

Cannabis and Health

Module 12: Neurocognitive/Brain Disorders Part II

Lecture 3: Etiology of Parkinson's Disease and
Alzheimer's Disease

Etiology: Alzheimer's

- The causes of Alzheimer's disease are poorly understood
- Amyloid Hypothesis: AD is caused by beta-amyloid ($A\beta$) plaques
 - Accepted by majority of researchers but, not conclusively established
 - $A\beta$ peptides underlie neuronal death in AD
 - $A\beta$ peptide levels are correlated with the presence of cholesterol in the brain
 - $A\beta$ contributes to cerebrovascular lesions and is neurotoxic

Etiology: Alzheimer's

- Amyloid Hypothesis: AD is caused by beta-amyloid ($A\beta$) plaques

- Brains of healthy controls and AD are differentiated by $A\beta$

A: healthy controls

B: low $A\beta$

C: medium $A\beta$

D: high $A\beta$

E: Alzheimer's

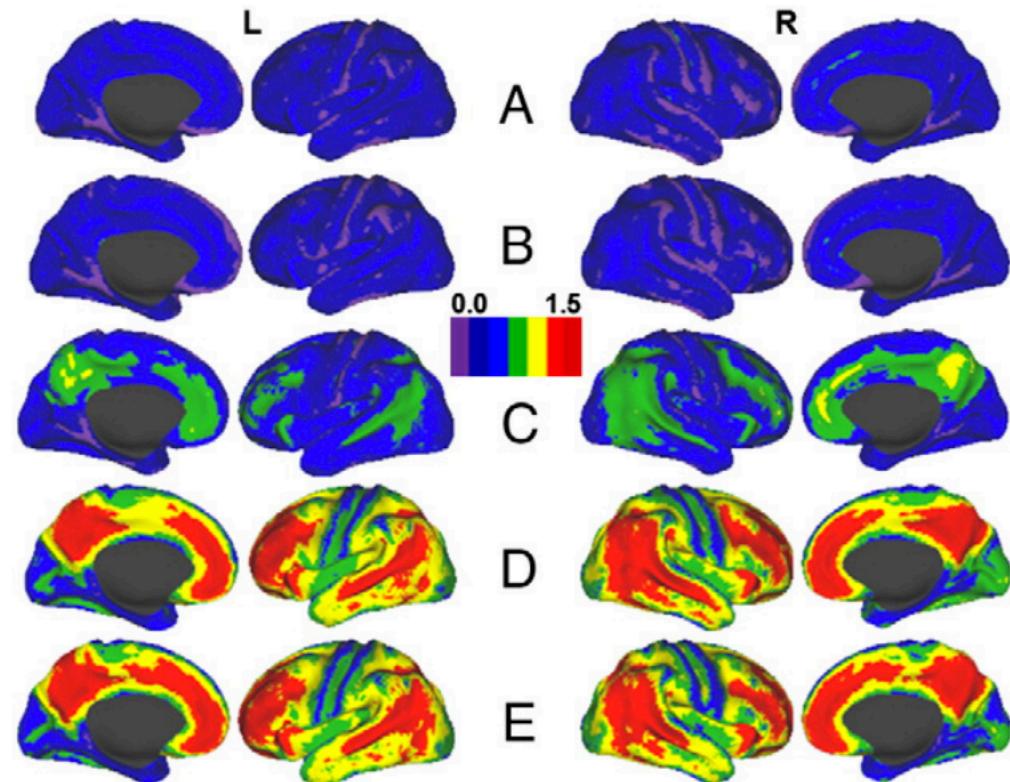


Review

PET amyloid-beta imaging in preclinical Alzheimer's disease[☆]

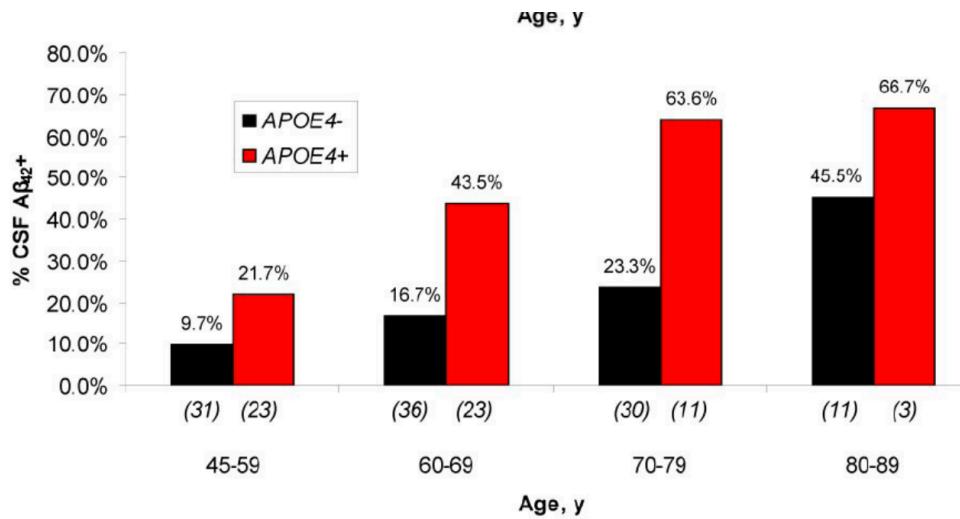
Andrei G. Vlassenko ^{a,c}, Tammie L.S. Benzinger ^{a,c}, John C. Morris ^{b,c,*}

PET Tracer of $A\beta$



Etiology: Alzheimer's

- 60-70% of the risk is attributed to genetics
 - Probably many genes involved.
- The Apolipoprotein E gene (APOE, E4 variant) is the largest known genetic risk factor for AD
 - APOE enhances break-down of A β
 - Vulnerability to AD in individuals with that gene variation



Morris et al., 2010, *Ann Neurol*

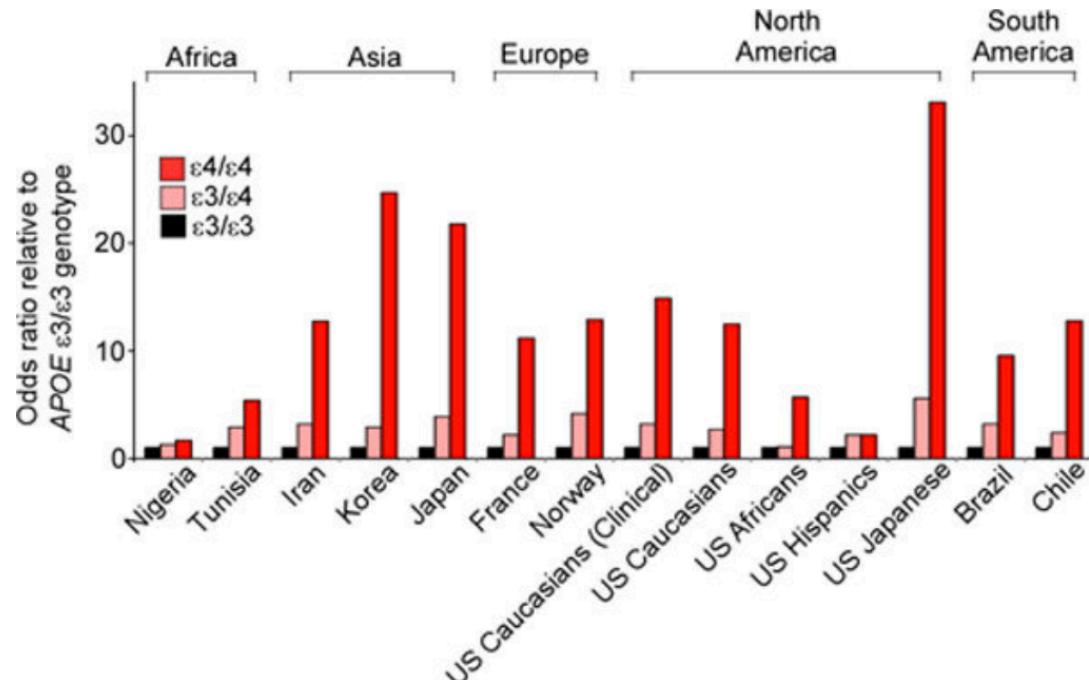
Etiology: Alzheimer's

CNS Drugs. 2016 September ; 30(9): 773–789. doi:10.1007/s40263-016-0361-4.

Apolipoprotein E as a Therapeutic Target in Alzheimer's disease: A Review of Basic Research and Clinical Evidence

Yu Yamazaki, Meghan M. Painter, Guojun Bu, and Takahisa Kanekiyo

- APOE risk varies by population
 - Nigerians have the highest frequency of the APOE E4 allele, but AD is rare among them
 - May be due to their low cholesterol diets
 - Caucasian and Japanese carriers of 2 E4 alleles have a 10-30x greater risk AD by age 75



Etiology: Alzheimer's

- APOE risk varies by population
 - The risk conferred by the APOE gene also differs by sex (F > M)
 - Premorbid women with the $\epsilon 4$ allele have significantly more neurological dysfunction than men

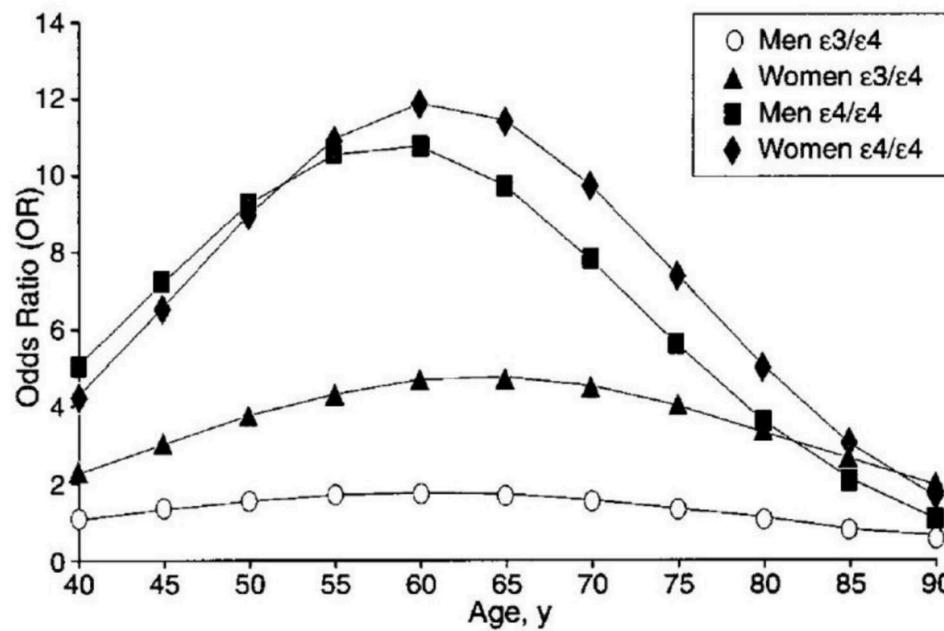


Figure 1. APOE4 risk is greater in women

Etiology: Alzheimer's

- Although 40–65% of AD patients have at least one copy of the $\epsilon 4$ allele, *ApoE4* is not a determinant of the disease (Kivipelto et al., 2002, *Annals of Int Med*)
 - At least a third of patients with AD are *ApoE4* negative and some *ApoE4* homozygotes never develop the disease
 - The APOE E4 gene, high cholesterol, and high blood pressure are independent risk factors, which together can nearly triple the risk that the individual will later develop AD

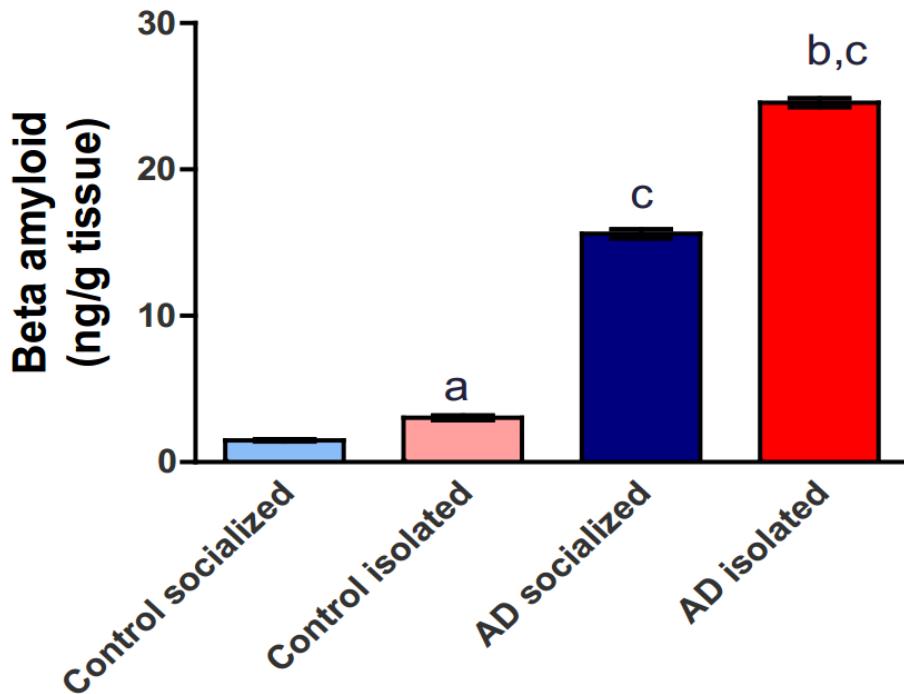
Etiology: Alzheimer's

Study on Social Isolation as a Risk Factor in Development of Alzheimer's Disease in Rats

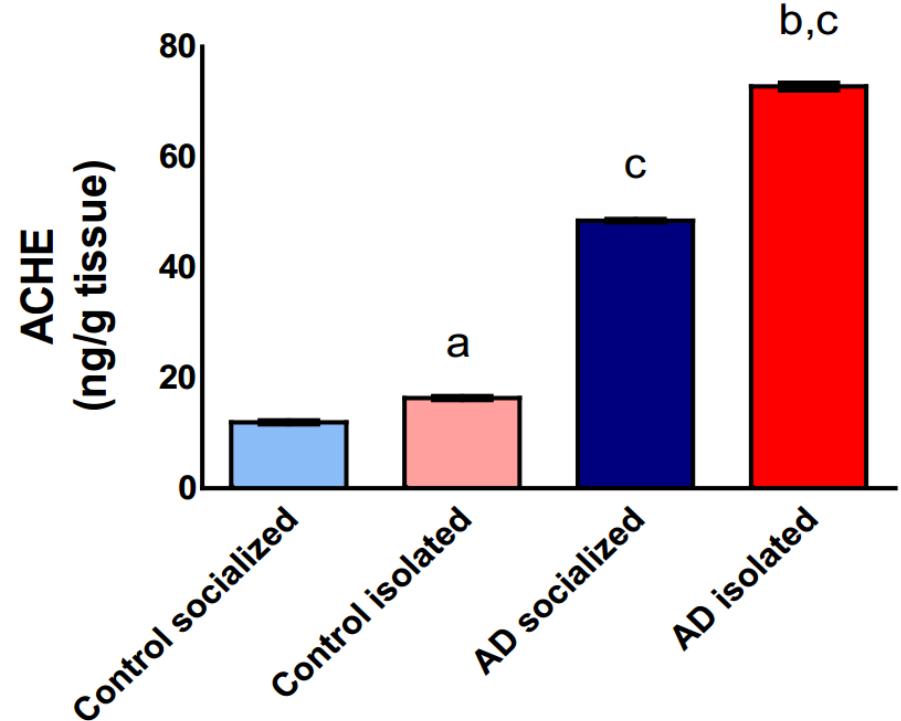
Asza A Ali^{1*}, Mona G Khalil², Hemat A Elarainy¹ and karema Abu-Elfotuh¹

- The accumulation of amyloid plaques is thought to cause symptoms via acetylcholine dysfunction.

Beta Amyloid Markers

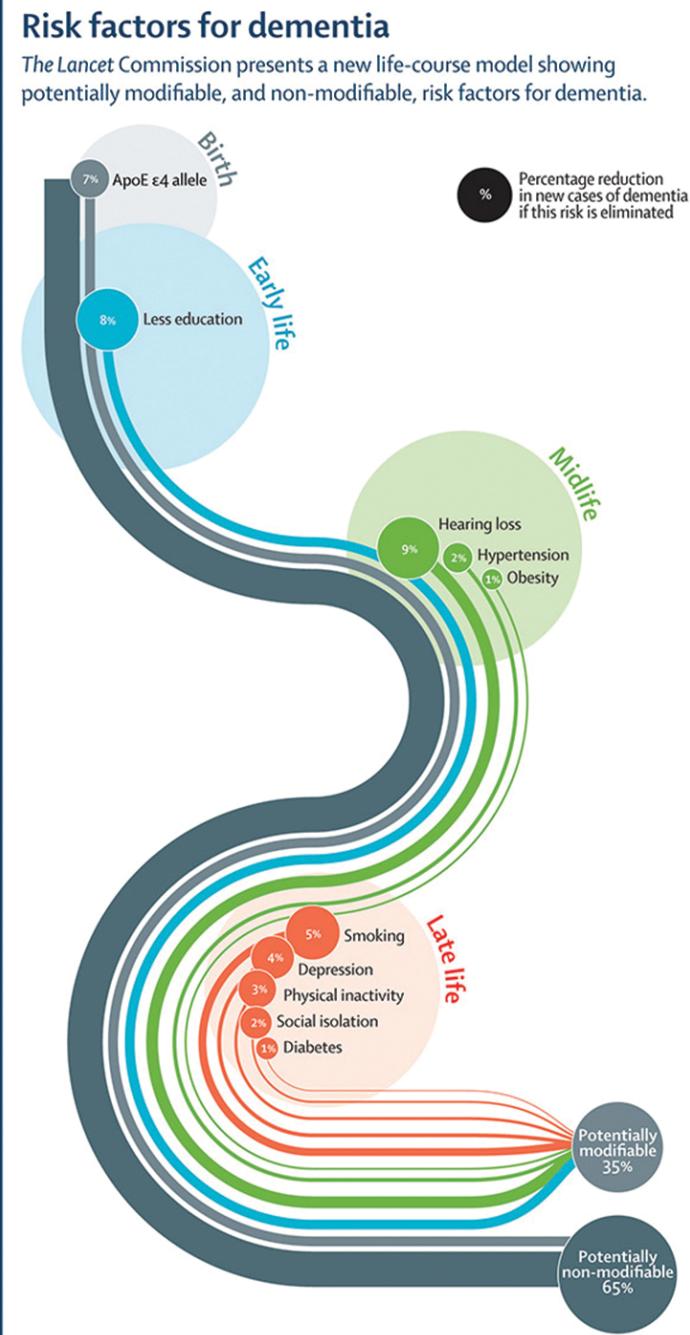


Acetylcholine Markers



Etiology: Alzheimer's

- Other risk factors include a history of head injuries, depression, hypertension, lack of physical exercise, and obesity
- 35% of risk is potentially modifiable

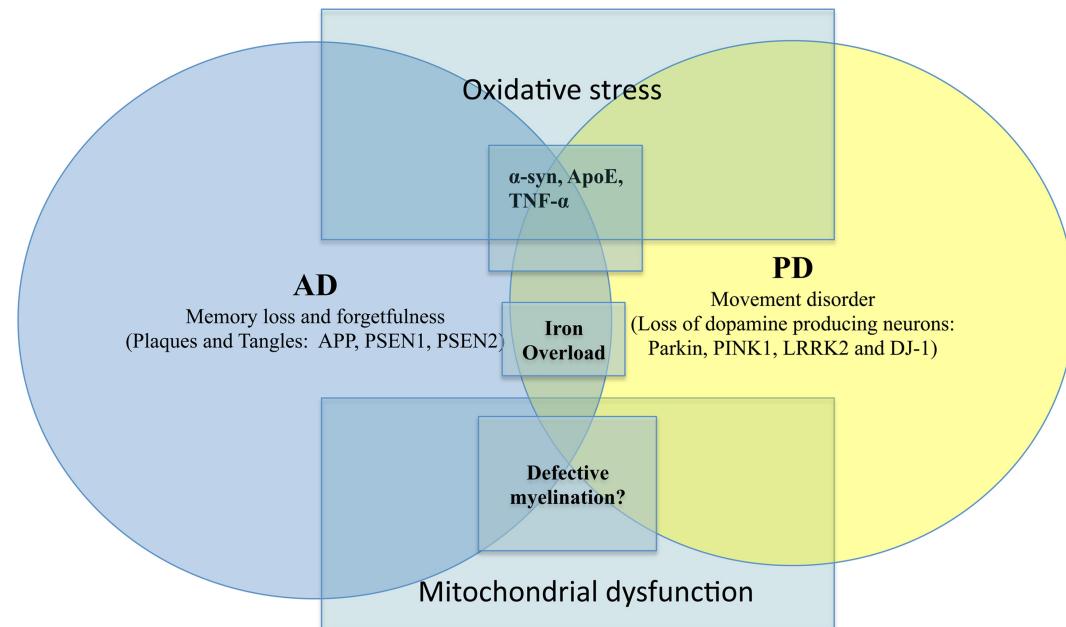


Etiology: Parkinson's

Neurodegenerative diseases: exercising toward neurogenesis and neuroregeneration

Eng-Tat Ang¹, Yee-Kit Tai², Shun-Qiang Lo², Raymond Seet³ and Tuck-Wah Soong^{2,4*}

- PD and AD have some common causal risk factors, in the way of accumulating compounds in the body (e.g., cholesterol, iron).
 - Oxidative stress predisposes cells to undergo damage to DNA and is a common factor involved in the pathogenesis of AD and PD.
 - Some evidence suggests that sustained exercise and diet restriction may be ways to slow the rate of neurodegeneration and promote neurogenesis



Etiology: Parkinson's

- Like AD, the cause(s) of PD are generally unknown
 - Believed to involve genetic and environmental factors
 - Involves loss of function of dopamine neurons in substantia nigra
 - Having a family member affected increases the likelihood of having PD
 - But, just 15% of those with PD have an affected relative.



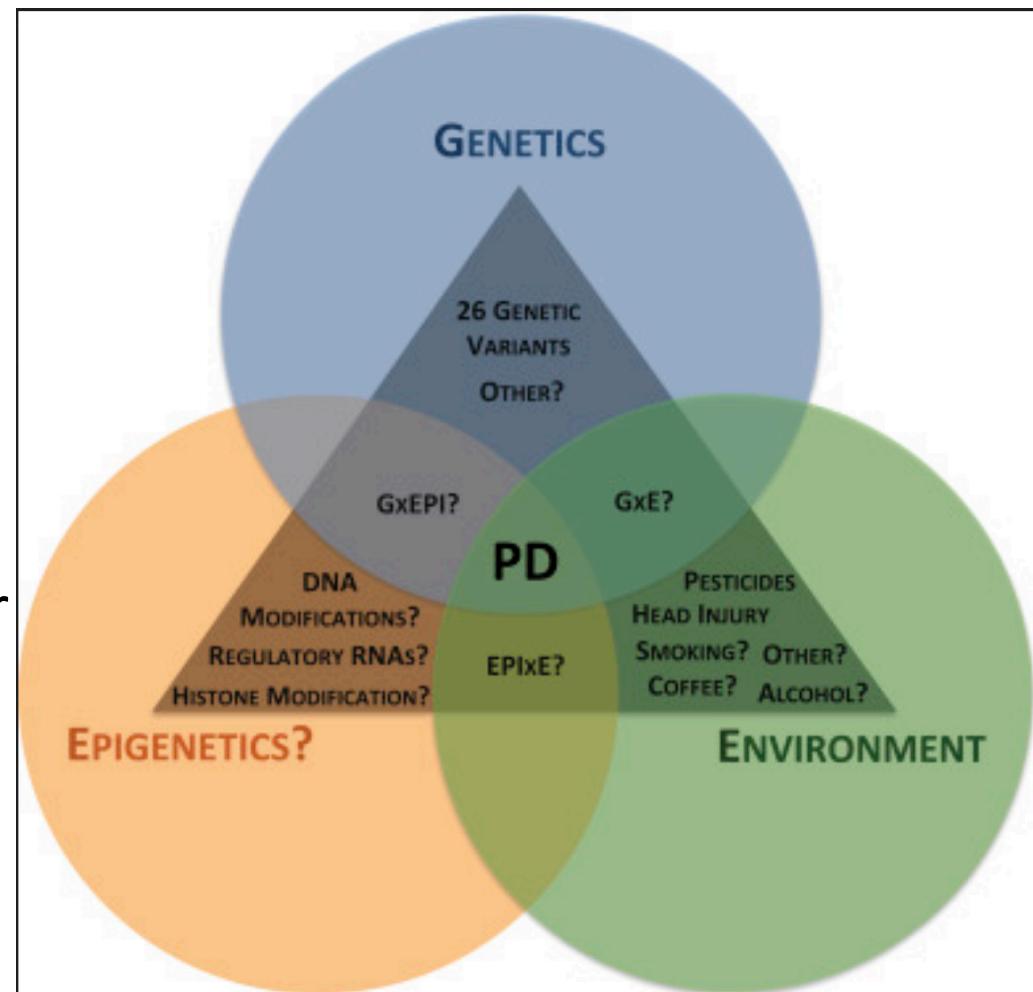
Molecular and Cellular Probes

journal homepage: www.elsevier.com/locate/ymcp

Review

Genetics of Parkinson's disease[☆]

Christina M. Lill



Etiology: Parkinson's

- There is an increased risk for PD in:
 - People exposed to certain pesticides and among those who have had prior head injuries.
 - Findings for occupational pesticide exposures linked with PD, but small sample sizes have limited power/any pattern of statistical significance.
 - Even less support for home-based exposures and rural exposures (e.g., farming).

Table 2. Occupational Exposures and Risk of Parkinson Disease in Men

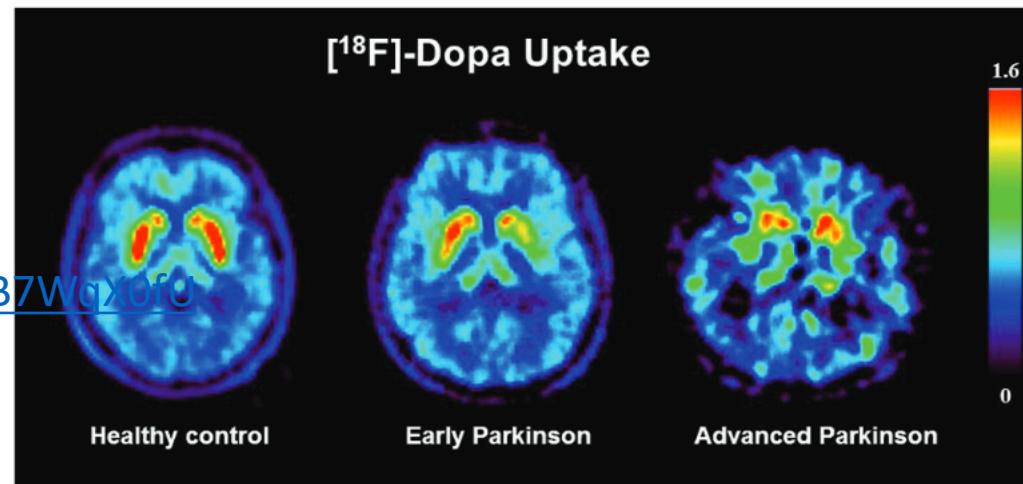
Variable	Cases (n = 156)	Controls (n = 241)	Odds Ratio (95% Confidence Interval)*
Occupational title			
Pesticide worker	7	6	2.07 (0.67-6.38)
Crop farmer	19	20	1.65 (0.84-3.27)
Animal and crop farmer	21	33	1.10 (0.60-2.00)
Dairy farmer	16	30	0.88 (0.46-1.70)

Etiology: Parkinson's

The Role of Functional Dopamine-Transporter SPECT Imaging in Parkinsonian Syndromes, Part 1

T.C. Booth, M. Nathan, A.D. Waldman, A.-M. Quigley, A.H. Schapira, and J. Buscombe

- Pathway from risk/protective factor (genes, pesticides, caffeine) to PD is unclear, but cell death in the substantia nigra is critical
 - This region is involved in motor movement and relies heavily on dopamine.
 - Just as AD has a build up of plaques, PD results from a build up of proteins that form “Lewy Bodies” in neurons.



<https://www.youtube.com/watch?v=cRLB7WqX0f0>

Conclusions

- The etiology of AD involves genetic risk (e.g., APOE is one but not the only genetic risk factor), formation of beta amyloid plaques, tau proteins, and cholesterol
 - Yet 35% of risk is modifiable
- Like AD, PD involves genetic and environmental risk factors that lead to neurodegeneration of dopaminergic pathways involving the substantia nigra
 - There may also be modifiable risk factors
 - Exercise thought to slow progression