

Integrative population-based characterization of mosaic chromosomal alterations uncovers etiologic insights for hematologic malignancies

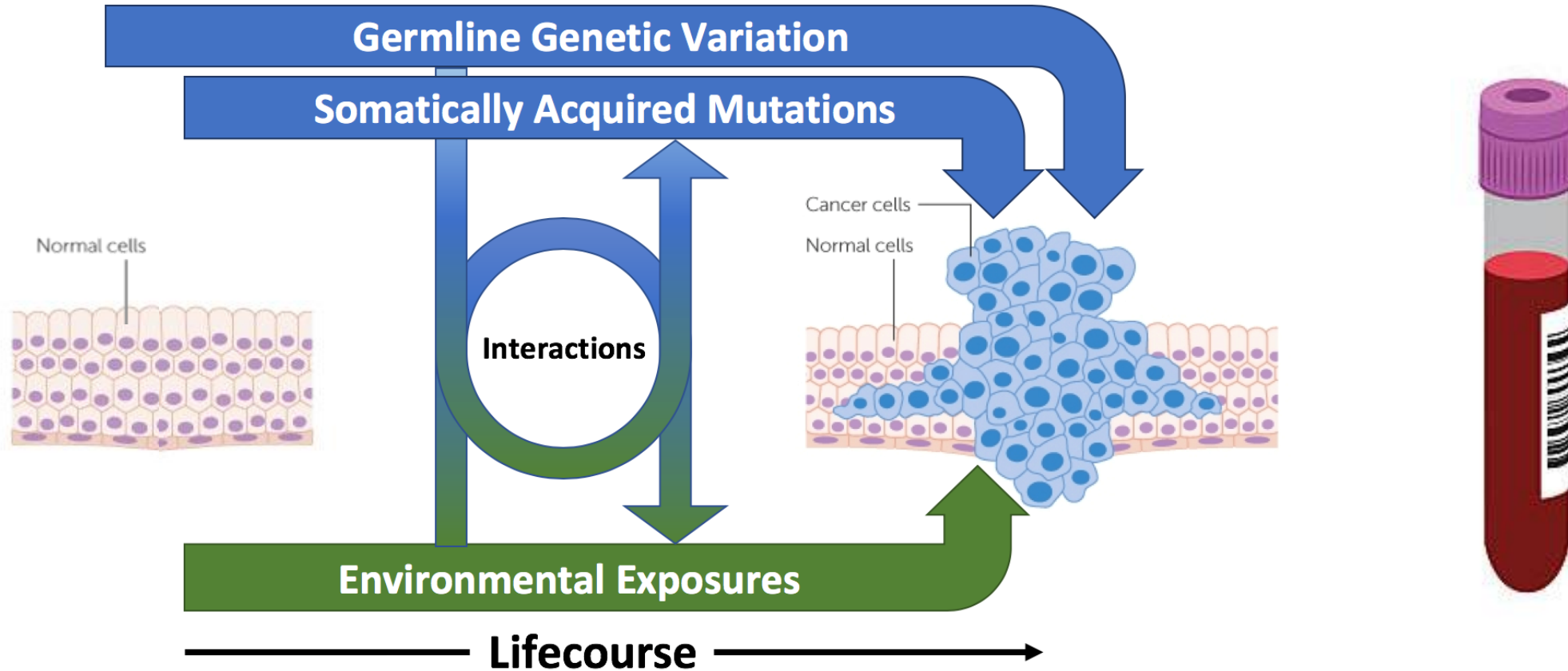
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Earl Stadtman Investigator

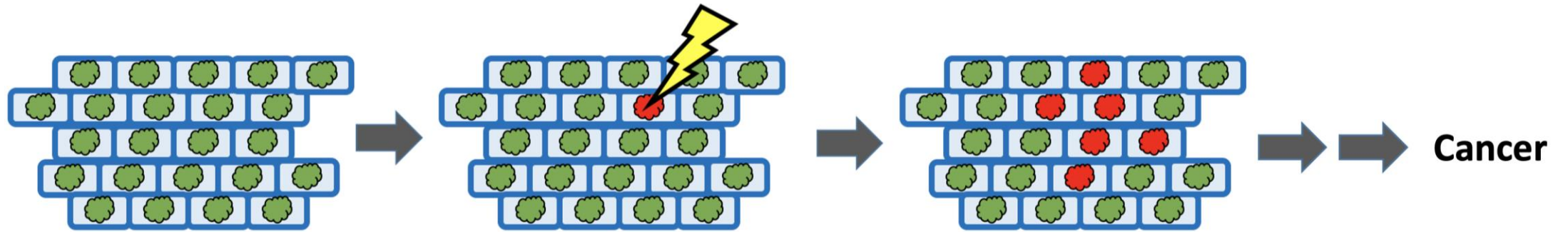
Integrative Tumor Epidemiology Branch

Division of Cancer Epidemiology and Genetics

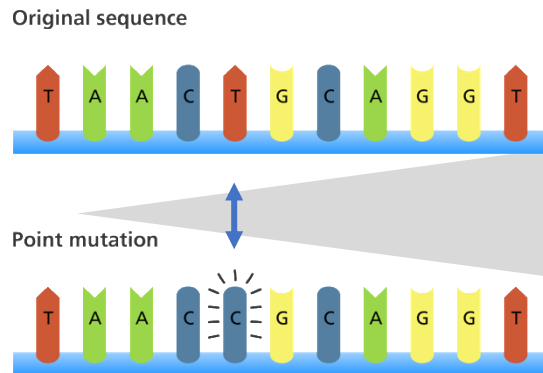
Integrative Analyses in Normal Tissues Expand Knowledge of the Genetic Etiology of Cancer



Detectable Clonal Hematopoiesis (CH)



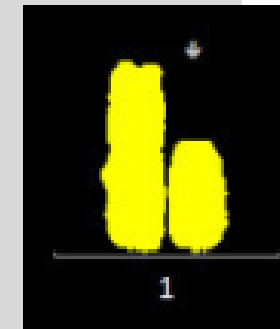
Clonal Hematopoiesis of Indeterminant Potential (CHIP)



Next generation sequencing

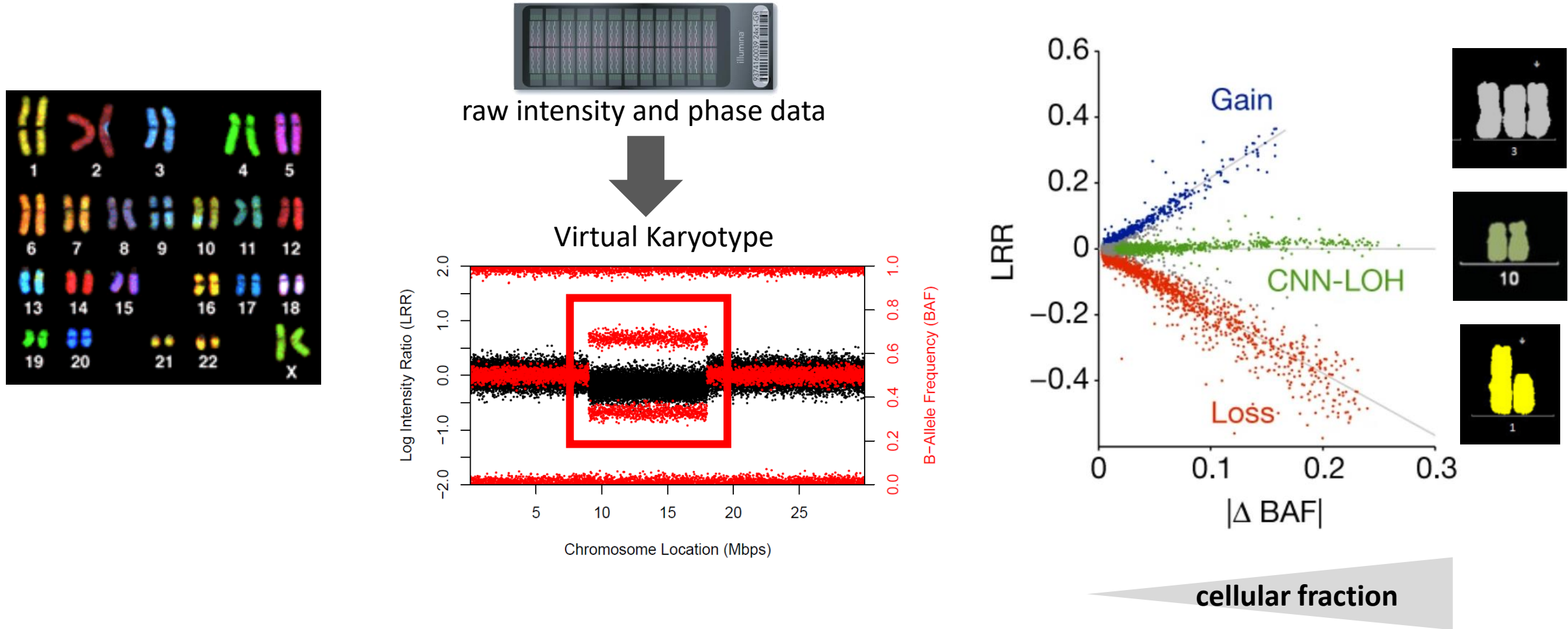
Size spectrum of CH

Mosaic Chromosomal Alterations (mCAs)



Genotyping arrays

Repurposing Genotyping Array Intensity Data to Detect Mosaic Chromosomal Alterations (mCAs)



Estimates of mCA Frequency Vary by Chromosome

Autosomal mCAs (3-5%)



Machiela AJHG 2015

Mosaic Y Loss (20%+)



Zhou Nat Genet 2016

Mosaic X Loss (10-12%)



Machiela Nat Comm 2016, Liu Nature (in press)

Male X Mosaicism (0.006%)



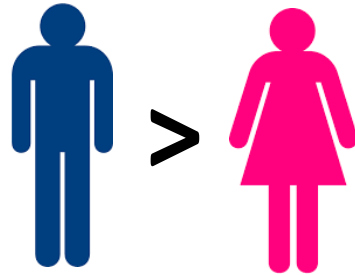
Zhou Sci Rep 2021

mCA Frequencies Differ by Individual Characteristics

Aging



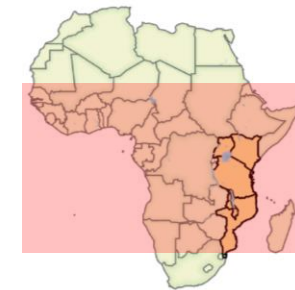
Sex



Ancestry



Geography



malaria
belt

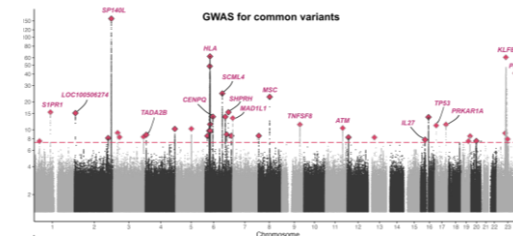
Smoking



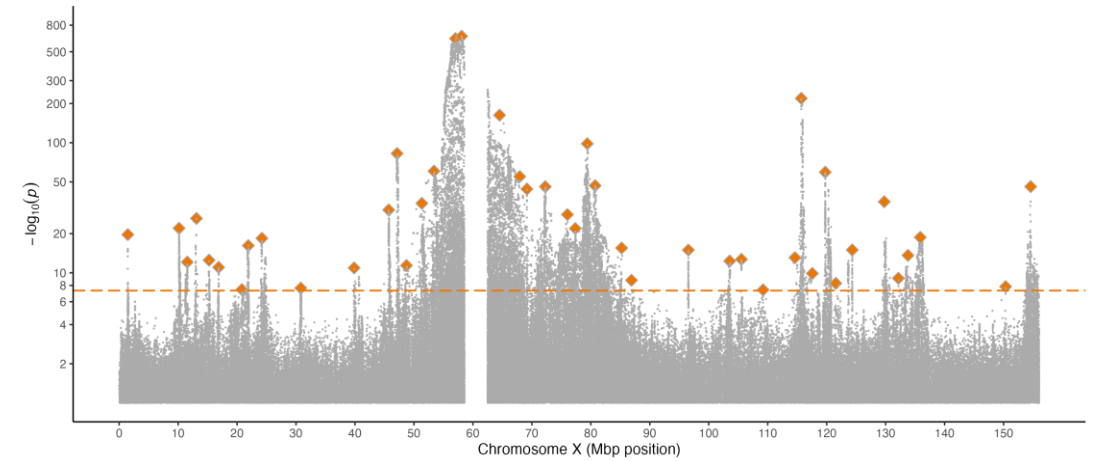
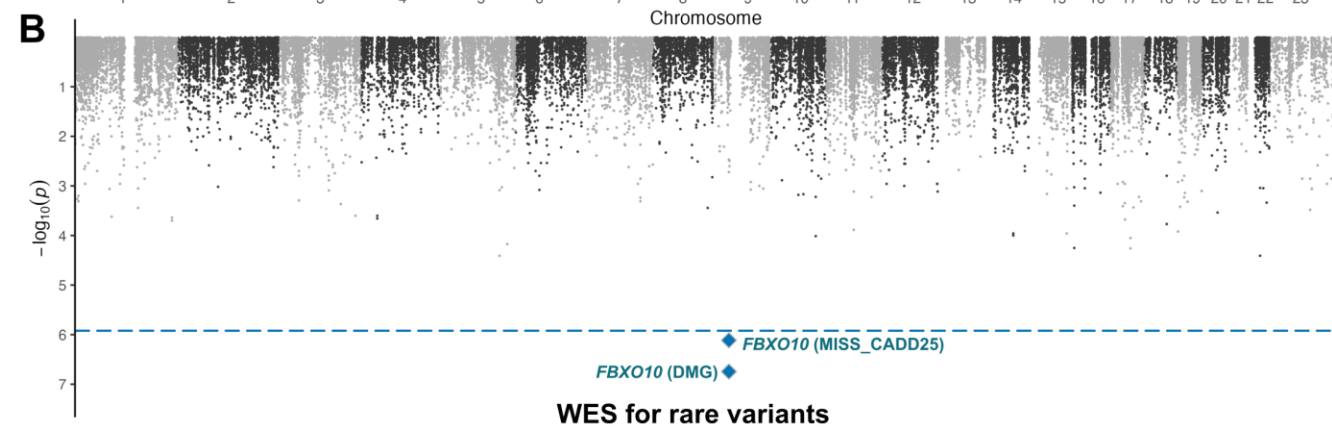
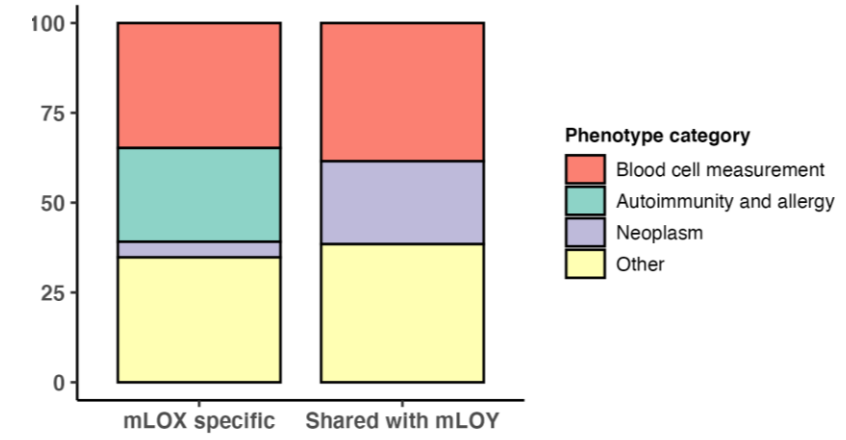
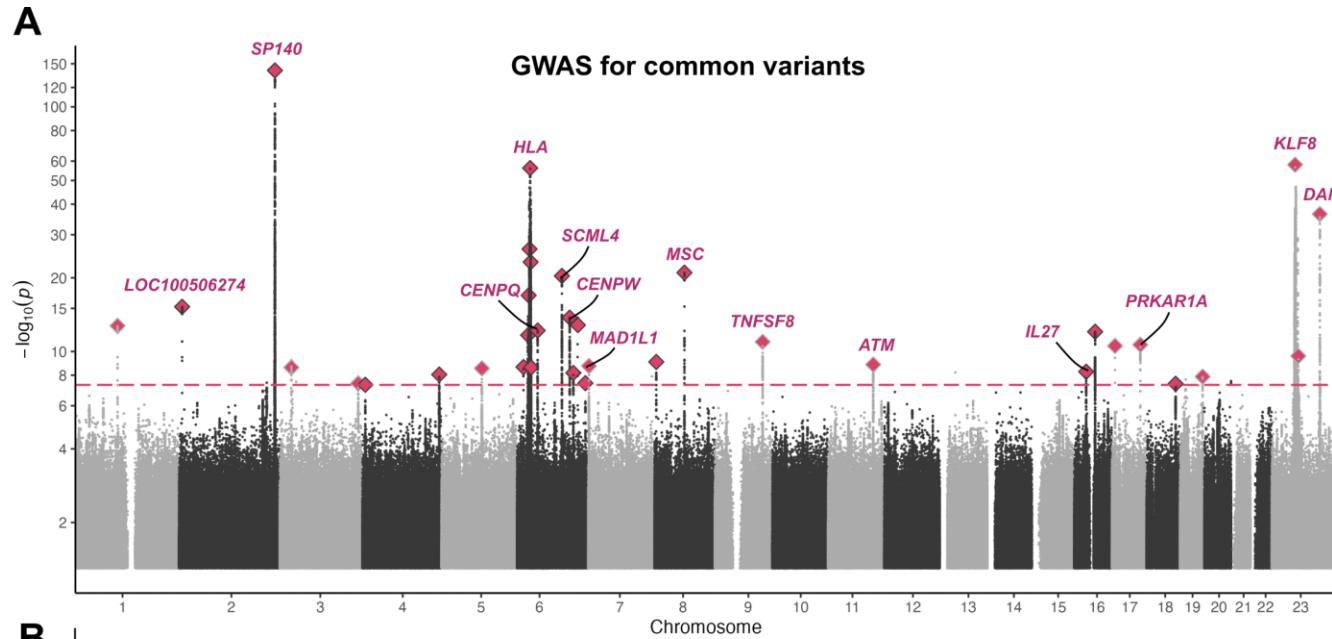
Telomere Length



Germline Variation

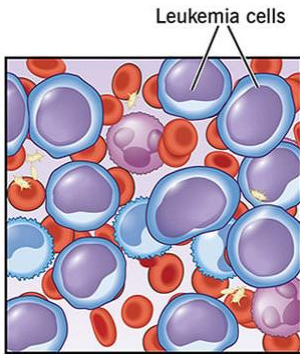


Genetic Drivers and Widespread Signatures of Cellular Selection for Mosaic X Loss



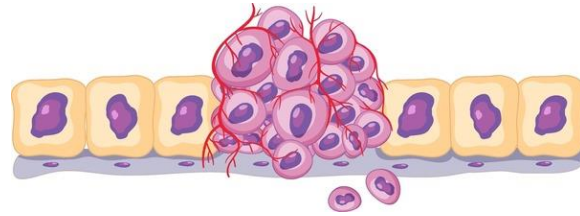
Various Outcomes are Associated with mCAs

Leukemia Risk



HR>15

Solid Tumor Risk



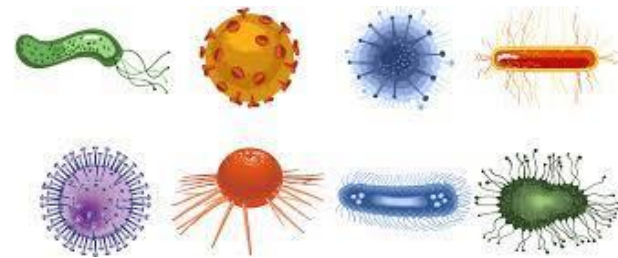
Telomere Length Attrition



Alterations in Blood Counts



Infectious Disease Risk

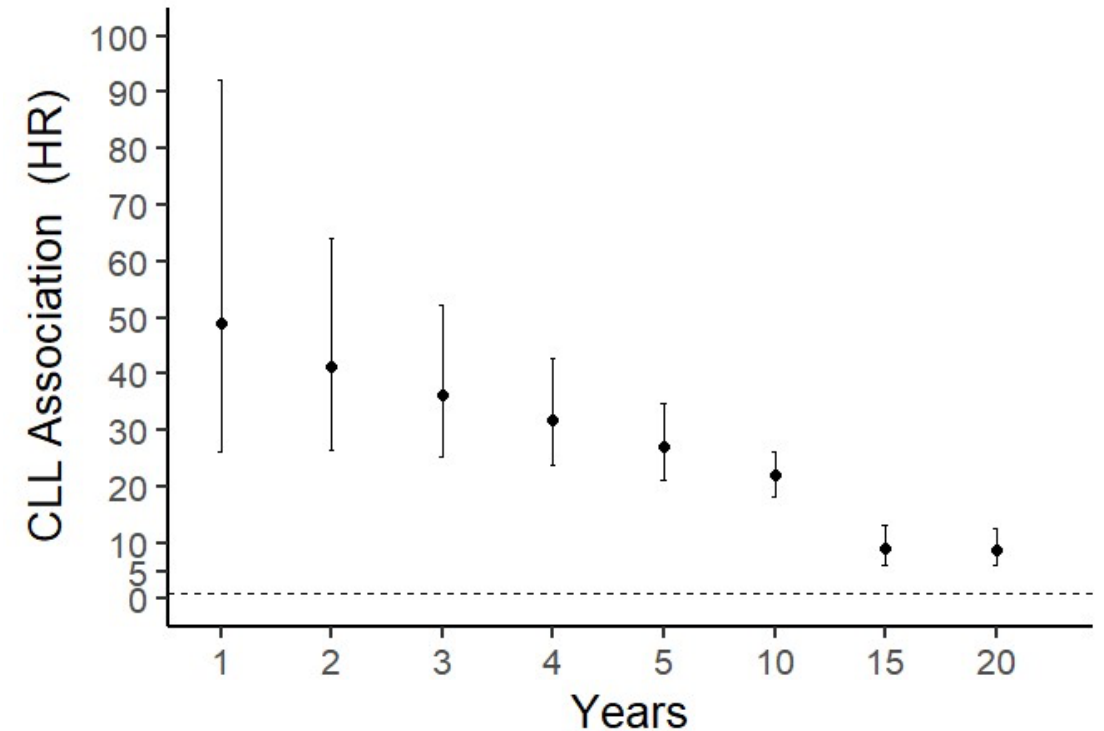


Building Integrative Models for Chronic Lymphocytic Leukemia (CLL) Risk Stratification

UK Biobank

Model	Test Set AUC
Model 1: Age, age-squared, sex, genetic ancestry, smoking + blood cell count	0.84
Model 2: Model 0 + CLL PGS	0.86*
Model 3: Model 2 + any autosomal mCA + any CHIP mutation	0.89*

*Genomic findings replicated in NCI PLCO study



Conclusions

- mCAs detectable in the blood of cancer-free individuals indicate increasing genomic erosion with age
- The distribution of mCAs differs by chromosome
- Risk factors for mCAs have a high degree of similarity with hematologic cancer risk factors
- mCAs are associated with multiple outcomes and could be particularly important for hematopoietic cancers

Collaborators

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Pradeep Natarajan (Mass General Hospital)
John Perry (MRC Cambridge)
Vijay Sankaran (Harvard Stem Cell Institute)
Paul Scheet (MD Anderson)
Chikashi Terao (RIKEN)

Resources

Biobank Japan
Cancer Prevention Study II
DCEG Total Genotyping Set I & II
Estonian Biobank
FinnGen
Mass General Brigham Biobank
Million Veteran Program
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
TOPMed
UK Biobank

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Division of Cancer Epidemiology and Genetics



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Who can apply?

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- Design, carry out, analyze, publish research
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- Build grant writing, communication, and leadership skills
- Prepare for a wide variety of careers



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