Clonal hematopoiesis of indeterminate potential: A joint risk factor for cancer and atherosclerosis

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  – Spousal employment: Vertex

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  – None
‘Clonal Hematopoiesis of Indeterminate Potential’

Welch JS et al. *Cell.* 2012

1 in 10 individuals >70 years have CHIP

Clinical risk factors of CHIP mirror CVD risk factors

<table>
<thead>
<tr>
<th></th>
<th>Beta coefficient</th>
<th>OR(95 CI)</th>
<th>p-value</th>
<th>Variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.07</td>
<td>1.08(1.07-1.09)</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>European (referent)</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>African-American</td>
<td>0.15</td>
<td>1.16(0.93-1.44)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>East-Asian</td>
<td>-0.08</td>
<td>0.92(0.71-1.2)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>-0.37</td>
<td>0.69(0.56-0.85)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>South Asian</td>
<td>-0.25</td>
<td>0.78(0.61-1)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>No T2D (referent)</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Has T2D</td>
<td>0.28</td>
<td>1.32(1.14-1.54)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male (referent)</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.01</td>
<td></td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02</td>
<td>0.98(0.96-0.99)</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Age:Female</td>
<td>-0.02</td>
<td></td>
<td>0.009</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1.4-fold risk for all-cause mortality


CHIP is associated with increased CAD and early-onset MI risk

### A CHIP and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants with Coronary Heart Disease/No. at Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biolmage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>94/326</td>
<td>1.8 (1.1–2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mutation</td>
<td>19/44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>299/607</td>
<td>2.0 (1.2–3.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mutation</td>
<td>21/33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-effects meta-analysis</td>
<td></td>
<td>1.9 (1.4–2.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### B CHIP and Early-Onset Myocardial Infarction

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants with Myocardial Infarction/No. at Risk</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>1716/3293</td>
<td>5.4 (2.3–13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mutation</td>
<td>37/43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROMIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>2488/3844</td>
<td>3.4 (1.8–6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mutation</td>
<td>52/65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-effects meta-analysis</td>
<td></td>
<td>4.0 (2.4–6.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
CHIP, particularly ‘large CHIP,’ is associated with incident CVD risk

Bick A*, Pirruccello J*, …Natarajan P.
Circulation. 2020
Another form of clonal hematopoiesis is not linked to CAD


Humans and mice with CHIP have a greater burden of subclinical atherosclerosis

A Aortic-Root Sections, According to Tet2 Status

5 Wk

WT

KO

9 Wk

B CHIP and CAC Score of ≥615 Agatston Units, According to Variant Allele Fraction

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants with High CAC/No. at Risk</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation (reference)</td>
<td>30/207</td>
<td>3.0 (1.0–8.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mutation</td>
<td>7/19</td>
<td>0.9 (0.2–4.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>VAF &lt;0.10</td>
<td>2/11</td>
<td>12.0 (2.4–64.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>VAF ≥0.10</td>
<td>5/8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inhibition of NLRP3 inflammasome mitigates atherogenesis in murine model

Fuster JJ et al. Science. 2017
CANTOS Trial

B Primary End Point with Canakinumab, 150 mg, vs. Placebo

Hazard ratio, 0.85 (95% CI, 0.74–0.98)
P=0.021

Cumulative Incidence of Primary End Point (%)

Years

No. at Risk
Placebo 3344 3141 2973 2632 1266 210
Canakinumab 2284 2151 2057 1849 907 207

Ridker PM et al. N Eng J Med. 2017
CANTOS: TET2 CHIP may predict greater CVD relative risk reduction from IL1B inhibition

• Overall trial: HR 0.85 (Ridker P et al. *NEJM* 2017)

• TET2 CHIP carriers (104 / 3925): HR 0.36 (Svensson EC et al. AHA Abstract 15111. 2018)
CHIP-associated CHD risk is specifically abrogated when IL6R p.Asp358Ala is present.

Bick A*, Pirruccello J*, ...Natarajan P. Circulation. 2020
Accelerated ovarian aging is correlated with clonal hematopoiesis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surgical Premature Menopause</th>
<th>Natural Premature Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>First cardiovascular disease diagnosis</td>
<td>2.21 (1.66-2.92)</td>
<td>1.60 (1.42-1.80)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.76 (2.42-5.86)</td>
<td>1.81 (1.44-2.28)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.74 (1.42-5.29)</td>
<td>1.56 (1.14-2.16)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>3.41 (1.27-9.16)</td>
<td>2.48 (1.62-3.80)</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>3.40 (1.41-8.27)</td>
<td>0.95 (0.52-1.74)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.87 (1.14-3.06)</td>
<td>1.44 (1.18-1.77)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.18 (0.38-3.66)</td>
<td>1.59 (1.12-2.28)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2.19 (0.70-6.83)</td>
<td>1.96 (1.27-3.03)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.57 (1.41-4.67)</td>
<td>1.68 (1.29-2.20)</td>
</tr>
</tbody>
</table>


CHIP is more common among people living with HIV


CHIP is enriched for individuals with an unhealthy diet, and stratifies CHIP-associated CAD risk.

Germline genetic factors influence CHIP

TERT

KPNA4

TET2

MBD3

4,431 cases / 85,405 controls

Prognosis is worse in the setting of other cardiovascular conditions

**Heart Failure**

Overall survival of patients with **DNMT3A** or **TET2** mutations

- No mutation
- TET2/DNMT3A

*Take home figure* Overall survival of patients with **DNMT3A**- or **TET2**-CHP-driver mutations with a variant allele frequency ≥ 2% vs. patients without **DNMT3A** or **TET2** mutations. *Patients with follow-up <30 days have been excluded in order to remove mortality due to peri-procedural complications.*

Dorsheimer L, et al. *JAMA Cardio*. 2019

**Aortic Stenosis**

Conclusions

• Clonal hematopoiesis of indeterminate potential (CHIP) represents a new risk factor for ASCVD

• CHIP is not readily identifiable by current clinical assessments

• NLRP3/IL1B/IL6 axis inhibition may be a particularly effective strategy to reduce ASCVD risk conferred by CHIP

• CHIP may be implicated in other age-related cardiovascular condition
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Rachel Bernardo, BS

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Tinamarie Desmarais, RN

Computational biologist
Akhil Pampana, MS

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Undergraduate students
Adyant Shankar

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NHLBI R01HL148050 (Natarajan, Ballantyne)
NHLBI R01HL151283 (Natarajan)
NHLBI R01HL127564 (Natarajan, Peloso)
NHLBI R01HL148565 (Reiner, Whitsel)
NHLBI R01HL135242 (Nguyen)
NHLBI R01HL151152 (Kooperberg)
NIDDK R01DK125782 (Kelly)
Leducq TNE-18CVD04 (Tall, Sohnlein)
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