Clonal hematopoiesis of indeterminate potential and MDS

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Clonal evolution from birth to death
Might “pre-malignant” clones, bearing only the initiating lesion, be present in a much larger fraction of people than those with cancer?

Does the presence of these lesions increase risk for cancer, or other diseases?
Type 2 diabetes (T2D) exome sequencing project

22 population based cohorts in 3 consortia

~17,000 subjects:
- Unselected for hematologic or malignant phenotypes
- Half with T2D
- Multiple ancestry groups
- Median age 59
- Exome sequencing performed at the Broad Institute

Importantly:
- Buffy coat derived DNA!
- Prospective, longitudinal, with outcome data on some subjects
Type 2 diabetes (T2D) exome sequencing project

- BAMs from Picard alignment
- Run Mutect (OxoG) and Indelocator
- Make **pre-specified** variant calls for a panel of 160 genes known to be involved in myeloid and lymphoid malignancies
At least ten percent of everyone over the age of 70 has a detectable clonal mutation.
Commonly mutated genes in clonal hematopoiesis
Mutation effects

• DNMT3A
  – Frameshift, nonsense, and splice-site throughout coding sequence
  – Missense in key domains (methyltransferase, ADD, PWWP)
• TET2
  – Frameshift and nonsense throughout coding sequence
  – Very rare splice-site mutations
  – Missense in catalytic domains
• ASXL1
  – Frameshift and nonsense in exons 11 and 12
• JAK2
  – Constitutively activating mutation (V617F)
Most subjects had only 1 detectable mutation
Unlike other pre-malignant states, clonal hematopoiesis affects a large proportion of the affected organ. On average, ~18% of blood cells are part of the clone.
Mutations persist over time

17 variants in 13 persons were detectable 4 to 8 years later
Clonal hematopoiesis is associated with increased risk of hematologic malignancy

HR 11, 95% CI 3.9 to 33, p<0.001, adjusted for age, sex and T2D status
Clonal hematopoiesis antecedes myeloid and lymphoid malignancies

<table>
<thead>
<tr>
<th>Age at sampling</th>
<th>Diagnosis</th>
<th>Cohort</th>
<th>Latency (years)</th>
<th>Mutations (VAF)</th>
<th>WBC ($10^9$/L)</th>
<th>HGB (g/dL)</th>
<th>PLT ($10^9$/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>CANCER OF SPLEEN</td>
<td>AJ</td>
<td>6</td>
<td>JAK2 p.V617F (0.23)</td>
<td>7.8</td>
<td>11</td>
<td>247</td>
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<tr>
<td>64</td>
<td>LEUKEMIA (prior NHL)</td>
<td>AJ</td>
<td>7</td>
<td>ASXL1 p.D616fs (0.18)</td>
<td>3.5</td>
<td>12.9</td>
<td>189</td>
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<tr>
<td>57</td>
<td>LYMPHOMA</td>
<td>AJ</td>
<td>2</td>
<td>DNMT3A p.R882H (0.29)</td>
<td>14.3 (51.3% lymphocytes)</td>
<td>11</td>
<td>248</td>
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<tr>
<td>85</td>
<td>DLBCL, large intestine</td>
<td>MEC</td>
<td>5</td>
<td>TET2 p.C1135Y (0.35)</td>
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<td>TET2 p.G1192V (0.30)</td>
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<td>ASXL1 p.I919fs (0.26)</td>
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<tr>
<td>82</td>
<td>MDS-RAEB</td>
<td>MEC</td>
<td>7</td>
<td>ASXL1 p.T514fs (0.30)</td>
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<td>TET2 p.1616fs (0.15)</td>
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</table>
A new clinical entity: Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Defined as a detectable clonal mutation in the blood of healthy persons without known hematologic disorder
- Is common with aging (present in at least 10% of all persons age>70)
- Associated with increased relative risk of malignancy, but low absolute risk (~0.5-1% per year)
- Associated with cardiovascular disease, but unclear if it is a risk factor, or merely correlated
- No current rationale for screening of healthy persons
Clonal hematopoiesis without known drivers occurs frequently

1. Large structural variation
2. Exonic mutations in unknown genes
3. Non-exonic mutations
4. “Epi-mutation”
5. Loss of clonal diversity due to stem cell attrition

Genovese et al., *NEJM* 2014
Clonal hematopoiesis as a natural “saturation mutagenesis” experiment of human HSCs

Hypothesis:
All possible somatic mutations that can occur will occur in a large enough population.

Those that are neutral or deleterious will not be detected.

Those which become detectable will point to biological pathways that promote self-renewal, block differentiation, or inhibit apoptosis, all of which result in clonal expansion.
Binomial probability as a somatic mutation classifier
Nonsense somatic mutation screen (46K)

409,387 nonsense variants (76,378 unique in 16,585 genes)

\[ \downarrow \]

Variants due to Oxo-G artifact

406,258

\[ \downarrow \]

Genes with low VAF for known germline SNPs (<0.40)

324,422 (65,376 unique in 14,351 genes)

\[ \downarrow \]

Genes that have 50% or more variants at >0.35 VAF

25,155 (2,163 unique in 978 genes)

\[ \downarrow \]

Variants present 7 or more times

2,575 (2,059 unique in 967 genes)

\[ \downarrow \]

Variants that segregate by ancestry (chi-sq test)

2,371 (1,956 unique in 936 genes)

\[ \downarrow \]

Deviation from binomial distribution at \( q < 0.05 \)

1,844 (1,544 unique in 853 genes)

Exome Aggregation Consortium
New genes account for ~15% of mutations
• Zinc finger containing protein; unknown binding specificity
• May function as a co-repressor for androgen receptor target genes
• Required for IgD expression from shared IgD/IgM \( lgh \) transcript
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