RCCN Workshop: Measuring Biologic Age

How Useful are Phenotypic Extremes (Centenarians)?

Sofiya Milman, MD, MSc
Centenarians are a model of successful aging

Adapted from Mark Collins-Glenn Foundation

Biological Mechanism of Healthy Longevity
## Phenotypic approach: Centenarians vs. General Population Control

### Cross-sectional analysis

**Prevalence of Abdominal Obesity**

- Centenarians: 35.7%
- < 100 years: 28.2%

### Retrospective analysis

**Maximum BMI and Prevalence of Overweight/Obesity During the Lifetime in Females**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Centenarians (n=249)</th>
<th>NHANES I (n=7,924)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum, mean ± SD</td>
<td>25.0 ± 3.5</td>
<td>24.9 ± 5.4</td>
<td>0.90</td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>56.2</td>
<td>58.8</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt;25.0</td>
<td>43.8</td>
<td>41.2</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*Fu S et al. Cellular and Molecular Immunology 2020*  
Genetic Approach to Exceptional Longevity

Milman S et al. Curr Vasc Pharm 2012
Genetic Approach to Exceptional Longevity: IGF/Insulin Signaling Pathway

<table>
<thead>
<tr>
<th>Genetic variation</th>
<th>Centenarians (n=384)</th>
<th>Controls (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala 37 Thr</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Arg 407 His</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

\[ p = 0.02 \]

Suh Y et al. PNAS 2008

Lin JR et al. Nat Aging 2021; in press
Phenotypic approach: Centenarians’ Offspring vs. General Pop Control

Barzilai et al. JAMA 2003
Milman et al. Curr Vasc Pharm 2014

*p<0.001
Centenarians and their offspring have lower prevalence of age-related diseases

Plasma proteomic profile of age in Offspring (OPEL) vs. Control (OPUS)

Sathyan S et al. Aging Cell 2020
Plasma proteomic profile of age in Offspring (OPEL) vs. Control (OPUS)

Sathyan S et al. Aging Cell 2020

<table>
<thead>
<tr>
<th>Module</th>
<th>Trait</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEred</td>
<td>Age</td>
<td>-0.041</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Frailty Index</td>
<td>0.024</td>
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<tr>
<td></td>
<td>Death</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>0.0036</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>Glucose Fasting</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>-0.031</td>
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<tr>
<td></td>
<td>LDL</td>
<td>0.057</td>
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<tr>
<td></td>
<td>Triglycerides</td>
<td>0.0035</td>
</tr>
<tr>
<td></td>
<td>Gait velocity</td>
<td>0.004</td>
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<tr>
<td></td>
<td>Grip Strength</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Language</td>
<td>0.009</td>
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<tr>
<td></td>
<td>Attention</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>VisuoMotor</td>
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<tr>
<td></td>
<td>Executive</td>
<td>0.007</td>
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<tr>
<td></td>
<td>Memory</td>
<td>0.0051</td>
</tr>
<tr>
<td></td>
<td>Overall Cognition</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Module-trait relationships

- MEyellow
- MEblue
- MEPink
- MEblack
- MEGreen
- MEMagenta
- MEBrown
- METurquoise

Sathyan S et al. Aging Cell 2020
Conclusions

- Centenarians are a model of delayed biological aging
- At end of life, centenarians’ biochemical phenotype may not always reflect longevity, but be a marker of aging
- Centenarians’ offspring should be used for identifying healthy aging and resilience biomarkers
- Centenarians and their offspring are valuable for identifying genetic determinants of delayed aging
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