The Hidden Job Of The Cell’s Powerhouse

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Energy hypothesis of aging

Public Health Significance

- Energy central to health in later life
- Paths that lead to energy dysregulation are not well characterized
- Examine a key component of the energy machinery and its relationship to aging and aging-related disease

Mitochondria

Disability

What are Mitochondria?

• “Powerhouse of the cell” (primary site of ATP synthesis in aerobic metabolism)

• Tens to thousands exist within each cell in your body

• Each mitochondrion has its own DNA

• Other roles
  ➢ Cell-to-cell communication
  ➢ Programmed cell death
Hypothesis

Given the central role of the mitochondria in energy production and maintenance, we hypothesize that the number of mitochondria will influence aging and age-related disease.
How do we measure the number of mitochondria?

- Mitochondria have their own DNA (mtDNA)

- Nuclear DNA (nucDNA) is always in 2 copies (inherited from Mom and Dad)

- The ratio of the mtDNA to nucDNA gives a standardized measure of mtDNA.

- Can be measured in DNA extracted from blood.
Association of mitochondrial DNA levels with frailty and all-cause mortality

Foram N. Ashar · Anna Moes · Ann Z. Moore · Megan L. Grove · Paulo H. M. Chaves · Josef Coresh · Anne B. Newman · Amy M. Matteini · Karen Bandeen-Roche · Eric Boerwinkle · Jeremy D. Walston · Dan E. Arking

15-year survival

Q1: 43%
Q5: 61%

50% survival (yrs): 13.5 >16.5

15-year survival

Q1: 27%
Q5: 41%

50% survival (yrs): 9.5 13.5
Association between mitochondrial DNA copy number and sudden cardiac death: findings from the Atherosclerosis Risk in Communities study (ARIC)

Yiyi Zhang¹, Eliseo Guallar¹, Foram N. Ashar², Ryan J. Longchamps², Christina A. Castellan³, John Lane³, Megan L. Grove⁴, Josef Coresh¹, Nona Sotoodehnia⁵, Leonard Ilkhanoff²,⁷, Eric Boerwinkle⁶,⁸, Nathan Pankratz¹, and Dan E. Arking²*
Association between Mitochondrial DNA Copy Number in Peripheral Blood and Incident CKD in the Atherosclerosis Risk in Communities Study

Adrienne Tin,* Morgan E. Grams,† Foram N. Ashar,‡ John A. Lane,§ Avi Z. Rosenberg,‖ Megan L. Grove,** Eric Boerwinkle,** Elizabeth Selvin,* Josef Coresh,* Nathan Pankratz,§ and Dan E. Arking†
### Incident cardiovascular disease

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No.</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>10150</td>
<td>1500</td>
<td>1.40 (1.34-1.46)</td>
</tr>
<tr>
<td>CHS</td>
<td>4126</td>
<td>1743</td>
<td>1.06 (1.01-1.12)</td>
</tr>
<tr>
<td>MESA</td>
<td>5887</td>
<td>422</td>
<td>1.14 (1.03-1.25)</td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>3236</td>
<td>142</td>
<td>1.30 (1.10-1.53)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>2651</td>
<td>280</td>
<td>1.06 (0.95-1.20)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>20163</td>
<td>3665</td>
<td>1.23 (1.19-1.26)</td>
</tr>
</tbody>
</table>

Approximately 70% higher risk of CVD comparing bottom 20% to top 20% of samples.
Does including mtDNA-CN in the ACC/AHA risk score improve sensitivity and specificity for initiating statin therapy?

Excluded individuals whose risk score would not impact therapy decisions based on the 2013 ACC/AHA guidelines (i.e., prevalent CVD, age >75 years, prevalent diabetes, LDL≥190, or LDL<70)

Overall, a net of 15 individuals with events were appropriately upclassified, and 221 individuals without events were appropriately downclassified.

Using a hard cutoff of 7.5% 10-year CVD risk for starting statin therapy, a net of 6 additional individuals would appropriately take a statin, and 139 would be appropriately not recommended to take a statin.

### Table 4. Net Reclassification Index and IDI Comparing AHA Risk Score With and Without mtDNA-CN in the Pooled Cohorts

<table>
<thead>
<tr>
<th>Event</th>
<th>AHA Risk Score + mtDNA-CN</th>
<th>Recalibrated AHA Risk Score + mtDNA-CN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5% Risk</td>
<td>5% to 10% Risk</td>
</tr>
<tr>
<td>Persons without event, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5% Risk</td>
<td>4833</td>
<td>241</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimate (95% CI)</th>
<th>P Value</th>
<th>Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI Categorical</td>
<td>0.032 (0.015-0.049)</td>
<td>&lt;.001</td>
<td>0.022 (0.004-0.039)</td>
</tr>
<tr>
<td>NRI Continuous</td>
<td>0.194 (0.130-0.258)</td>
<td>&lt;.001</td>
<td>0.156 (0.092-0.220)</td>
</tr>
<tr>
<td>IDI</td>
<td>0.009 (0.005-0.012)</td>
<td>&lt;.001</td>
<td>0.004 (0.002-0.007)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; IDI, integrated discrimination improvement; mtDNA-CN, mitochondrial DNA copy number; NRI, net reclassification index.

* Categorical NRI with <5.0% and 5% to <7.5% risk cutoffs. Ten-year hard atherosclerotic cardiovascular disease risk was estimated in the pooled cohorts using Cox proportional hazards regression, using similar criteria as the 2013 AHA/ACC guidelines. \(^{15}\)
Conclusions

• mtDNA-CN is a novel independent risk factor for aging-related disease (frailty, mortality, CVD, SCD), with potential clinical utility (CVD)

• Mendelian Randomization is suggestive for causality – important when considering drug therapy for patients
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