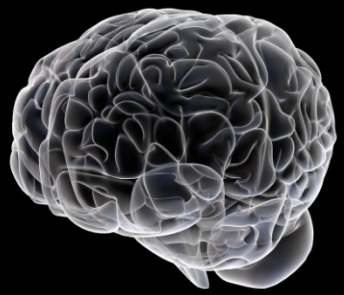


BRAIN Lab

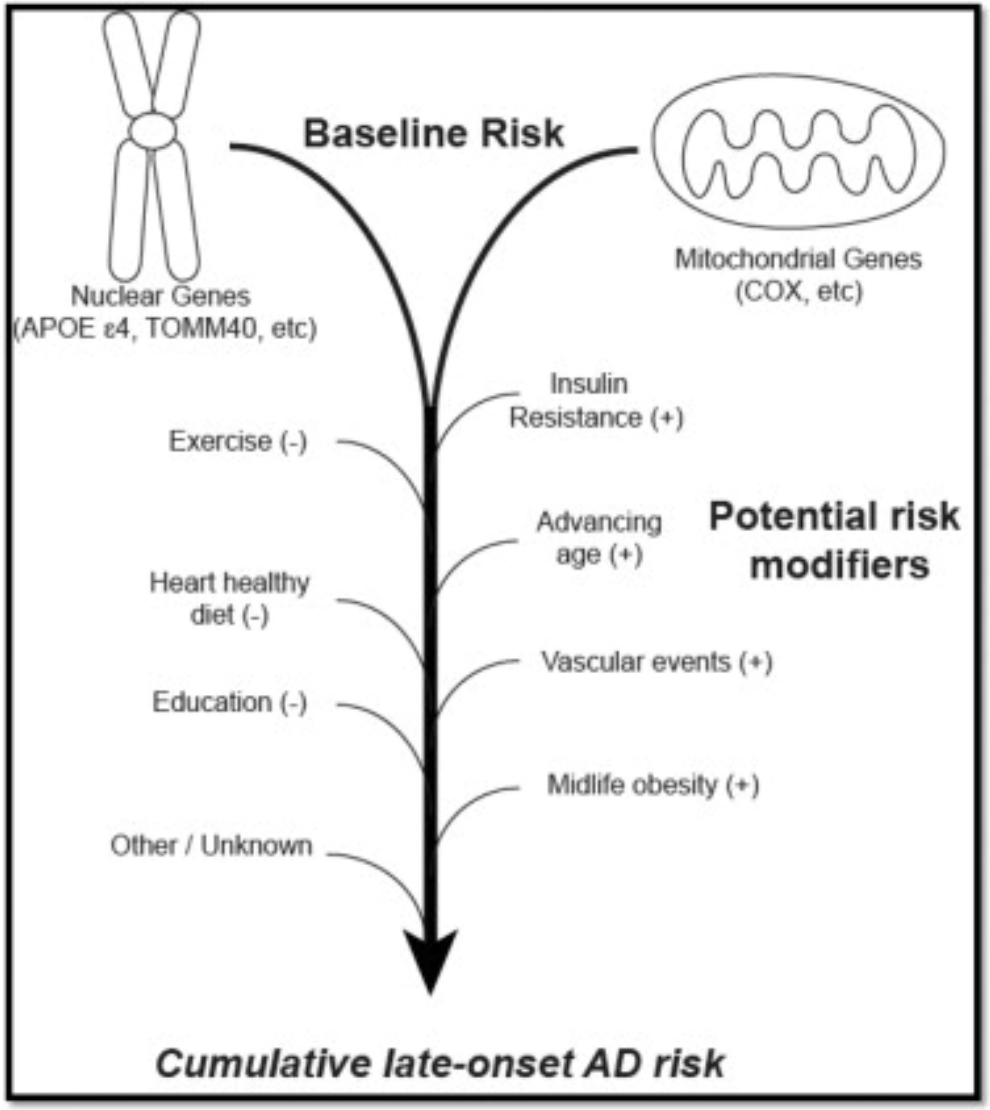
BRAin Imaging and Neurogenetics Laboratory

KU ALZHEIMER'S DISEASE CENTER
The University of Kansas Medical Center

Integrating Brain Imaging and Genetics to Uncover Risk for Alzheimer's Disease

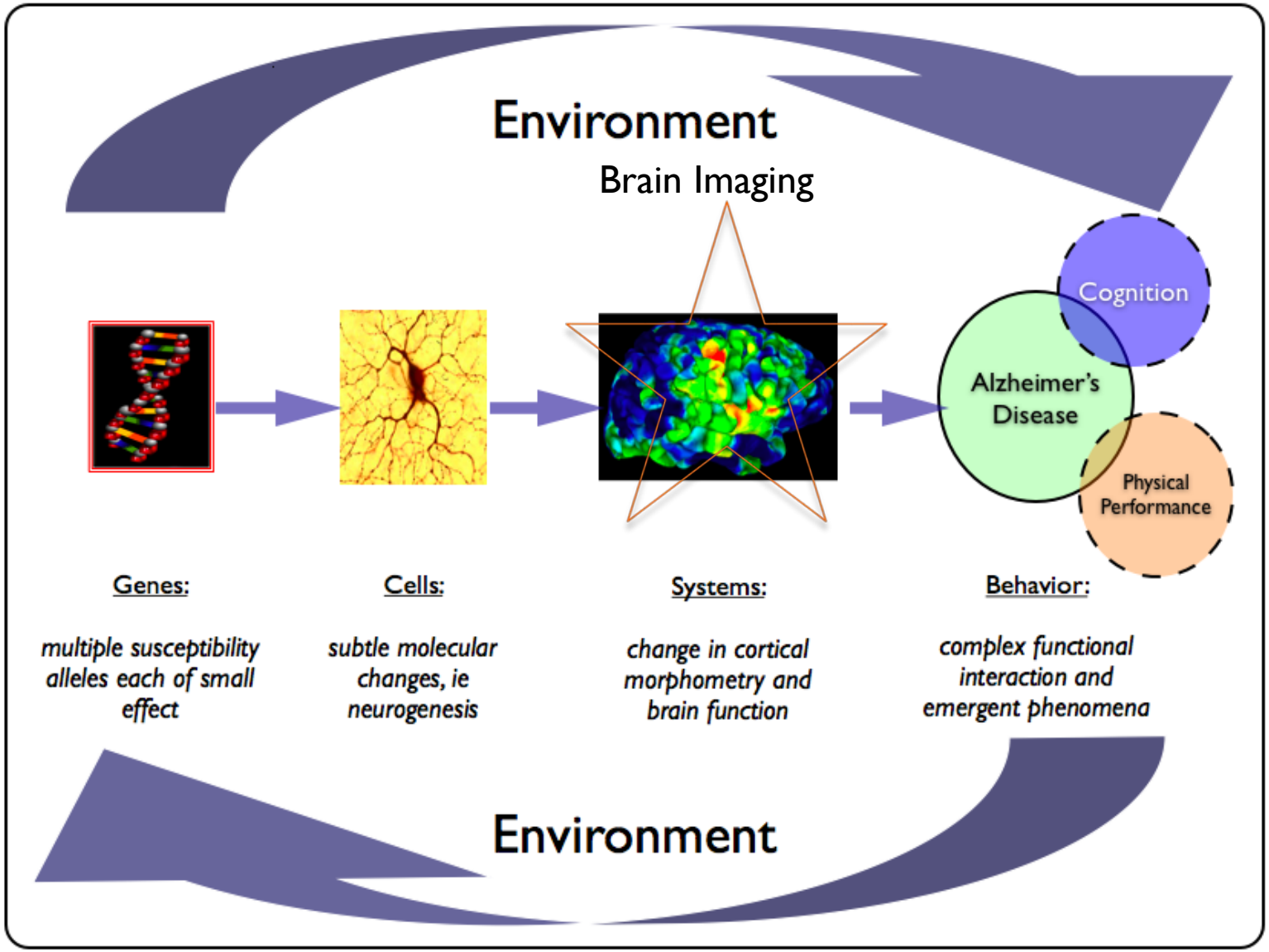
Robyn A. Honea, DPhil
Assistant Professor,
KUMC Department of Neurology
Supported by NIA K01AG035042,
KU Alzheimer's Disease Center P30AG035982,
and NIA R01AG033673

Late Onset Alzheimer's Disease Risk = Nuclear Genes + Mitochondrial Genes + Environment



Morris, Honea, et al. BBA Molecular Basis of Disease 2014

We Need Complex Tools for a Complex Disease; Imaging Genetics

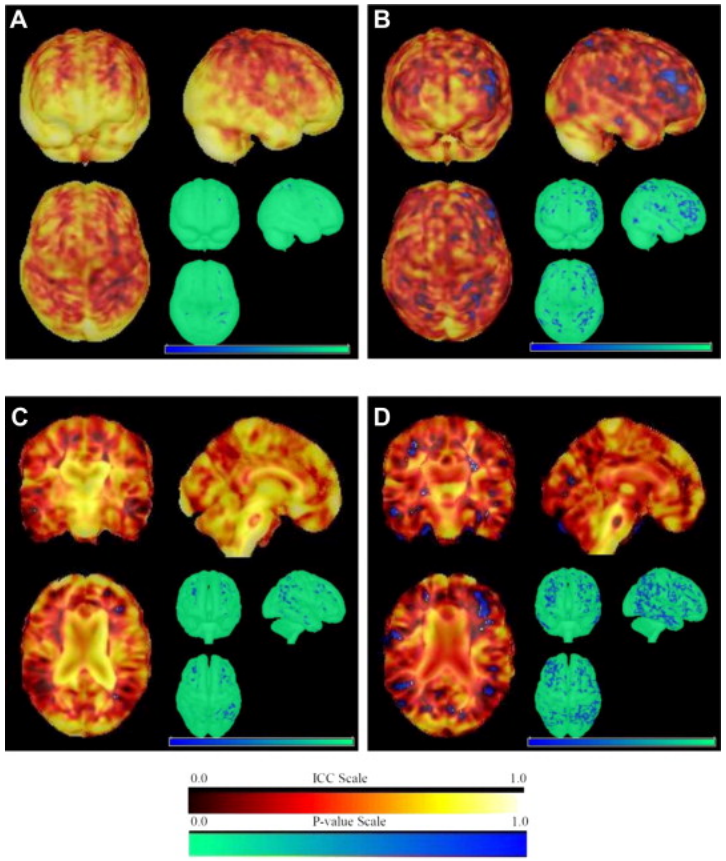


"Imaging Genetics"
A model to study complex diseases

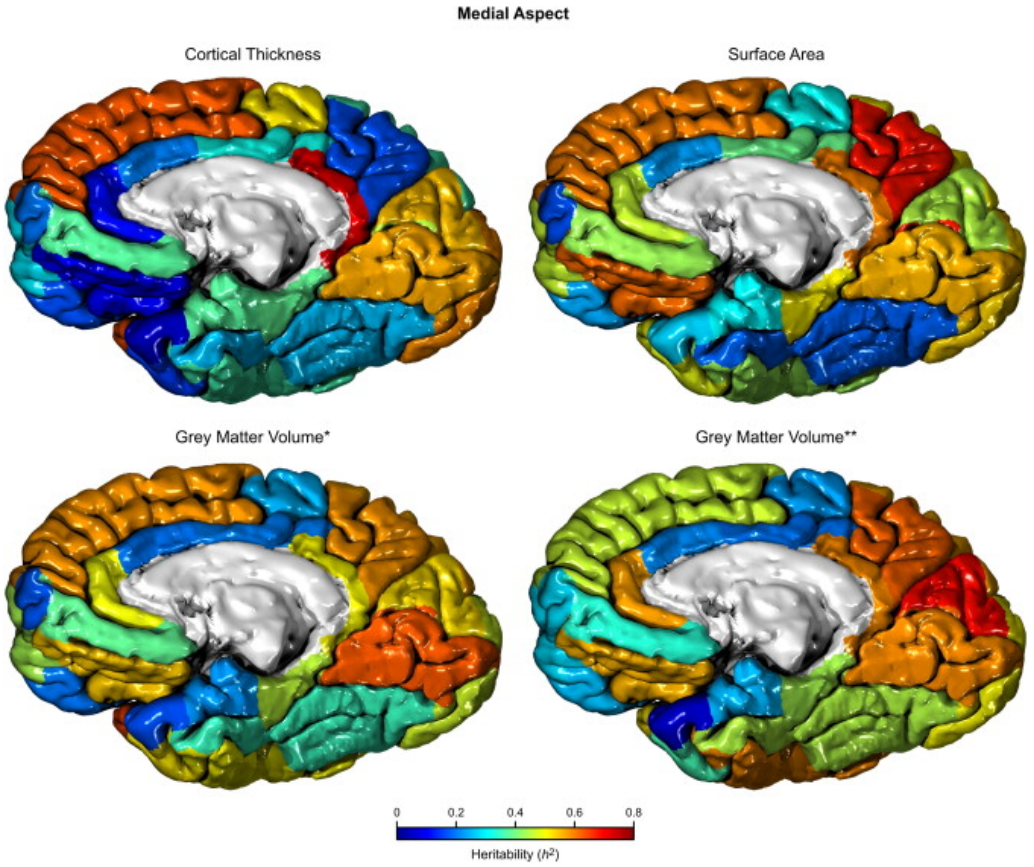
- Characterize Disease Using Imaging
- Define Imaging Endophenotype- *a heritable trait
- Identify Genetic Variants
- Study Impact of Genetic Variation on Disease Endophenotype, or quantifiable trait

Heritability of Brain Morphometry

Gray matter volume



Cortical Thickness and Surface Area



Seyed Amir Hossein Batouli et al. Neurobiology of Aging, 2014; http://dx.doi.org/10.1016/j.neurobiolaging.2013.10.079
Winkler et al, NeuroImage, Volume 53, Issue 3, 2010, 1135 - 1146

Alzheimer's Genes and Brain Atrophy

Contents lists available at ScienceDirect

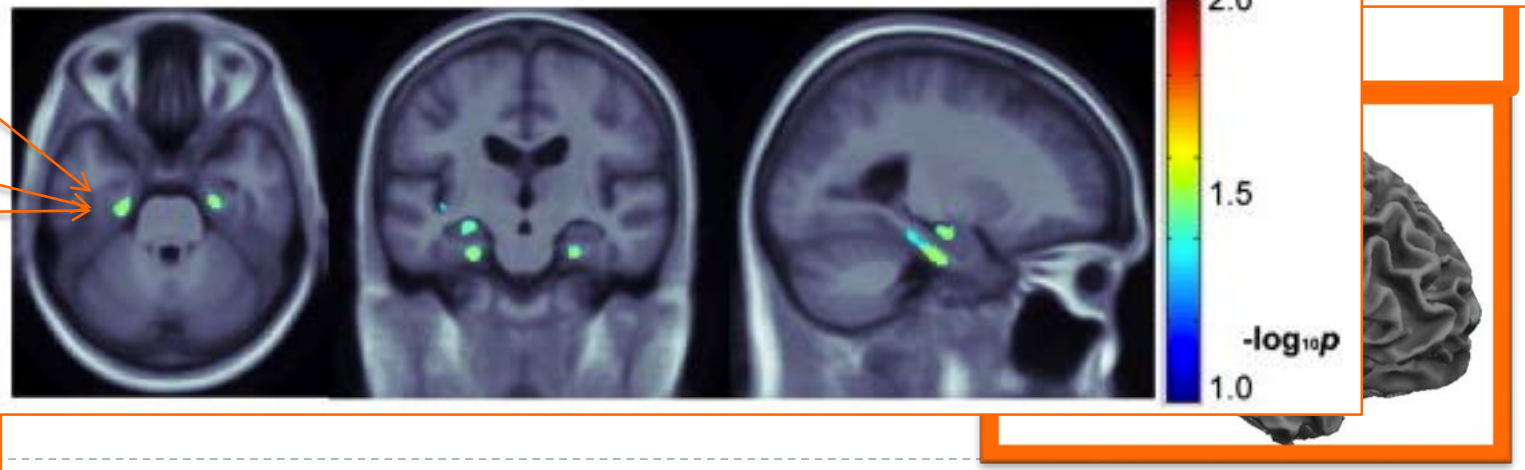
NeuroImage: Clinical

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

Multilocus genetic profiling to empower drug trials and predict brain atrophy☆

Omid Kohannim [a], Xue Hua [a], Priya Rajagopalan [a], Derrek P. Hibar [a], Neda Jahanshad [a], Joshua D. Grill [b], Liana G. Apostolova [b], Arthur W. Toga [a], Clifford R. Jack Jr. [c], Michael W. Weiner [d,e], Paul M. Thompson [a,*], for the Alzheimer's Disease Neuroimaging Initiative [1]

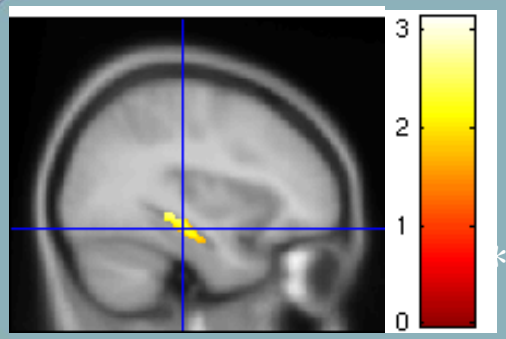
3	CLU
4	ABCA7
5	CR1
6	PICALM
7	MS4A6A
8	CD33
9	MS4A4E
10	CD2AP



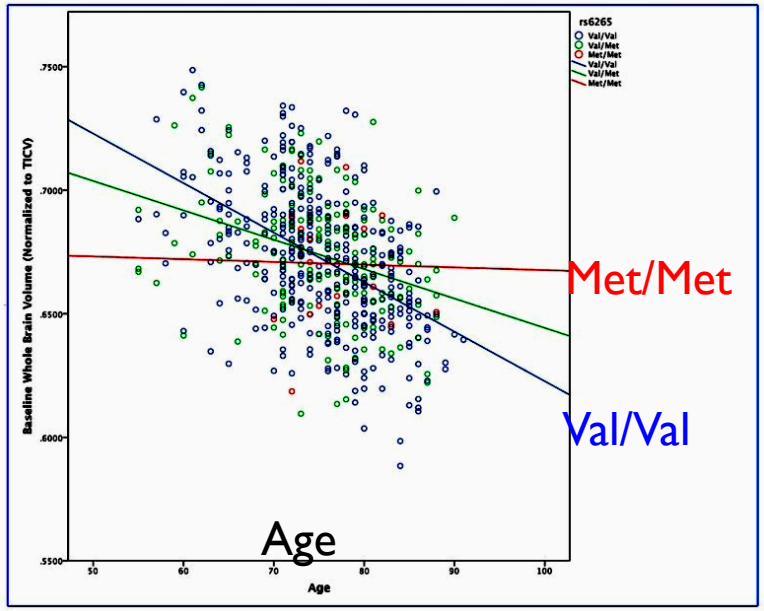
Honea et al. in preparation

BDNF- also associated Brain Atrophy

- Brain Derived Neurotrophic Factor is a neurotrophins that regulates cortical neuron survival, proliferation, and synaptic growth.
- Study: 645 participants from ADNI
- Six SNPs were significantly associated with hippocampal and/or whole brain atrophy, including Val66Met, which affects intracellular packing and secretion of neurotrophin



BDNF rs6265
Val> Met Carriers
Hippocampal Atrophy
*p<.02 FWE corrected



Honea et al. *Plos One 2013*

Family History of Dementia

- 25% of all people over 55 have a family history of dementia *(Loy C, Lancet 2014)*
- Nuclear Genes….are contributed by both parents
- However, more often subjects have an affected mother than an affected father AD *(Heyman A 1983, Edland SD 1996)*

Table 2

Prevalence of maternally vs paternally inherited late-onset Alzheimer's disease (AD)

Reference	AD cases	No affected parents	FH−	FHm	FHp	Mother:father ratio
Heyman *et al.*[81]	68	11	84%	10%	6%	1.8:1
Duara *et al.*[77]	311	69	78%	17%	5%	3.6:1
Edland *et al.*[78]	118	24	80%	16%	4%	3.8:1
Farrer *et al.*[70]	251	61	76%	16%	8%	1.9:1
Gomez-Tortosa *et al.*[80]	2594	817	68%	23%	9%	2.6:1

FH− = No family history of AD; FHm = maternal history of AD; FHp = paternal history of AD.

Maternal Family History and Imaging Phenotypes of Alzheimer's

-progressive atrophy in AD-regions (Honea et al., Neurology 2010, 2011)

-reduced glucose consumption (PET) (Mosconi et al. PNAS 2007)

-progressive reductions in glucose metabolism over time (Mosconi et al. Neurology 2009)

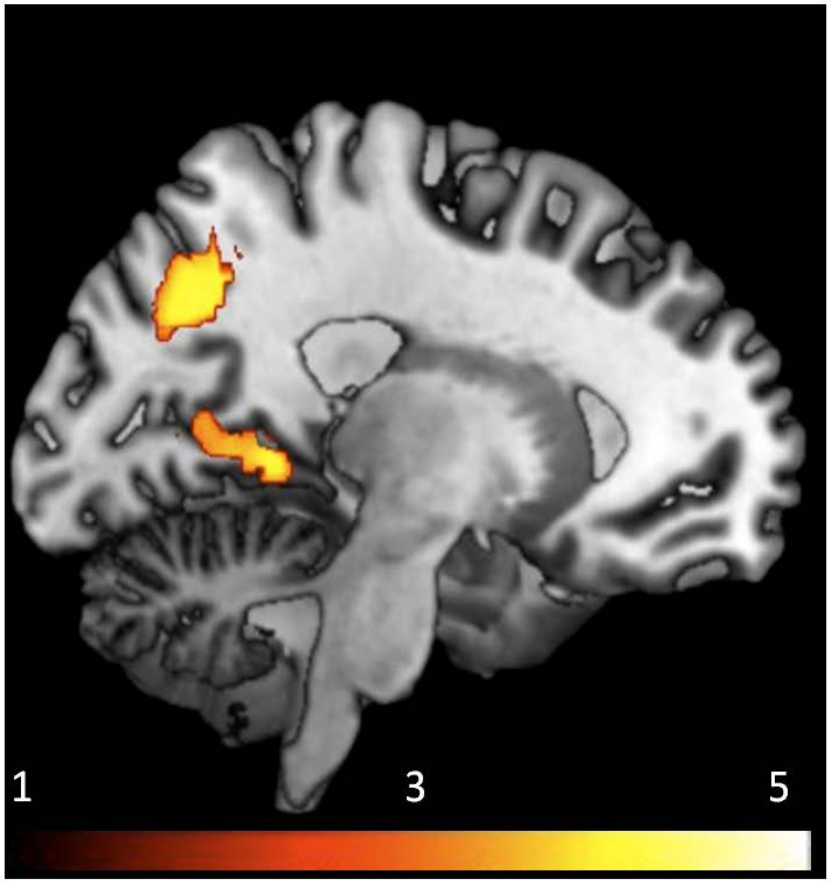
- Increased amyloid-beta load in key brain areas (Mosconi et al. PNAS 2010, Honea et al. JAD 2012)

-Hypoperfusion (reduced cerebral blood flow) in hippocampal and parietofrontal regions (Okonkwo OC et al. Cerebral Cortex 2014)

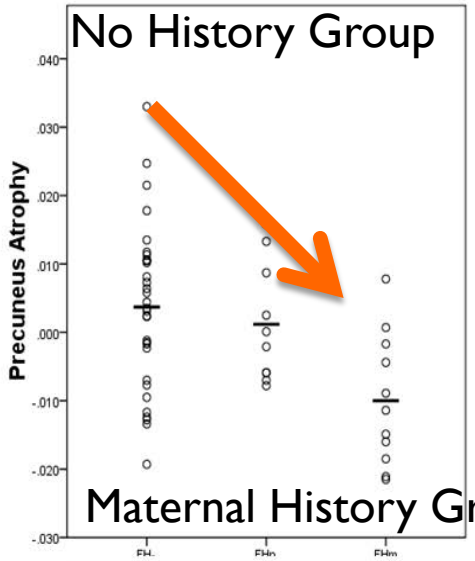
-Alterations in Resting State Connectivity (Wang et al. 2012; Honea et al in preparation)

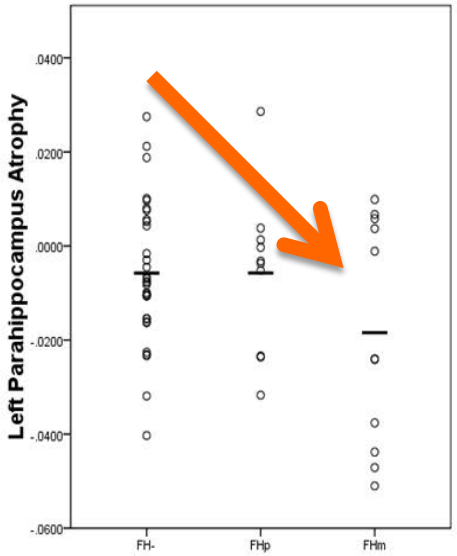
-MCI with a maternal family history have more markers of AD pathophysiology (CSF, PiB, glucose metabolism) (Honea et al. JAD 2012, Mosconi et al. JAD 2014)

A



B

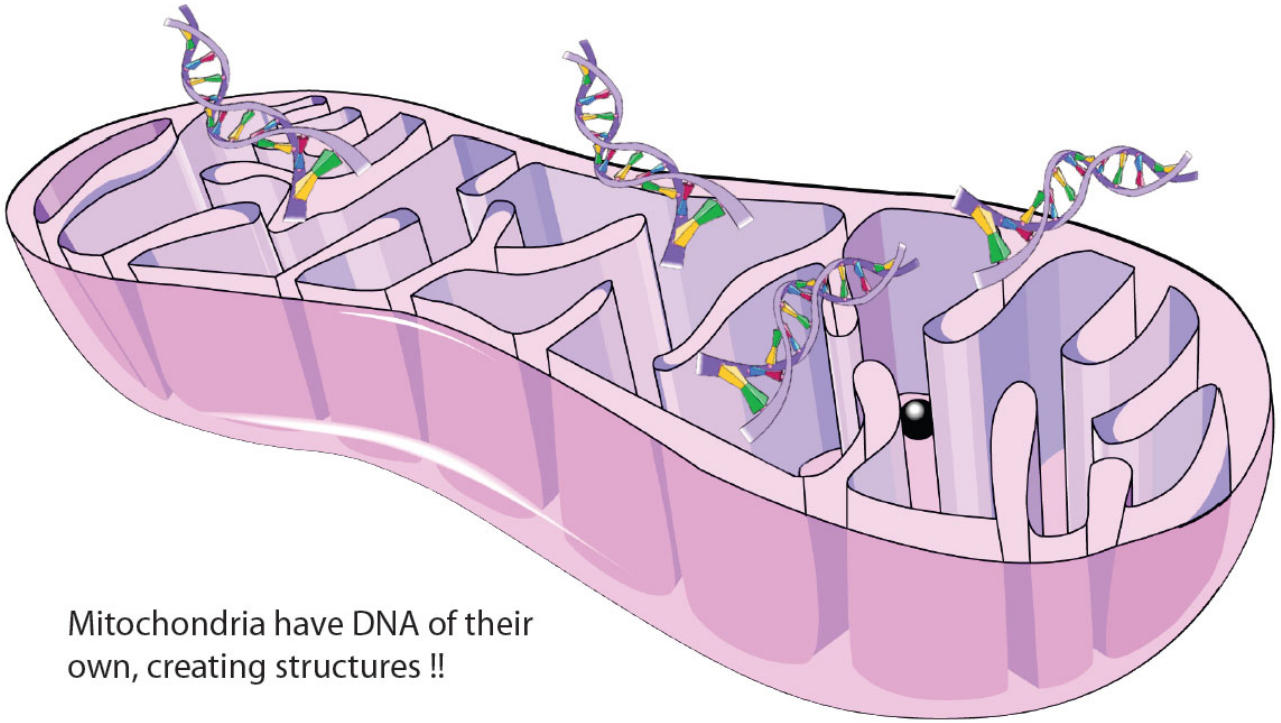




Honea et al., Neurology 2010, 2011

So, many nuclear genes relate to brain morphometry…

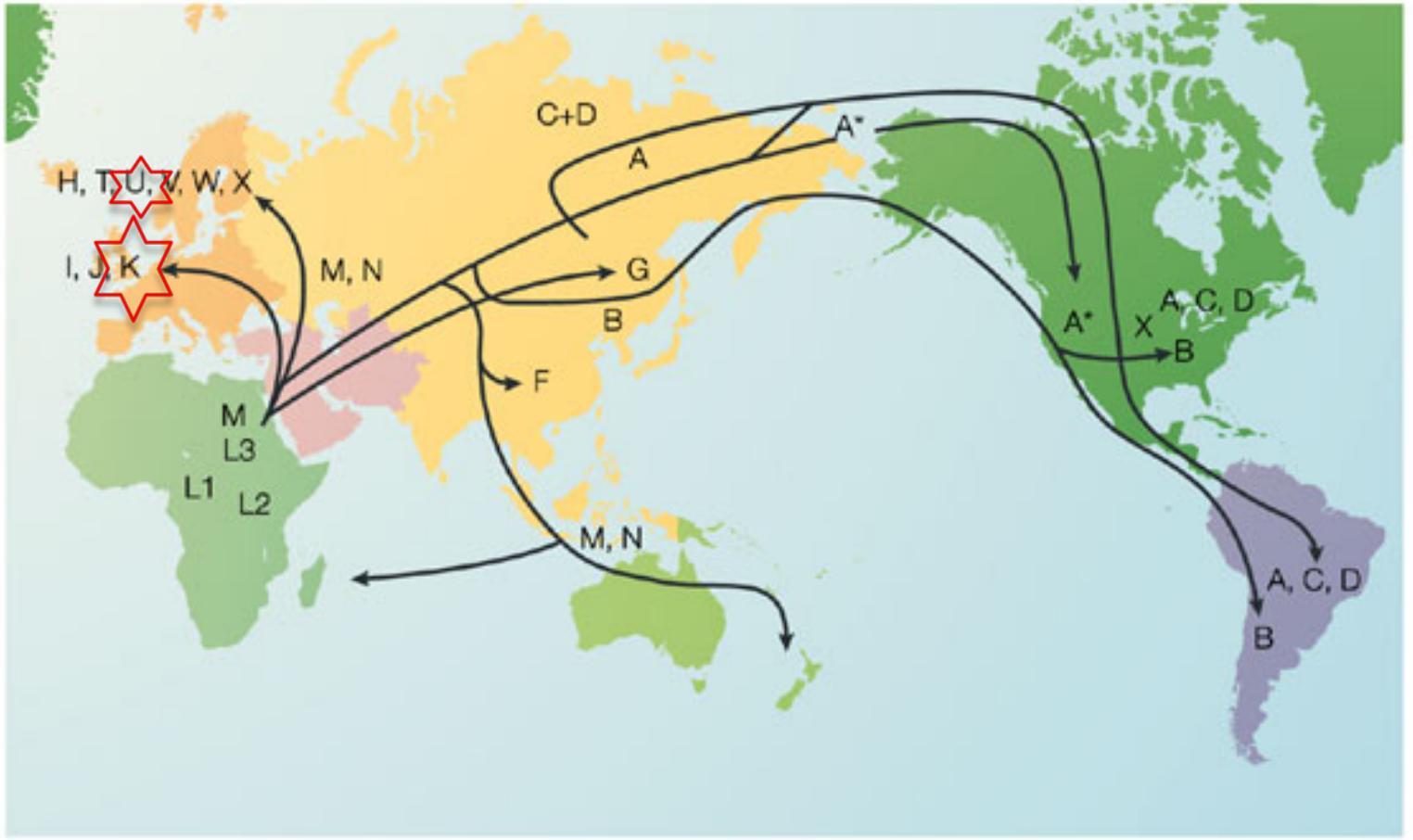
- What about the mitochondrial genome?
- Maternally inherited mutations of mtDNA may play a role in AD….but it is still unclear



Mitochondria have DNA of their own, creating structures !!

Mitochondrial Haplogroups

Role in AD?

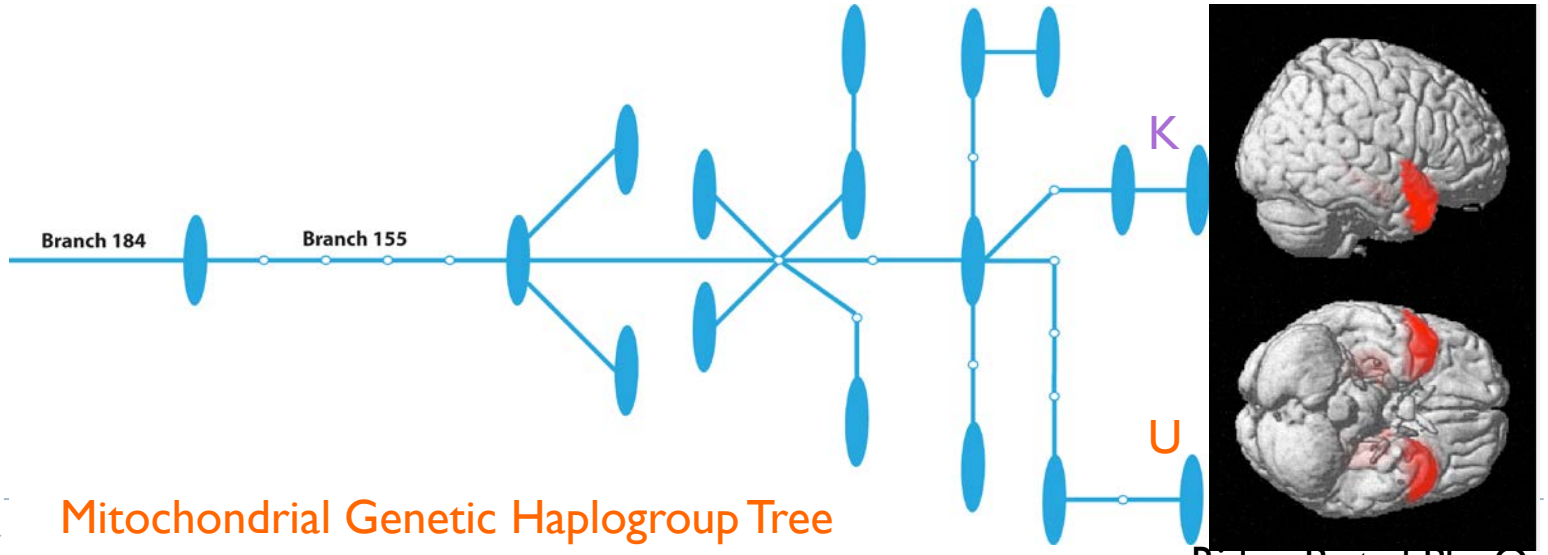


Haplogroups are the major branch points on the mitochondrial phylogenetic tree which began with Mitochondrial Eve in Africa.

Nature Reviews | Genetics

Association between Mitochondrial Genes and Temporal Cortex Atrophy

- ADNI longitudinal volume and thickness data
- Haplotype-based Treescanning approach to analyze evolutionarily meaningful groups of genes together for their association with phenotype
- 4 significant clades in Haplogroups U and K
- Next step, Next Generation mtDNA sequencing of 500 individuals from our KU Alzheimer's Disease Center

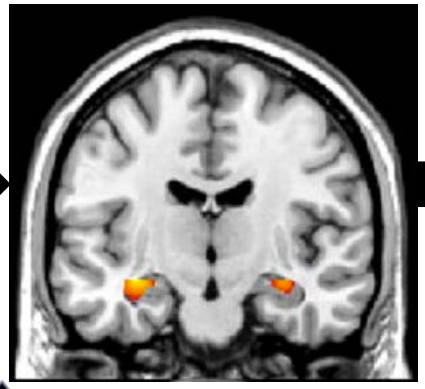


Mitochondrial Genetic Haplogroup Tree

Ridge, P. et al PlosOne 2013

Gene X Environment Interactions

BDNF
CLU
PICLAM
APOE
MtDNA



Slowed Alzheimer's Disease?

- Analyzing data from two 6 month exercise interventions, one in healthy elderly (R01AG033673- Burns PI) and one in Alzheimer's Disease (R01AG34614- Burns PI) with imaging and genetic data

Thank you!

- BRAIN Lab:
  - Rodrigo Perea, MS
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  - Jill Morris, PhD
  - Anne Arthur
  - Heather Anderson, MD
  - Phyllis Switzer
  - Diane Cunningham
  - Pat Laubinger
- Washington University in St. Louis ADC
  - Alison Goate, Dphil
  - Carlos Cruchaga, PhD
- BYU
  - John Kauwe, PhD
  - Perry Ridge, PhD
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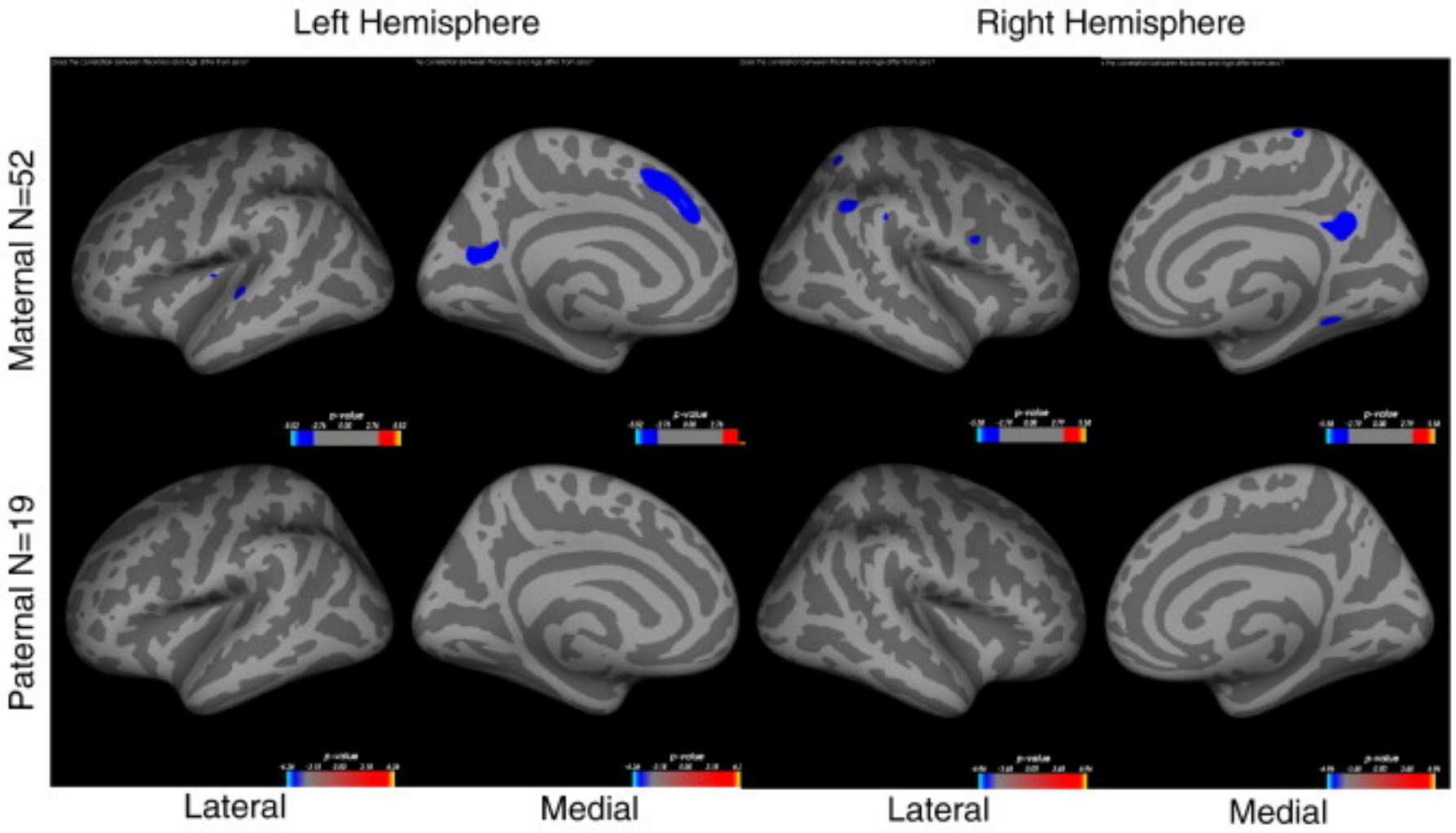
  - KU Alzheimer's Disease Center P30AG035982
  - NIA R01AG033673 (Burns PI)

Cognitively healthy individuals with a maternal family history have more AD-like cortical thinning patterns



Reiter et al. , NeuroImage, Volume 61, Issue 3, 2012, 525 – 532. http://dx.doi.org/10.1016/j.neuroimage.2012.03.083