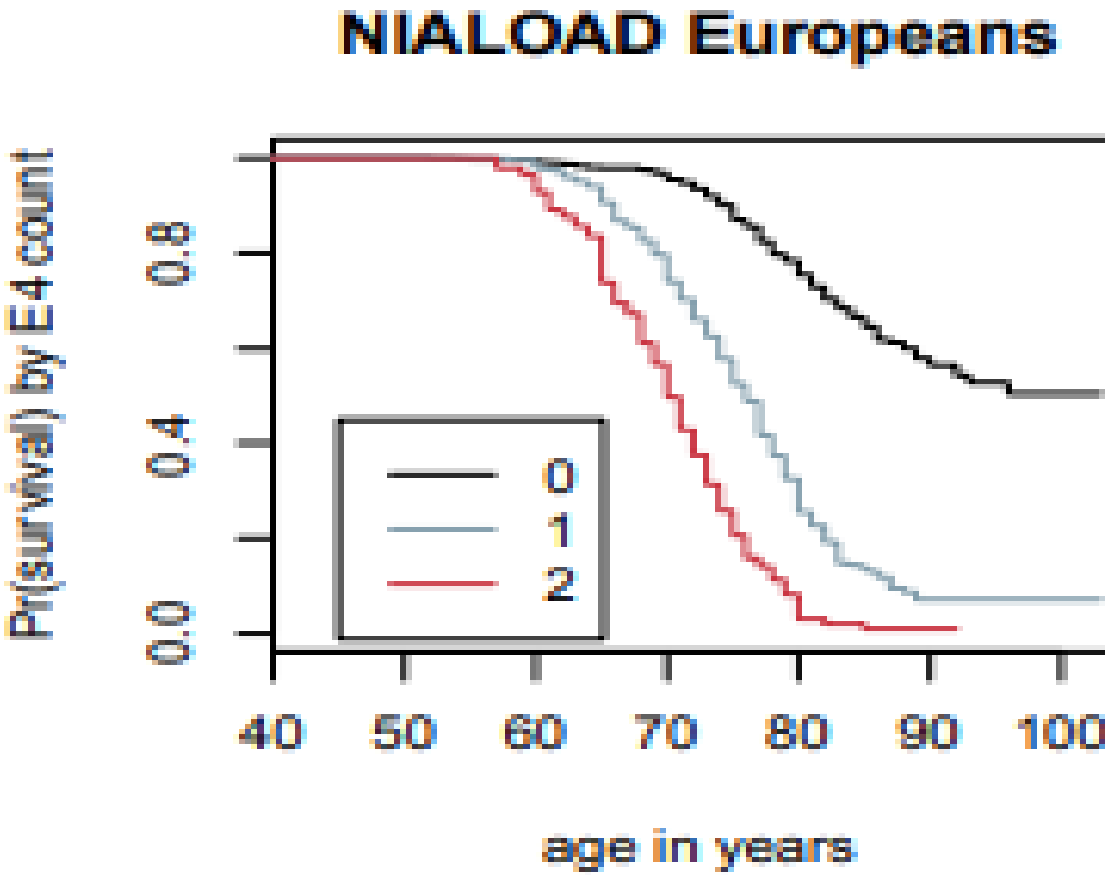
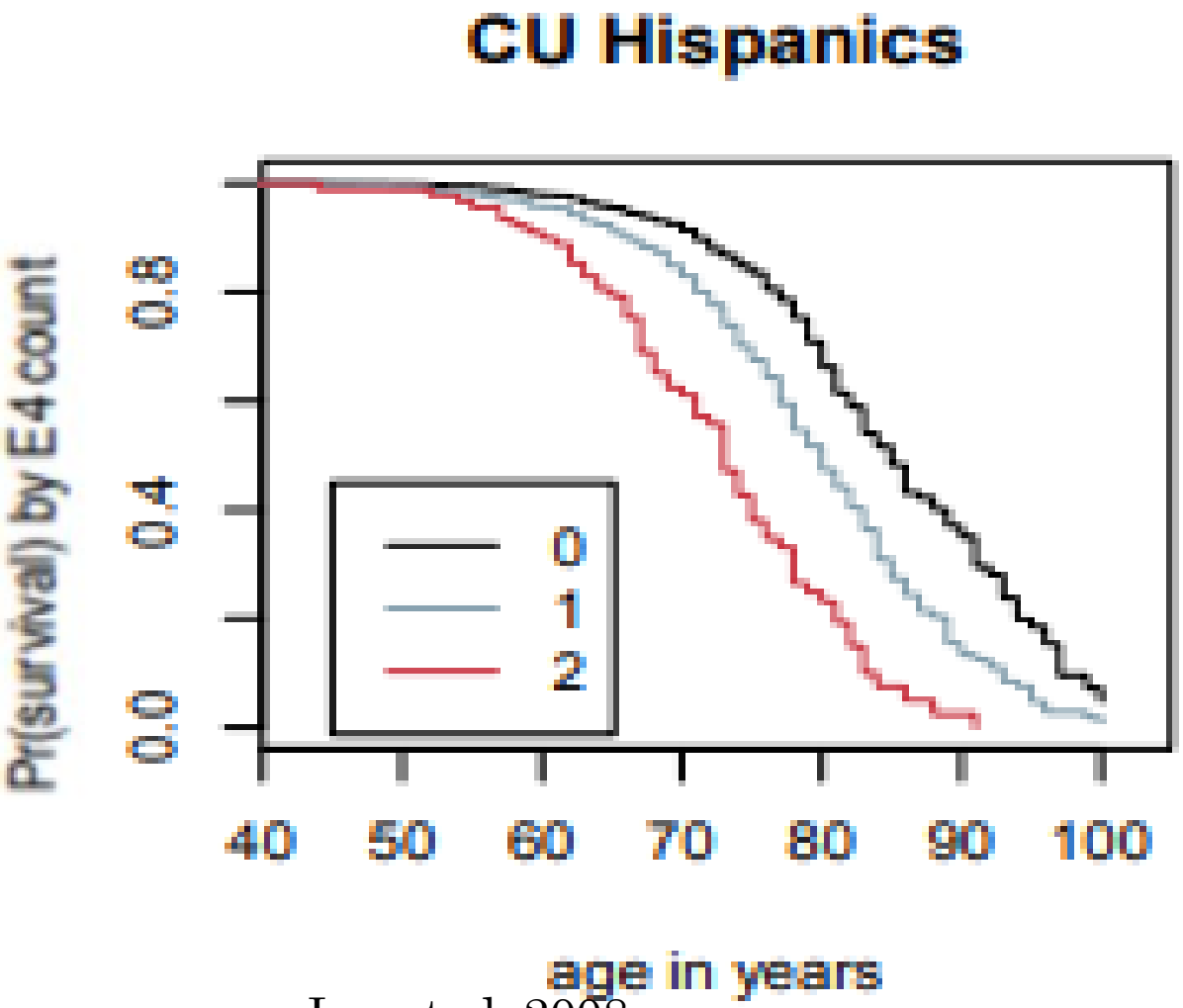


Lee et al. 2008

Kaplan-Meier survival curves used to assess the effect of gene on individual ethnic curve and inheritance

Anticipated Data and Results:



Lee et al. 2008

Kaplan-Meier survival curves used to assess the effect of gene on individual ethnic group and inheritance

Discussion:

Discussion:

CU Hispanics had less APOE frequency

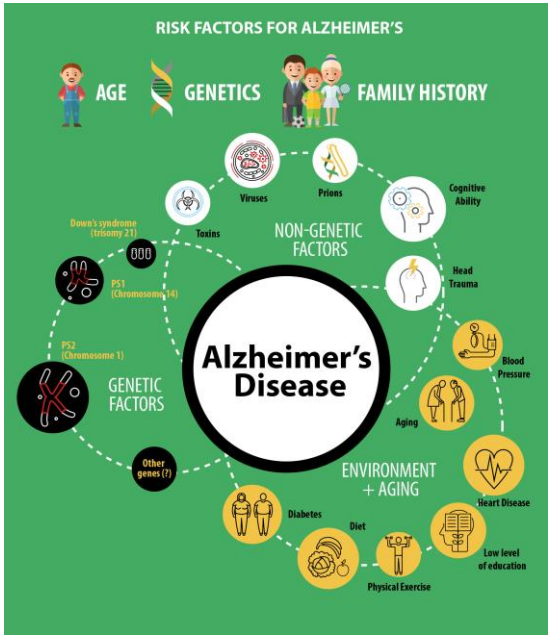
NIALOAD Europeans had greater APOE frequency

APOE ε2 increase AOO for both ethnic groups

APOE ε4 reduced AOO for both ethnic groups

Discussion:

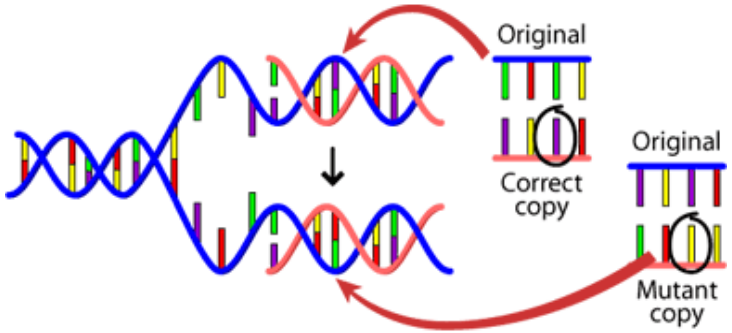
- APOE has weaker effect in Hispanic populations (9)
  - Indicates potential variants
- Variants can be genes, ancestry, etc. (5)
  - Local ancestry
  - Missense variants
  - MAPT, GRN, PSEN1, p.Gly206Ala, etc.
- Environmental Factors (11)
  - Education
  - Diet
  - Region



https://www.kindlycare.com/alzheimers-risks-causes-prevention/

Discussion:

- 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

Conclusion:

Conclusion:

AD is rising in Hispanic communities

No cure for AD

APOE alleles correlated with AD

Most studies use European-descent

Cause of surge in Hispanic communities is unknown

https://www.usagainstalzheimers.org/networks/latinos

Conclusion:

- **Purpose**: Investigate effect of APOE alleles and frequency in Hispanic communities
- **Methods**: Genotype/Phenotypes databases, regression analysis, ancestral estimates
- **Results**: CU Hispanics has lower APOE frequency than Europeans; APOE alleles differ in AOO
- **Conclusions:** APOE alleles do not play significant role in AD inheritance for Hispanics; variants may be underlying cause

Future Research:

- Research into variants
- Investigate environmental factors further
- Research other "at-risk" ethnic groups
- Further knowledge of APOE alleles effects

https://www.uclahealth.org/physiciansupdate/advances-in-neurogenetics-opens-window-to-rare-neurological-conditions

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  - Affiliation and Laboratories
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- Science Research Peers
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