Mitochondrial polygenic risk scores for Alzheimer's Disease

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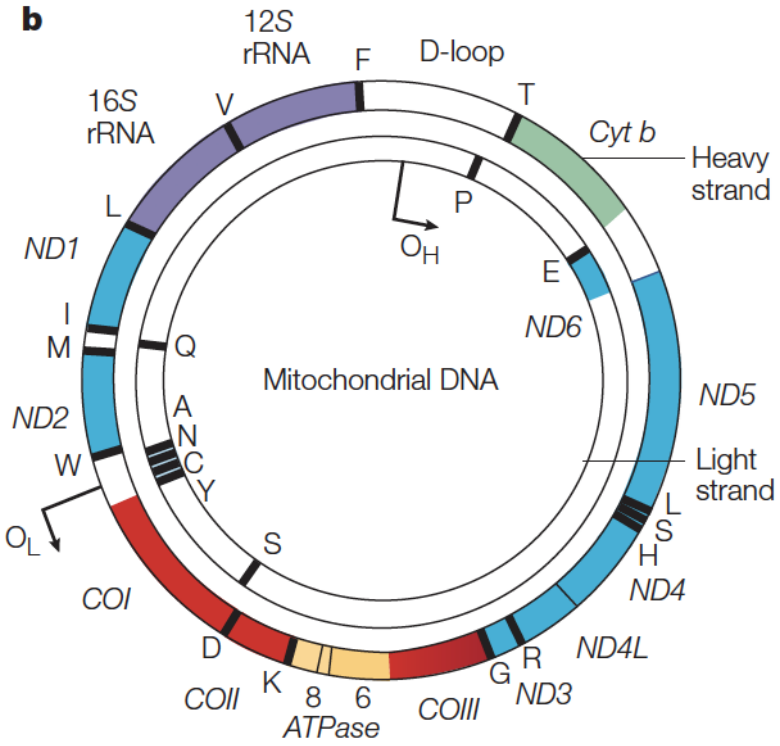
ADRC Spring Meeting
May 13th 2022

Icahn School of Medicine at Mount Sinai

The mitochondrial DNA is a maternally inherited genome dedicated to generation of cellular energy



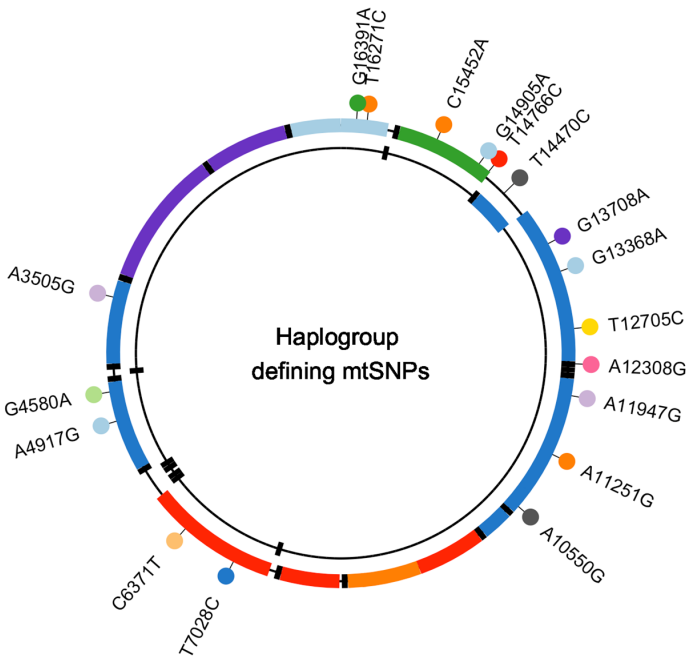
Mitochondria are involved in fundamental cellular processes

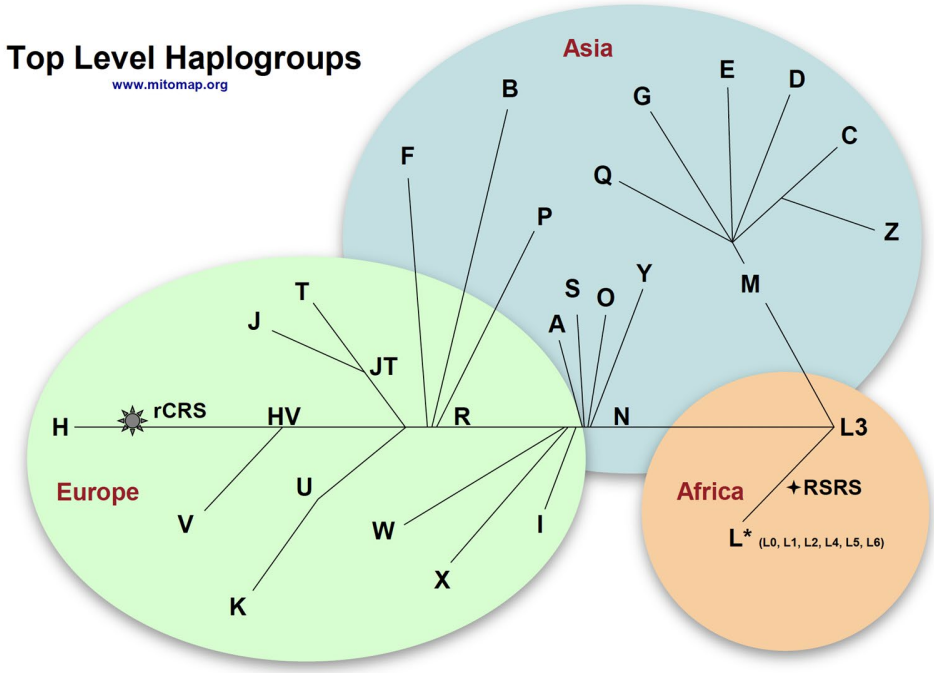
- Oxidative phosphorylation
- Calcium storage
- Apoptotic signaling
- Immunometabolism

Mitochondrial genome

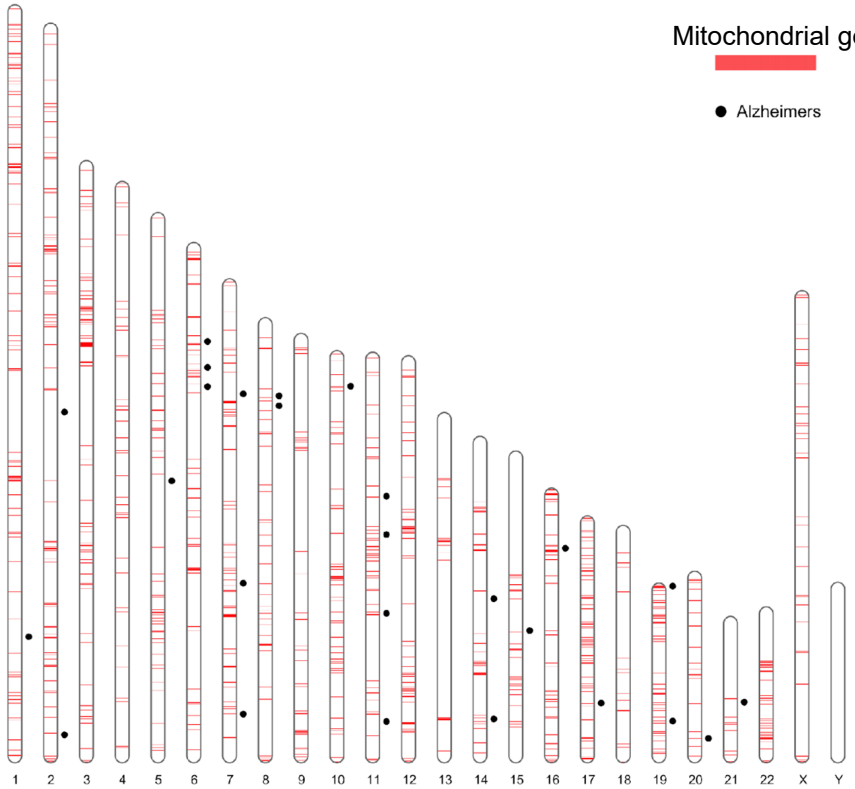
- 13 protein coding genes involved in the respiratory chain
- 22 tRNA and 2 rRNA

Mitochondrial haplogroups represent sets of similar haplotypes defined by SNVs that arrose as a result of sequential accumulation of mutations during prehistoric human migrations





One cell, two genomes: The nuclear genome contains 1,136 genes encoding proteins that localize to the mitochondria



Metabolism
461 genes

Central dogma
231 genes

OXPHOS
169 genes

Mitochondrial dynamics and surveillance
104 genes

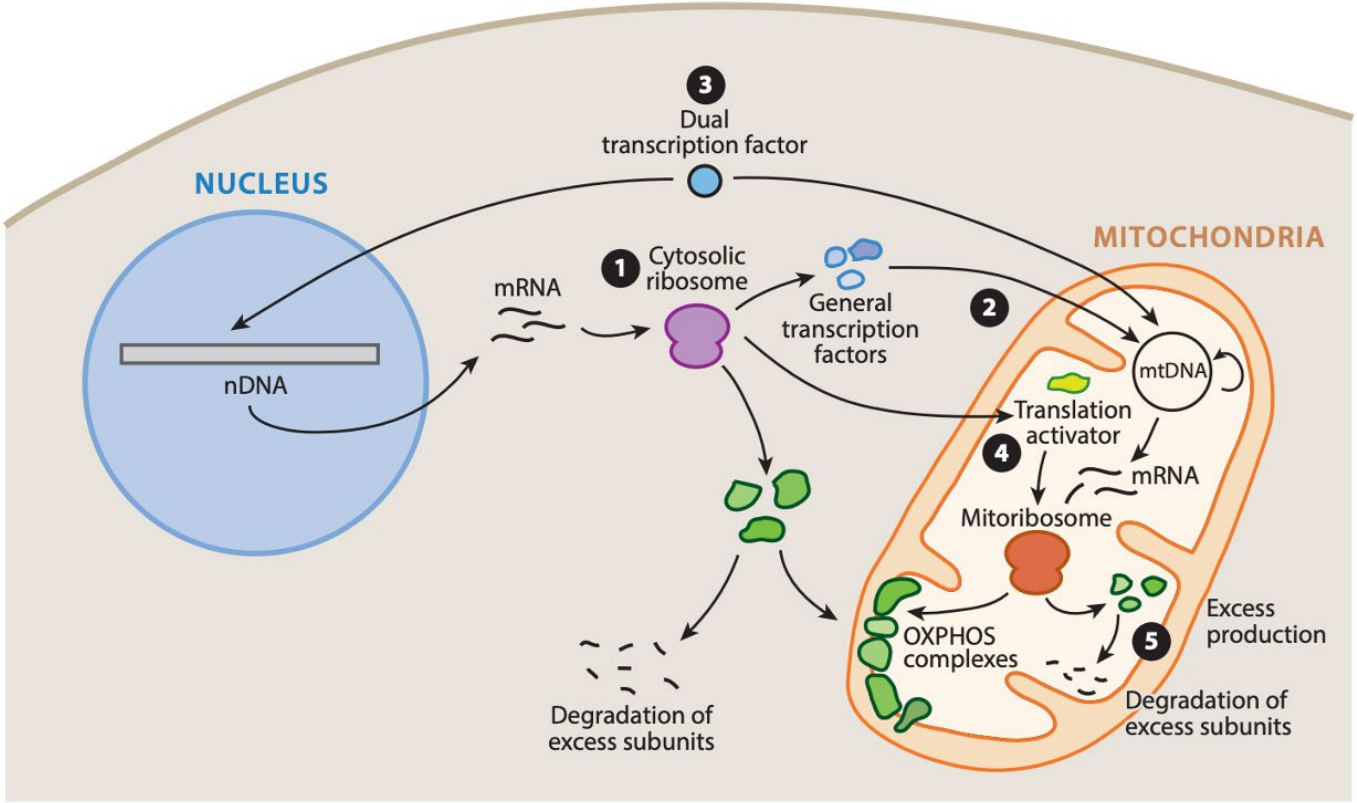
Small molecule transport
85 genes

Protein import, sorting, and homeostasis
86 genes

Signaling
48 genes

Adapted from Rath, S. et al. 2020. Nucleic Acids Res 49

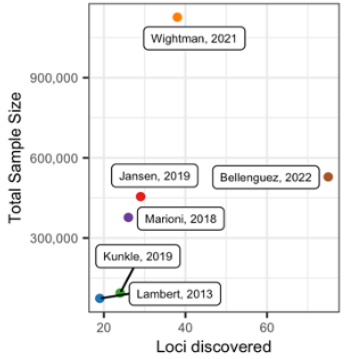
One cell, two genomes: To ensure optimal cellular function, the cell must coregulate two physically separated and evolutionarily distinct genomes.

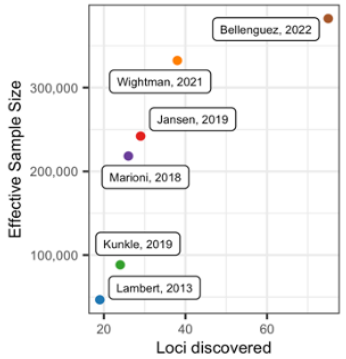


Isaac, R. S., McShane, E. & Churchman, L. S. *Annu Rev Genet* **52**, 511–533 (2018).

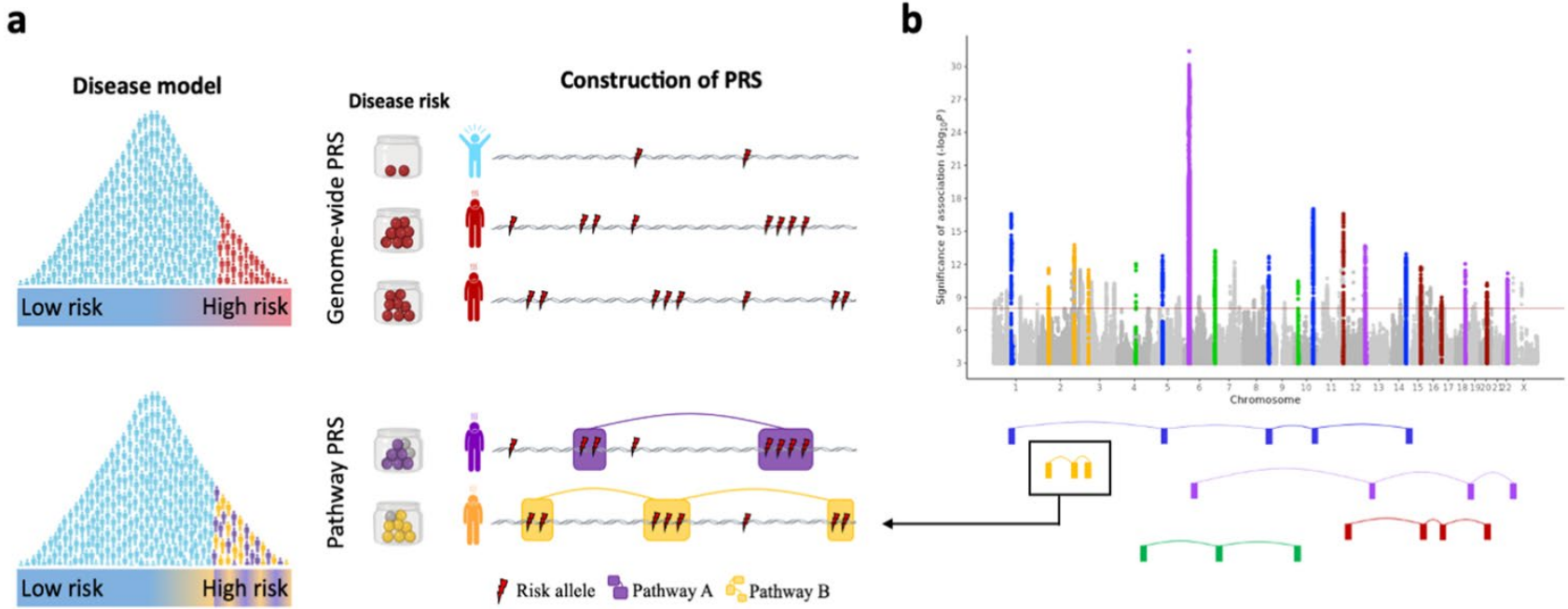
Do genetic risk variants for AD located within nuclear-encoded mitochondrial genes influence risk of AD and do mito-nuclear interactions further influence AD risk.

Genome-wide association studies have identified ~100 loci associated with Alzheimer's disease





Pathway-based polygenic risk scores (PRS) estimate the genetic liability to disease that is enriched within genomic pathways



Choi et al. 2021. Research square doi: 10.21203/rs.3.rs-643696/v1

Evaluate the interaction between mitochondrial haplogroups and a AD PRS composed of nuclear encoded mitochondrial genes

Mitochondrial Haplogroups

- Resequenced mitochondrial genomes for 612 participants using Phy-Mer
- 138 typed and 88 imputed SNPs in 435 participants using HaploGrep2

Andrews, S. J. et al. 2020. Neurobiology of Aging

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Nuclear-encoded mitochondrial PRS for AD

- Base dataset: Kunkle 2019 AD GWAS
- Target dataset: **ADNI**
- SNPs assigned to nuclear mitochondrial genes, ± 50kb of gene region
- Pruning (r^2 = 0.1; window = 250kb) and thresholding ($p < 0.5$) using PRSice

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Cross-sectional analysis: Effect of the MT-hgs and nMT-PRS on baseline risk of dementia

- binomial multivariate logistic regression models
- adjusting for age, APOE status, sex, and the first 2 principal components

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Survival analysis: Effect of the MT-hgs and nMT-PRS on Alzheimer's age of onset

- cox proportional hazards model
- age was used as the time to event scale
  - Cognitively normal or living with MCI at baseline: AD age at onset
  - Living with AD at baseline: the reported best estimate of onset of AD-dementia symptoms
- adjusting for APOE status, sex, and the first 2 principal components

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Evaluated the main effects of the MT-hgs and the nMT-PRS and their interaction on the likelihood of participants having AD at baseline.

Main Effects (Model 1)

- MT-hg K: OR: 2.00 [95% CI: 1.04, 3.97]
- MT-hg U: OR: 1.99 [95% CI: 0.99, 3.97]
- nMT-PRS: OR: 2.2 [95% CI: 1.68, 2.86]

Interaction Model (Model 2)

a significant interaction was observed between the nMT-PRS and:

- MT-hg T: OR: 0.22 [95% CI: 0.1, 0.49] RERI -2.8 (95% CI: 4.33, 1.26)
- MT-hg K: OR: 0.45 [95% CI: 0.22, 0.9] RERI -3.56 (95% CI: 5.54, 1.57)

Table 2
Association of a mitochondrial PRS and mitochondrial haplogroups (model 1) and their interactions (model 2) with baseline risk of Alzheimer's disease

Variable	Model 1			Model 2		
	β[a]	*SE*	*p*	β	*SE*	*p*
Age	0.02	0.02	0.213	0.03	0.02	0.122
Male	−0.01	0.22	0.975	−0.09	0.23	0.682
APOE status						
ε4+	1.2	0.24	6.47E-07	1.25	0.25	5.08E-07
ε2+	−0.7	0.58	0.227	−0.88	0.6	0.142
PC1	−0.14	0.13	0.274	−0.1	0.13	0.423
PC2	0.53	0.55	0.332	0.42	0.55	0.442
nMT-PRS	0.79	0.14	5.58E-09	1.09	0.2	5.68E-08
Haplogroup						
I	0.27	0.62	0.661	0.33	0.63	0.6
J	0.09	0.4	0.827	0.06	0.44	0.886
K	0.694	0.35	0.049	0.71	0.34	0.038
T	−0.23	0.4	0.564	0.04	0.38	0.909
U	0.687	0.35	0.052	0.81	0.38	0.033
V	0.01	0.63	0.988	0.07	0.76	0.926
W	0.66	0.9	0.464	0.74	0.86	0.391
X	−1.23	1.13	0.278	−2.04	1.77	0.247
Haplogroup × nMT-PRS						
I	-	-	-	−0.38	0.84	0.647
J	-	-	-	0.28	0.68	0.685
K	-	-	-	−0.8	0.36	0.026
T	-	-	-	−1.51	0.41	2.18E-04
U	-	-	-	0.07	0.52	0.886
V	-	-	-	1.01	1.44	0.482
W	-	-	-	−0.68	0.85	0.425
X	-	-	-	−2.31	1.97	0.24

Andrews, S. J. et al. 2020. Neurobiology of Aging

Evaluated the main effects of the MT-hgs and the nMT-PRS and their interaction on Alzheimer's Age of Onset

Main Effects (Model 1)

- nMT-PRS: HR: 1.44 [95% CI: 1.28, 1.61]

Interaction Model (Model 2)

significant interaction was observed between the nMT-PRS and:

- MT-hg T: HR: 0.62 [95% CI: 0.42, 0.91] RERI: -0.7 (95% CI: -1.24, -0.16)
- MT-hg V: HR: 2.28 [95% CI: 1.19, 4.35] RERI: 1.06 (95% CI: -0.9, 3.02)

Table 3
Association of a mitochondrial PRS and mitochondrial haplogroups (model 1) and their interactions (model 2) with Alzheimer's disease age of onset

Variable	Model 1			Model 2		
	β^a	*SE*	*p*	β^a	*SE*	*p*
Male	−0.21	0.1	0.0034	−0.22	0.1	0.028
APOE status						
ε4+	0.8	0.12	6.50E-12	0.78	0.12	2.70E-11
ε2+	−0.85	0.39	0.029	−0.86	0.39	0.027
PC1	−0.11	0.06	0.073	−0.1	0.06	0.104
PC2	0.03	0.04	0.525	0.03	0.04	0.509
nMT-PRS	0.36	0.06	3.54E-10	0.37	0.08	2.55E-06
Haplogroup						
I	−0.01	0.26	0.958	0.04	0.28	0.879
J	−0.06	0.17	0.707	−0.09	0.19	0.635
K	−0.06	0.18	0.742	−0.05	0.18	0.78
T	−0.31	0.17	0.073	−0.14	0.18	0.422
U	−0.1	0.15	0.528	−0.16	0.17	0.35
V	0.17	0.28	0.549	−0.26	0.38	0.496
W	0.38	0.33	0.247	0.38	0.33	0.241
X	0.08	0.32	0.794	0.16	0.36	0.664
Haplogroup × nMT-PRS						
I	-	-	-	−0.14	0.29	0.617
J	-	-	-	0.08	0.22	0.72
K	-	-	-	−0.06	0.17	0.74
T	-	-	-	−0.48	0.2	0.015
U	-	-	-	0.14	0.15	0.371
V	-	-	-	0.82	0.33	0.013
W	-	-	-	0.13	0.34	0.697
X	-	-	-	−0.13	0.32	0.68

Andrews, S. J. et al. 2020. Neurobiology of Aging

Evaluate the association of pathway specific mitochondrial PRS with AD

Devashi Paliwal

Nuclear-encoded mitochondrial pathway PRS for AD

- Base dataset: Kunkle 2019 AD GWAS
- Target dataset: **ADNI**
- SNPs assigned to nuclear mitochondrial genes, ± 50kb of gene region
- Pruning (r^2 = 0.1; window = 250kb) and thresholding ($p < 0.5$) using PRSet
- Mitochondrial pathways: 12 gene sets obtained from the Molecular signatures database

1. Mitonuclear cross talk
2. Calcium homeostasis and transport
3. Apoptotic mitochondrial changes
4. Mitochondrial fusion
5. Fatty acid and beta oxidation
6. Mitochondrial fission and regulation
7. Mitophagy and regulation
8. Mitochondrial membrane potential regulation
9. Hallmark oxidative phosphorylation
10. Mitochondrial transport
11. Response to oxidative stress
12. All mitochondrial genes

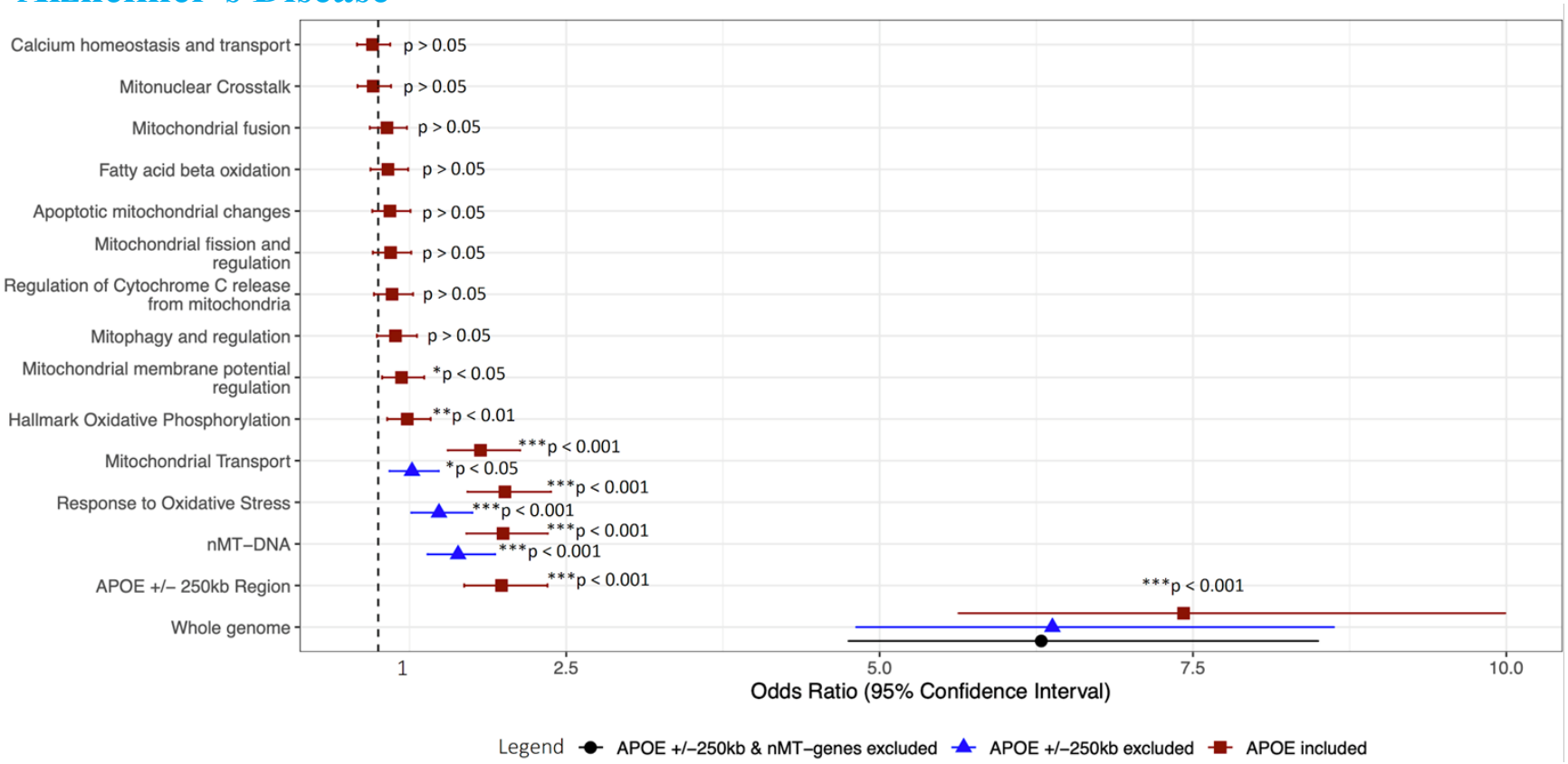
Effect of the pathway nMT-PRS on risk of dementia at last assessment

- binomial multivariate logistic regression models
- adjusting for age, APOE status, sex, and education, the first 3 principal components

Effect of the pathway nMT-PRS on risk CSF Aβ & tau, and cognitive function

- multivariate linear regression models
- adjusting for age, APOE status, sex, and education, the first 3 principal components

Specific mitochondrial pathway polygenic risk scores are associated with Alzheimer's Disease



Paliwal, D. et al. 2021. Neuro. Bio. aging.

Association of pathway specific nMT-PRS on AD endophenotypes

Hallmark oxidative phosphorylation: Increased CSF Tau levels

Response to oxidative stress: Higher ADAS Cog-score and lower mPACCdigit score

Mitochondrial fission and regulation & Mitophagy and regulation: lower mPACCdigit score

Summary

1. Genetic liability for AD is enriched in nuclear mitochondrial genes and increase AD risk
2. Genetic variation on the nuclear- and mitochondrial- genomes interact to influence risk of Alzheimer's disease
3. Genetic variation with specific mitochondrial pathways is associated with increased risk of Alzheimer's disease

Acknowledgements

MitoWAX


Russ Swerdlow


Judy Pa


Devashi Paliwal


Nadia Harerimana


Carmen Romero-Molina


Tim McInerney

alzheimer's association®

NIH National Institute on Aging

Goate Lab
Alison Goate
Edoardo Marcora
Brian Fulton-Howard

The Andrews Lab is now hiring!

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