Clonal Hematopoiesis of Indeterminate Potential (CHIP) & Cardiovascular Disease

Alexander Bick, MD PhD
abick@mgh.harvard.edu
WHI Investigator Meeting | 5/3/2019
Outline

Background: CHIP and Cardiovascular Disease

Findings from NHLBI TOPMed

CHIP Research Opportunities in WHI
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

CHIP Definition: Mutant clone in >2% peripheral leukocytes

Random Mutations

CHIP Driver Mutation

$DNMT3A, TET2, ASXL1, JAK2, [...]$
Identifying CHIP in sequence data

DNMT3A
CHIP Prevalence in the Population

Proportion Carriers

Age (y)

Genovese G et al 2014
Jaiswal S et al 2014
Xie M et al 2014

Natarajan, Jaiswal, Kathiresan, Circ Genomic Med. 2018
CHIP associated with mortality

Genovese, NEJM 2014

Jaiswal, NEJM 2014
CHIP associated with Atherosclerotic CVD

CHIP associates with Coronary Disease

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Mutation</td>
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<td>Mutation</td>
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<td>Fixed-effects meta-analysis</td>
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<tr>
<td></td>
<td>1.9 (1.4–2.7)</td>
<td>&lt;0.001</td>
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CHIP associates with Early MI

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<td>Fixed-effects meta-analysis</td>
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<td>4.0 (2.4–6.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Jaiswal*, Natarajan* et al, NEJM 2017
Mouse Models: TET2 CHIP accelerates atherosclerosis

Jaiswal*, Natarajan* et al, NEJM 2017
Similar findings: Fuster, Science, 2017
CHIP may guide CVD therapy

CANTOS trial:
Individuals with ASCVD and elevated hsCRP treated with IL-1β inhibitor had a 15% reduction in CVD events (p=0.005).

*Ridker et al, NEJM 2017*

CANTOS *TET2 CHIP* \(^+\) subgroup:
64% reduction in CVD events (p=0.034)

*Svensson et al, Abstract 15111, AHA 2018*
Summary: CHIP & CVD

Genes with CHIP Driver Mutations

- DNMT3A
- TET2
- ASXL1
- JAK2
- Unknown drivers

Risk of CHIP and CHIP-associated consequences

Age

Hematological malignancy
ASCVD
Myocardial Infarction
Heart Failure
VTE/PE

Bone Marrow
Peripheral Blood

Khetarpal, Bick, et al JACC (in press)
Outline

1. Background: CHIP and Cardiovascular Disease
2. Findings from NHLBI TOPMed
3. CHIP Research Opportunities in WHI
NHLBI TOPMed: 150,000+ Genomes

- European ancestry: 58,570 (40%)
- African ancestry: 45,840 (32%)
- Hispanic/Latino: 23,500 (16%)
- Asian ancestry: 13,700 (10%)
- Other: 3,410 (2%)

- Heart: 54,770 (38%)
- Lung: 48,360 (33%)
- Multi-phenotype: 28,460 (20%)
- Blood: 12,460 (8%)
- Sleep: 1,000 (1%)

- Hemophilia
- Sickle Cell Disease
- Platelets
- Lipids
- Hypertension
- Myocardial Infarction
- Coronary Artery Disease
- Stroke
- Small Vessel Disease
- Venous Thromboembolism
- Congenital Heart Disease
- Atrial Fibrillation
- Adiposity
- Congestive Heart Failure

4/4/2019
CHIP prevalence with aging in TOPMed
CHIP prevalence by study

WHI
N= 11,069
N_{chip}=1010
CHIP causes & consequences in TOPMed

1. Germline genetic variation & CHIP
2. Multi-omics to deconvolute how CHIP causes disease
3. Identify associations with heart, lung & blood diseases
Single variant genetic determinants of CHIP carrier status

TERT

TET2
Outline

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WHI: Scientific Questions

• Who develops CHIP?
• How does CHIP progress over time?
• What diseases and sub-clinical phenotypes are associated with CHIP and CHIP progression?
WHI: Identifying CHIP Carriers

• 11,069 WHI-TOPMed participants
  • Includes ~1,400 WHI-LLS participants

• New WHI R01: detect CHIP by targeted sequencing
  • 6,400 WHI-LLS at baseline
  • 7,800 WHI-LLS at LLS exam (~15 years later).

PIs: Eric Whitsel & Alex Reiner
WHI CHIP R01: Overview

Exposures
- Socio-demographic
  - Age
  - SES
  - Race/ethnicity
- Cardiometabolic
  - Lipids
  - Insulin resistance
  - Inflammation markers (CRP, IL-6, IL-1b)
- Behavioral
  - Smoking
  - Diet
  - Physical activity
- Pharmacologic
  - Hormone Therapy
- Environmental
  - Air pollution
  - Noise pollution
  - Radiation
- Aging-related
  - DNA methylation
  - Telomere length

Mutation

CHIP
Progression
Risk
Outcomes
- Cardiovascular
  - CHD & MI
  - Stroke
  - VTE
- Neurocognitive
  - Cognitive decline
  - Dementia
- Hematological
  - Quantitative blood cell traits
  - Benign disorders
    - anemia; MGUS; MBL
- Mortality
  - All-cause
  - Cause-specific

PIs: Eric Whitsel & Alex Reiner
WHI CHIP R01: Specific Aims

1) Estimate associations between prevalent CHIP (at baseline), incidence or progression of CHIP (between baseline and LLS exams), and exposures/ biomarkers

2) Assess **CHIP heritability** and identify novel germline genomic factors associated with CHIP

3) Using the combined WHI-TOPMed and WHI-LLS cohort baseline CHIP data (total N~17,000), estimate associations of CHIP with **disease outcomes**

4) Assess **causal mediation of exposure-outcome associations** by CHIP using an integrative multi-omics approach

PIs: Eric Whitsel & Alex Reiner
WHI CHIP Manuscript Proposals

Leadership: JoAnn Manson, Alex Reiner, Eric Whitsel

- CHIP & CVD: Natarajan, Reiner, Kooperberg, Manson
- Heart failure: Reiner, Eaton
- VTE: Natarajan
- Cancer: Desai
- Anemia: Reiner, Manson, Kooperberg
- Cognitive decline in WHIMS: Driscoll
- Diabetes: Manson, Tobias
- Healthy Lifestyle: Haring
- Bone/musculoskeletal outcomes: Jackson
- Germline gene variants: Reiner, Handelman
- Environmental exposures: Whitsel, Reiner, Assimes
- DNA methylation & telomeres: Whitsel, Reiner, Assimes, Kooperberg
- Sleep: Redline
- Autoimmune disorders: Lee
CHIP associates with CVD in humans & mouse models

Identifying CHIP in 100,000 people finds germline genetic causes of CHIP

Many opportunities to get involved in WHI CHIP Research
Acknowledgements

• Alex Reiner
• Charles Kooperberg
• JoAnn Manson

• Pradeep Natarajan
• Sek Kathiresan
• Sidd Jaiswal

• NHLBI TOPMed Project
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