DECEMBER 2023

Allele-specific expression may contribute to healthy aging, disease progression, and treatment outcomes

CanPath Webinar

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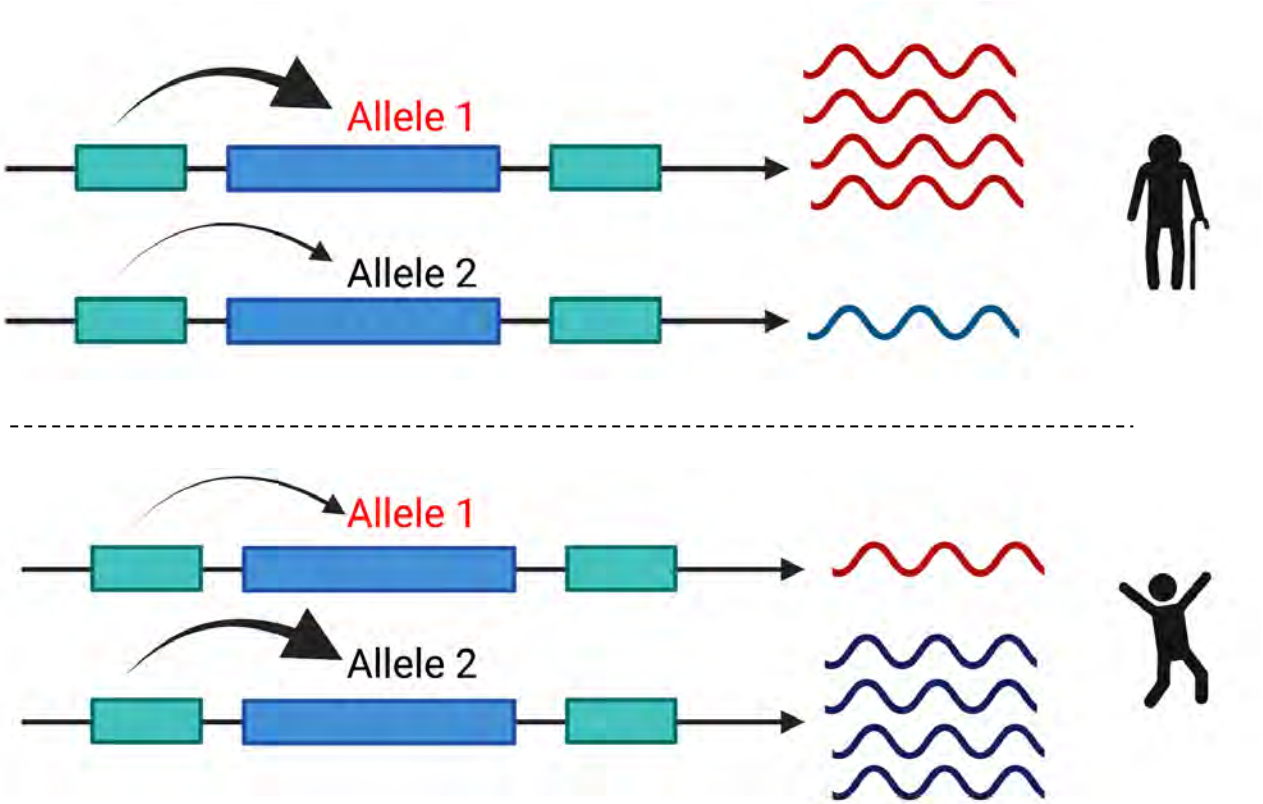
OICR Ontario Institute for Cancer Research

UNIVERSITY OF TORONTO

AWADALLA LAB
Pioneering Genomics for Precision Health.

Why do individuals with the same genotype display highly variable phenotypes?

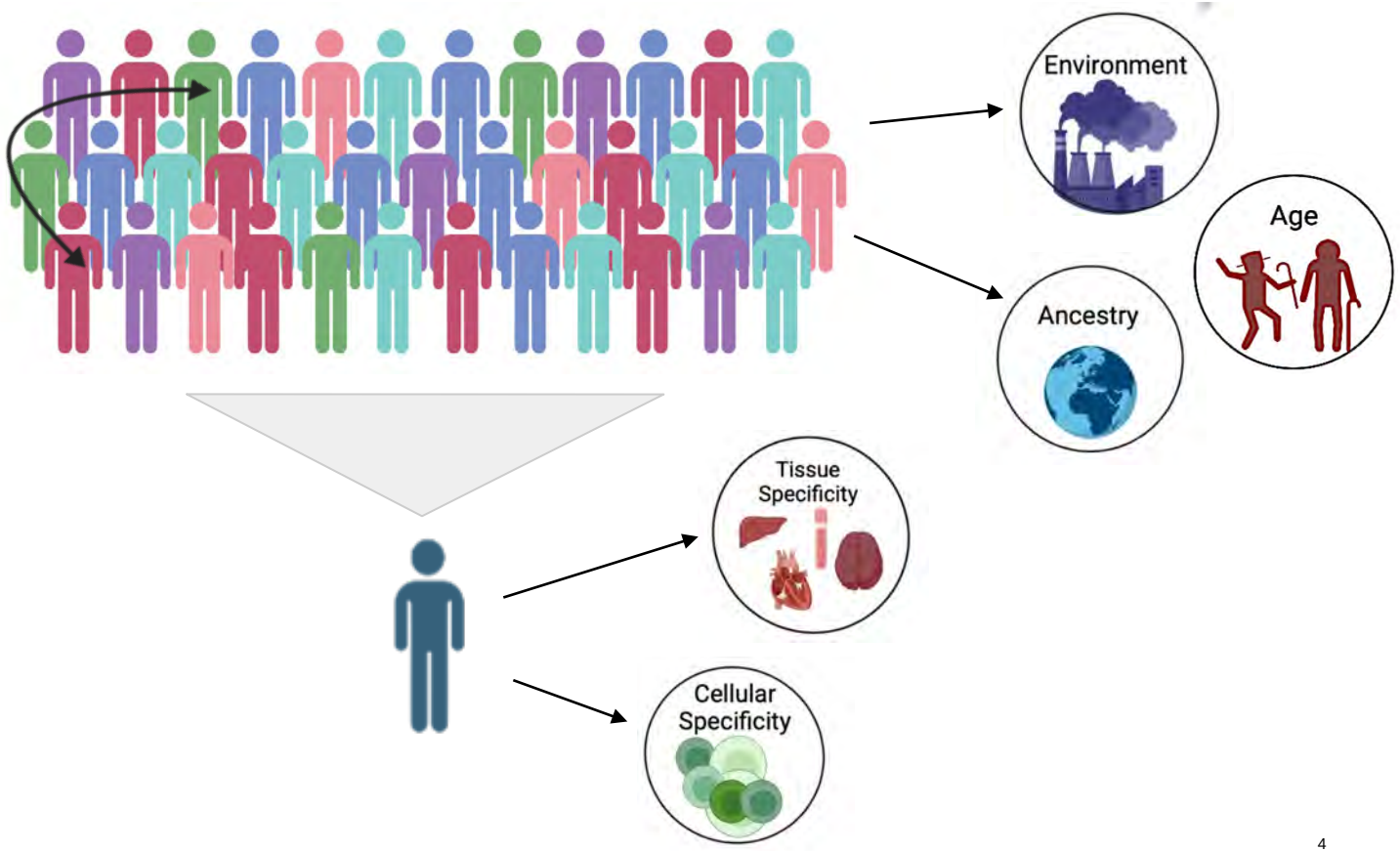
Allele-specific approaches are used to investigate gene regulation



Genetic and epigenetic factors influencing population variability of allele-specific expression

Inter-population variability

Inter-individual variability



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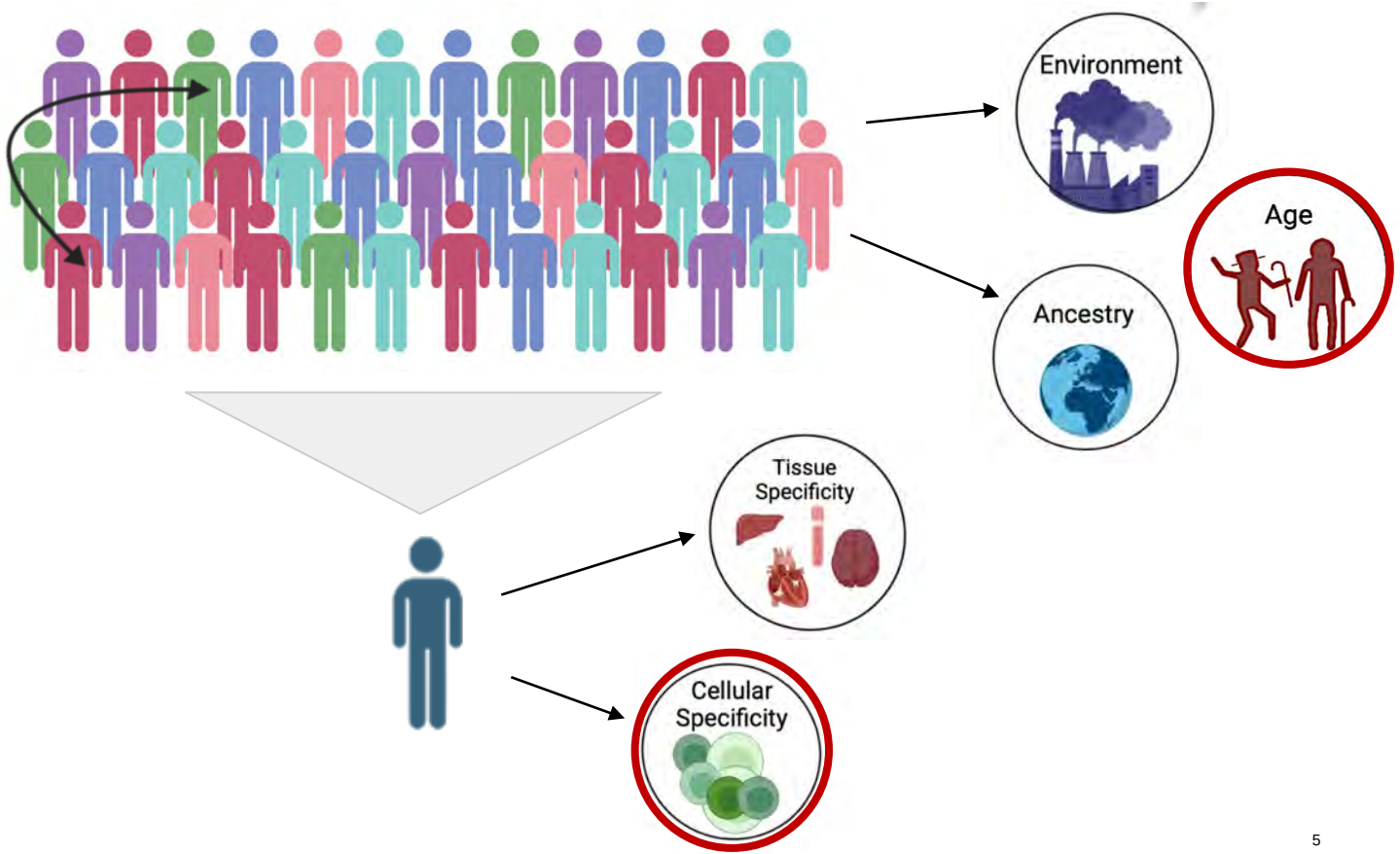

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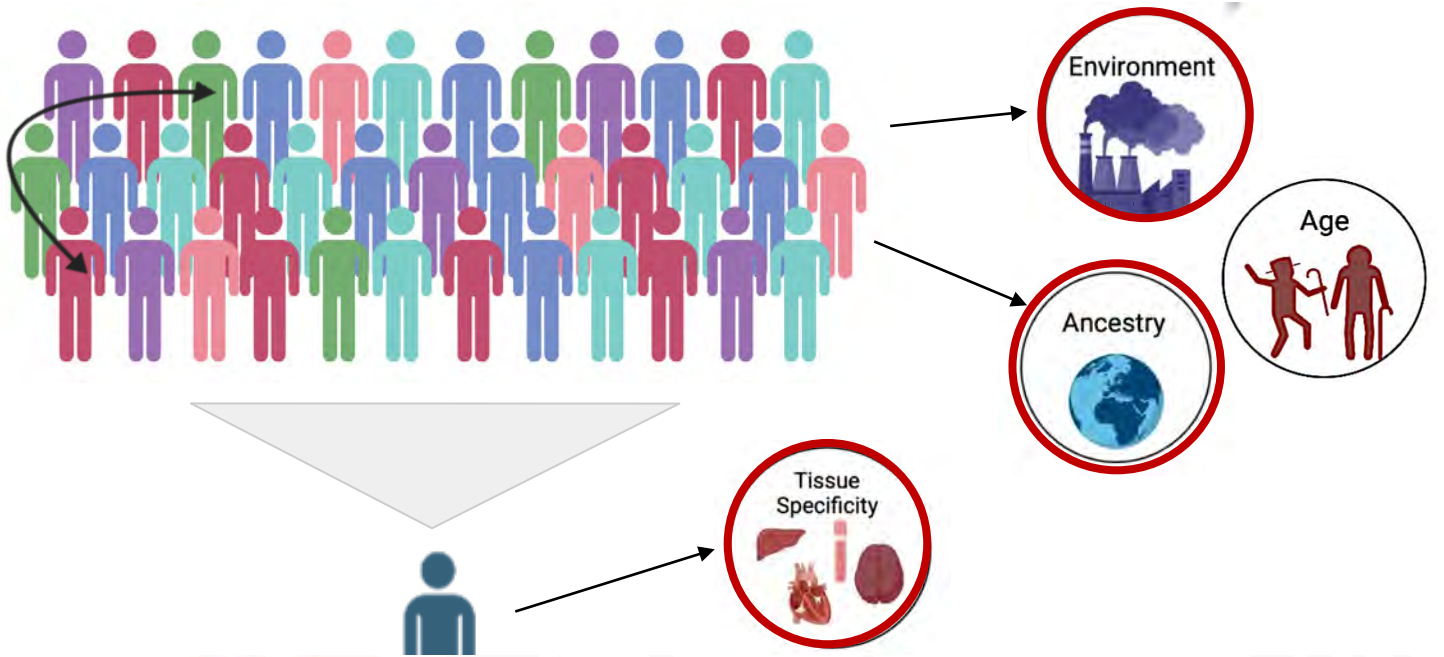

RESEARCH ARTICLE HUMAN GENETICS

Recombination affects allele-specific expression of deleterious variants in human populations

MICHELLE P. HARWOOD, ISABEL ALVES, HILARY EDGINGTON, MAWUSSE AGBESSI, [...] AND PHILIP AWADALLA +4 authors Authors Info & Affiliations

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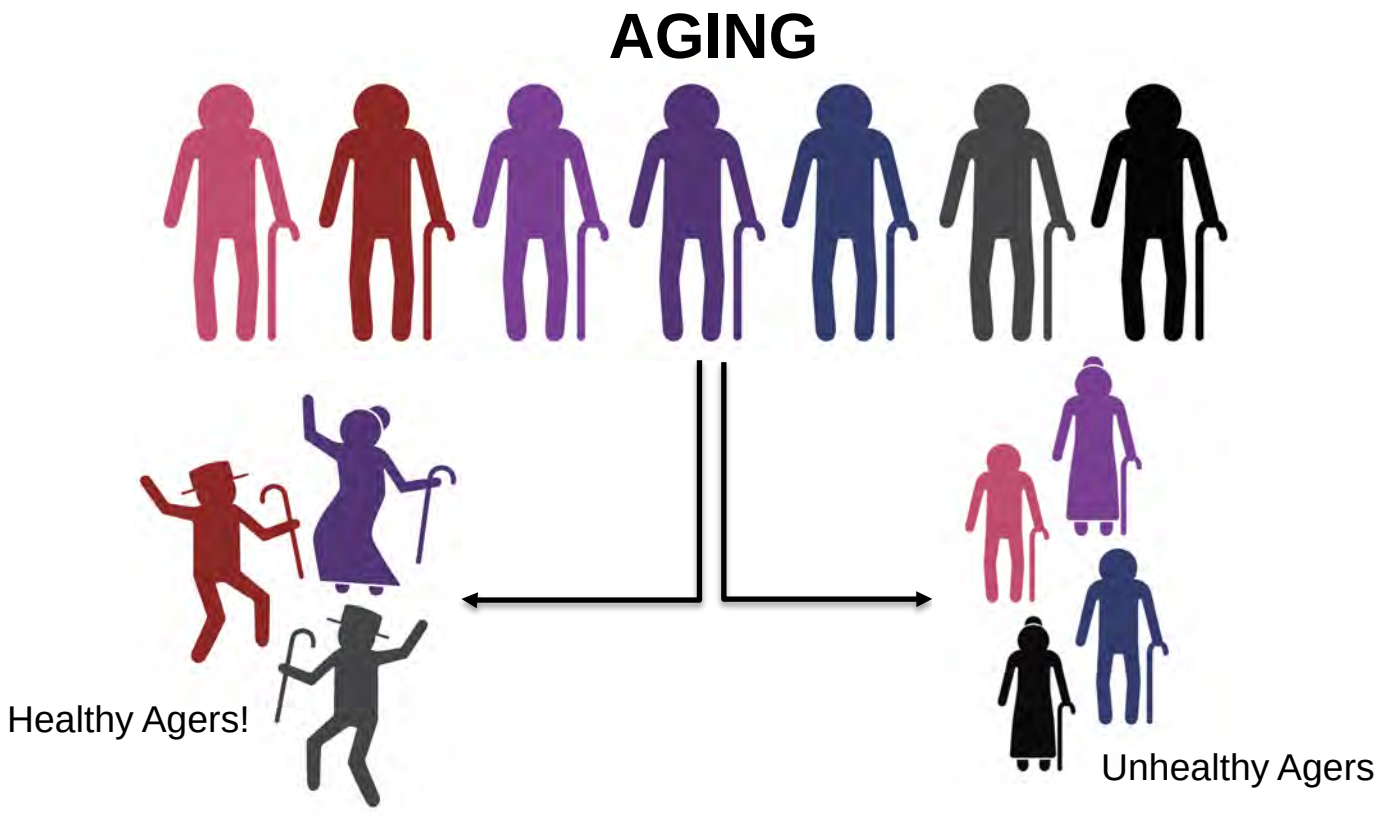
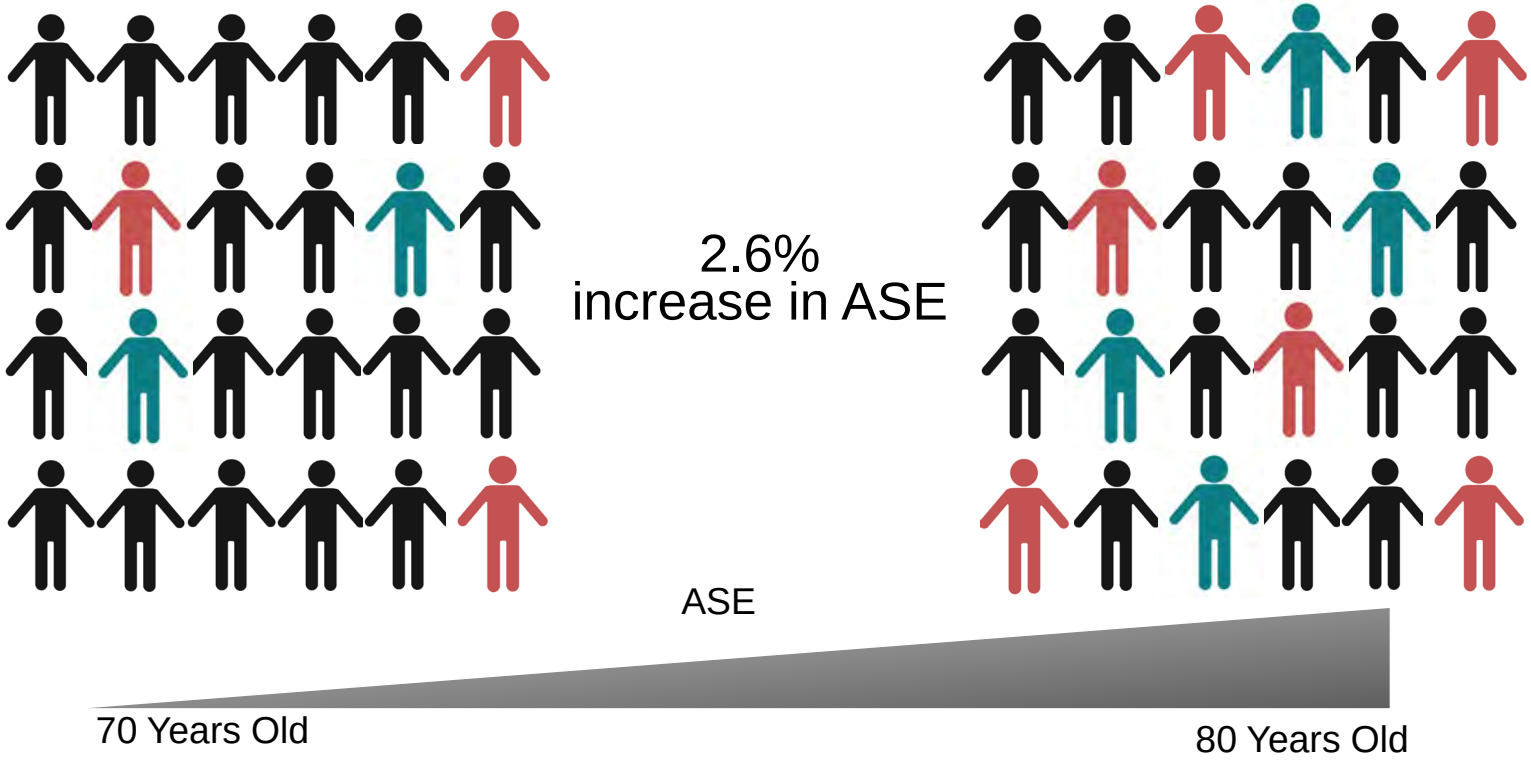
Why do individuals with the same genotype display highly variable phenotypes?

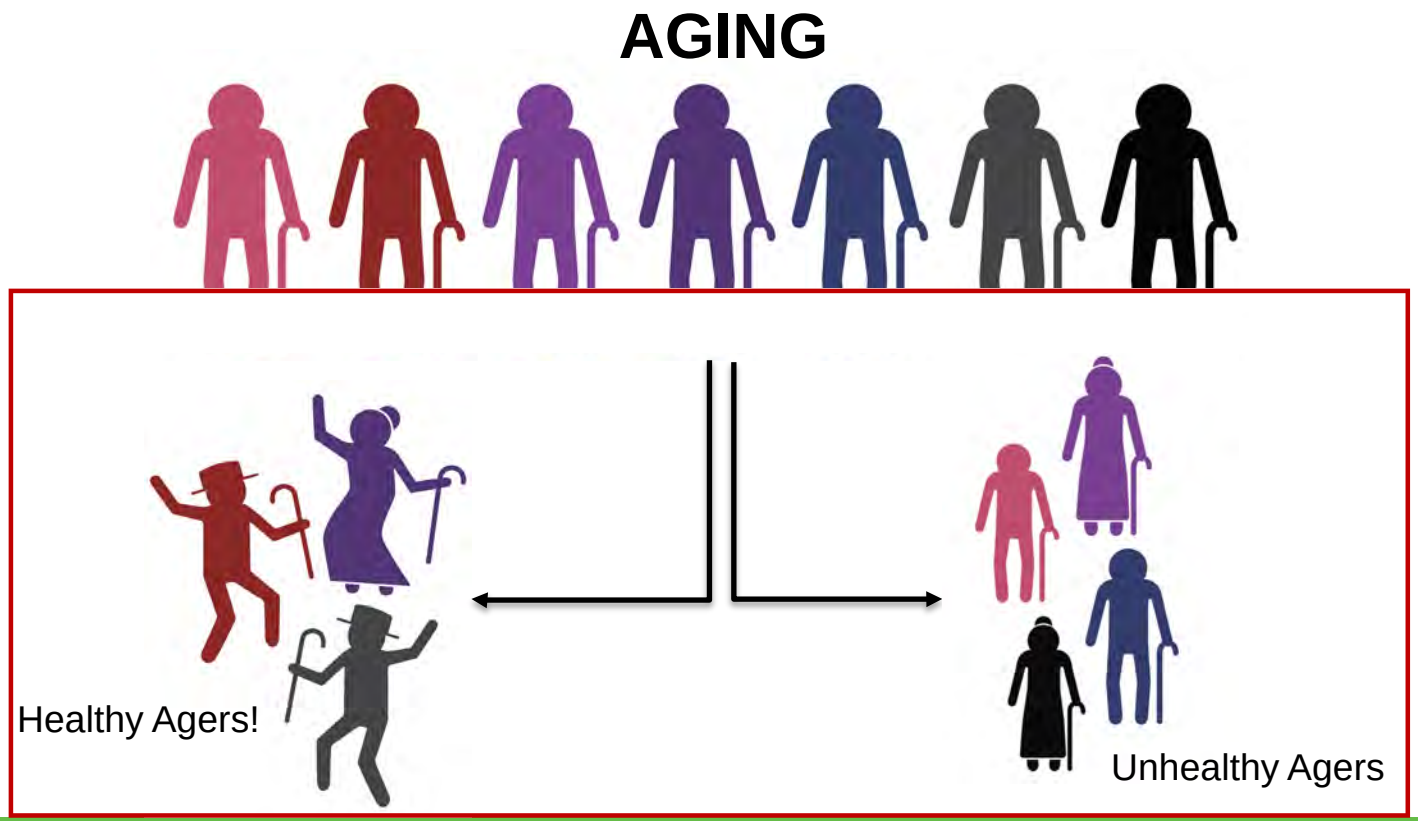


ASE increases with age

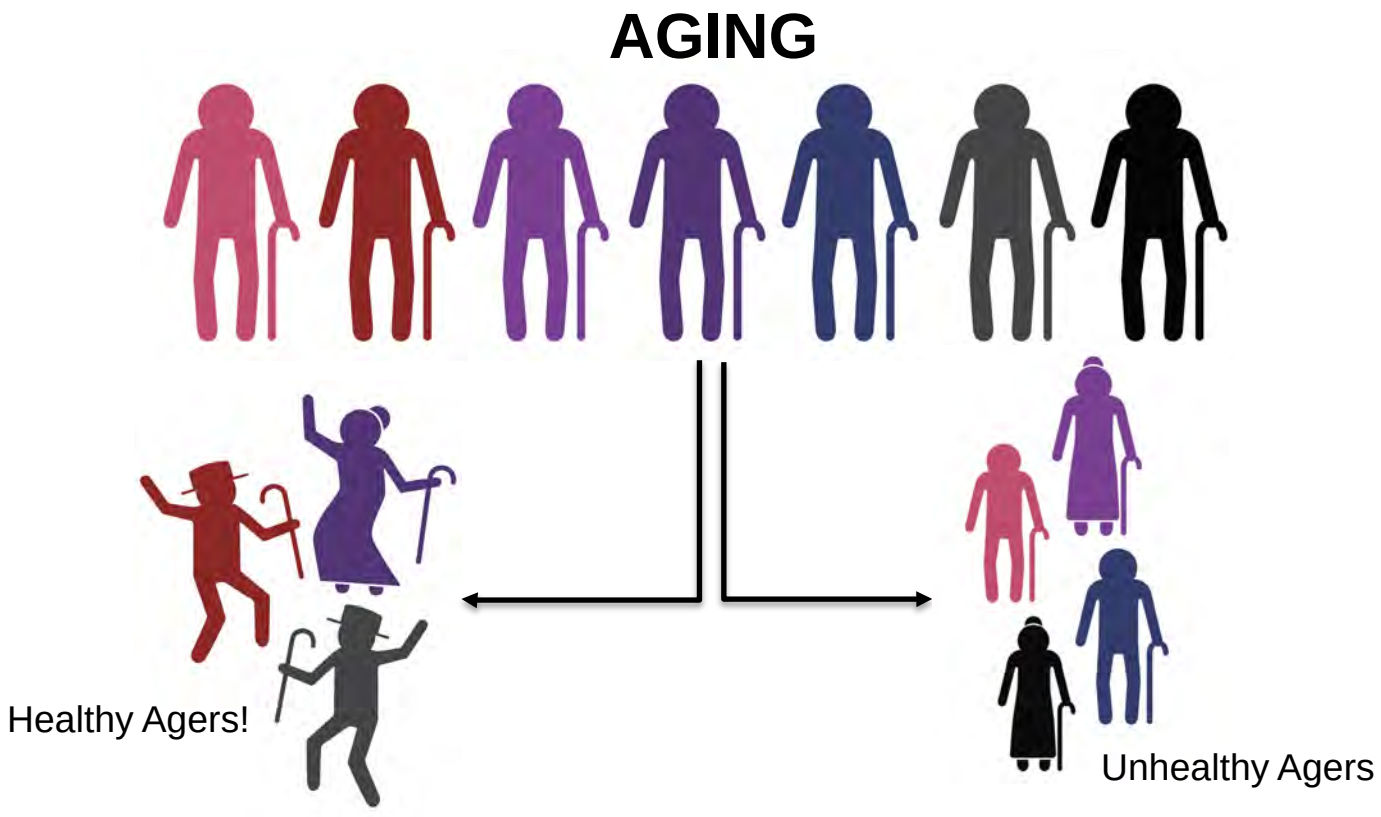


Balliu et al 2019

It remains unknown how increases in ASE impact aging processes



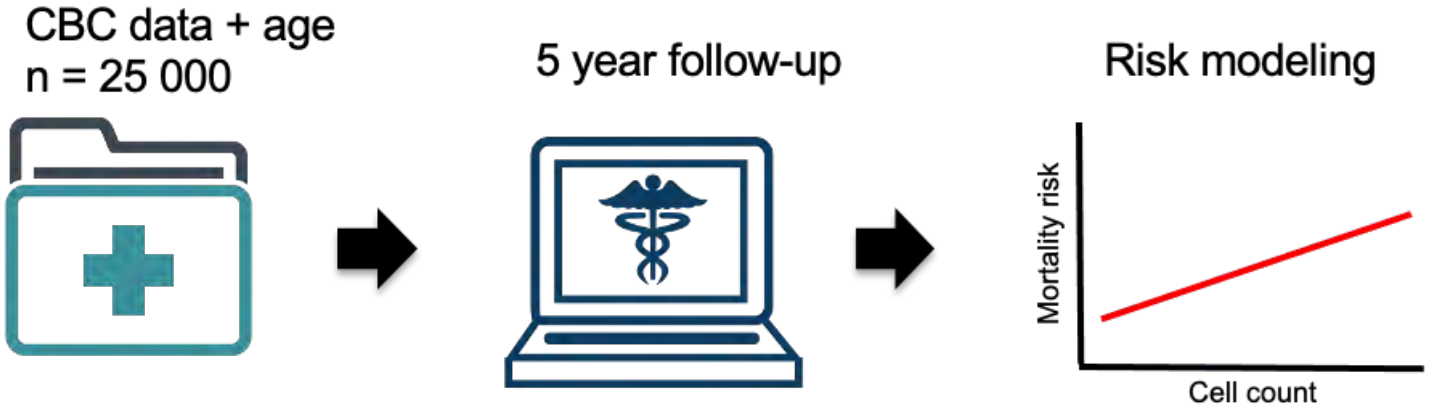
Does ASE contribute to phenotypic variation observed during aging?



Using population cohorts to investigate ASE

832	**Samples**	350
Blood	**Tissue**	Blood
Illumina Omni 2.5 Genotyping Array	**Genotyping**	Whole Genome Sequencing
Bulk paired-end RNA-seq	**RNA Sequencing**	10x Single Cell RNA-seq

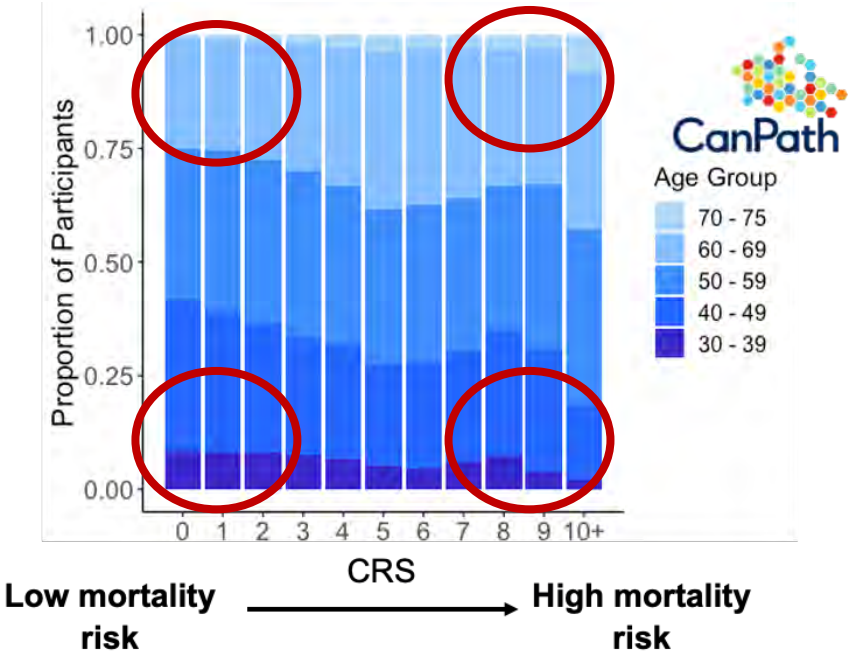
Intermountain risk score predicts 5-year mortality



Low IRS = low mortality risk = healthy blood

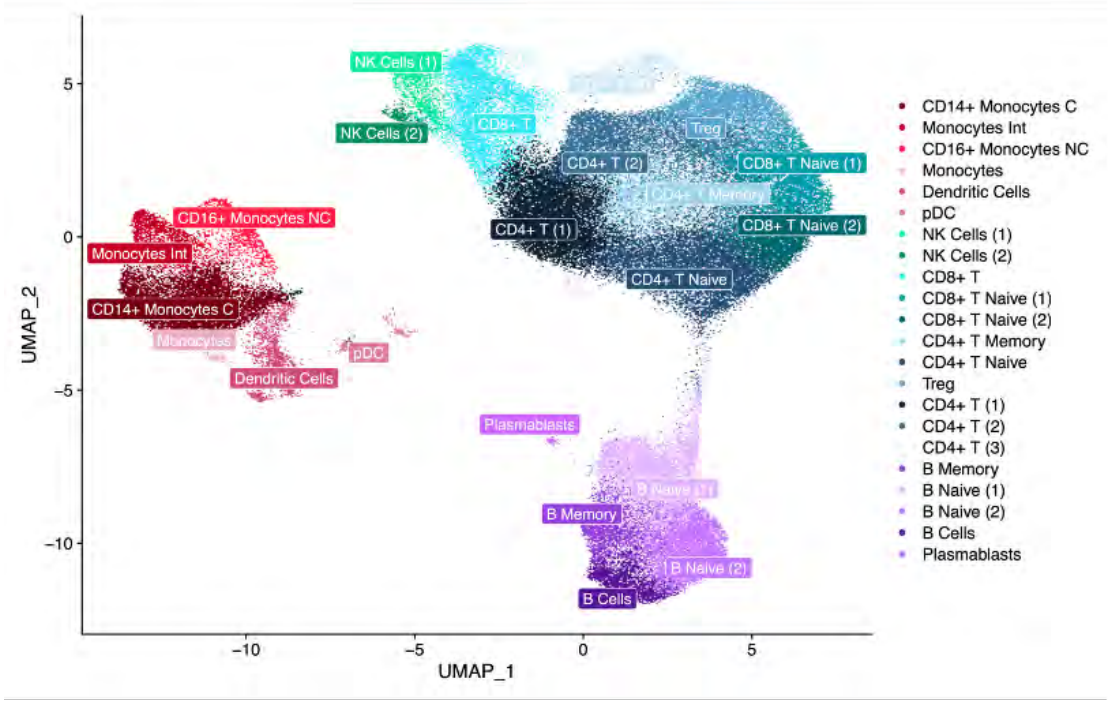
Horne et al. (2009) Am J Med

OHS participant selection



- OHS participants used extreme sampling approach with respect to risk score and age
  - no self-reported disease

OHS single-cell transcriptomics



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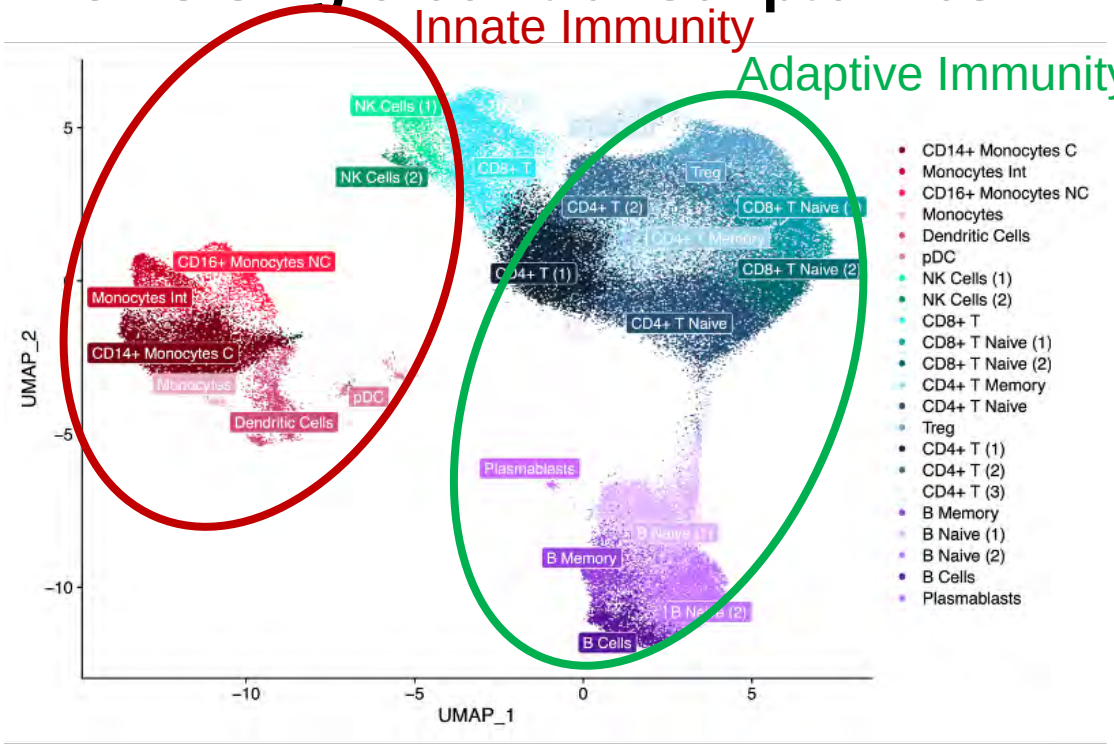
- 22 populations of blood cells identified from single-cell gene expression data

OHS single-cell transcriptomics



- OHS participants used extreme sampling approach with respect to risk score and age
  - no self-reported disease
- 22 populations of blood cells identified from single-cell gene expression data
- For ASE analyses, grouped cells based on adaptive vs innate immunity to improve detection at lower read depth

Using population cohorts to investigate ASE

CARTaGENE		Ontario Health Study
832	**Samples**	350
Blood	**Tissue**	Blood
Illumina Omni 2.5 Genotyping Array	**Genotyping**	Whole Genome Sequencing
Bulk paired-end RNA-seq	**RNA Sequencing**	10x Single Cell RNA-seq
3,039	**Total SNPs**	11,484

Adaptive	*Innate*
(CD8+ T cells, CD4+ T cells, B Cells)	*(Monocytes, Dendritic Cells, NK Cells)*
9,887	2,753

Using population cohorts to investigate ASE

	832 Samples		350 Samples	
	Young (40-45)	*Aged (65-70)*	*Young (30-45)*	*Aged (65-80)*
Low Risk	62	35	81	96
High Risk	55	50	83	89

Modified the Intermountain Risk Score (Horne et al 2009) to exclude age

- Uses complete blood count variables that is predictive of mortality

Dr. Elyssa Bader

Using population cohorts to investigate ASE

832	Samples	350

	Young (40-45)	Aged (65-70)		Young (30-45)	Aged (65-80)
Low Risk	62	35	Low Risk	81	96
High Risk	55	50	High Risk	83	89

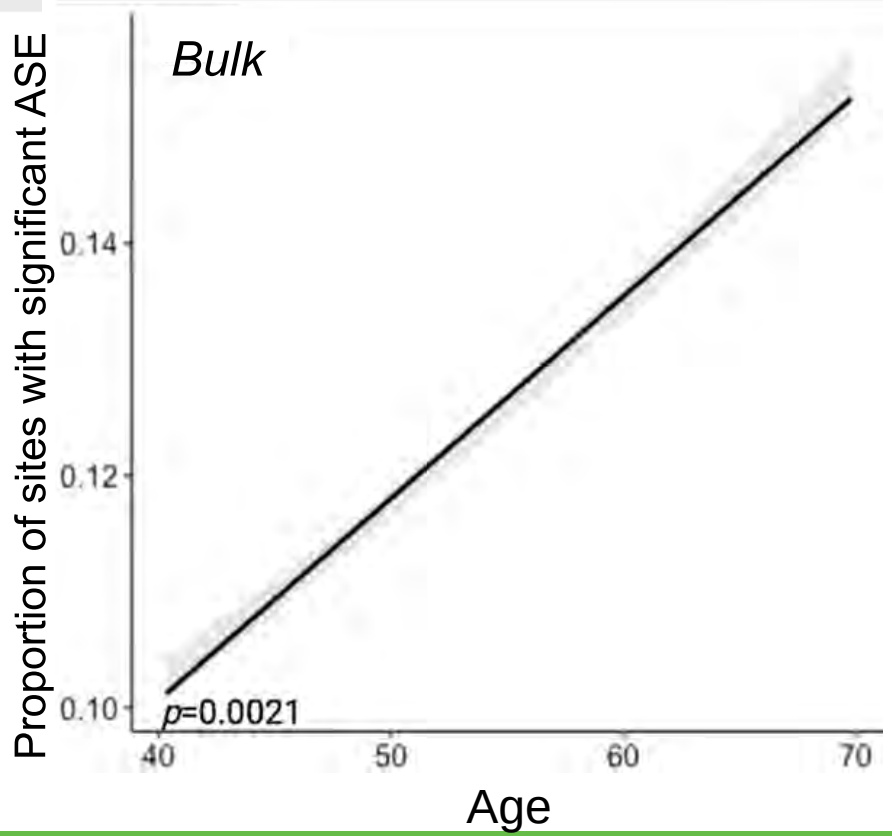
832	Disease	350

Cancer	Hypertension	Type 2 Diabetes	Dyslipidemia	Pre-Cancer
49	142	53	120	22

Aged individuals have larger proportion of ASE

CARTaGENE

$$\frac{\#\ significant\ sites}{\#\ heterozygote\ sites}$$



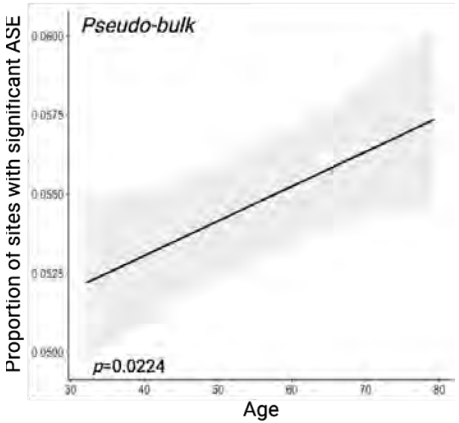
- Confirmed that ASE **increases with age** (Balliu et al. 2019)

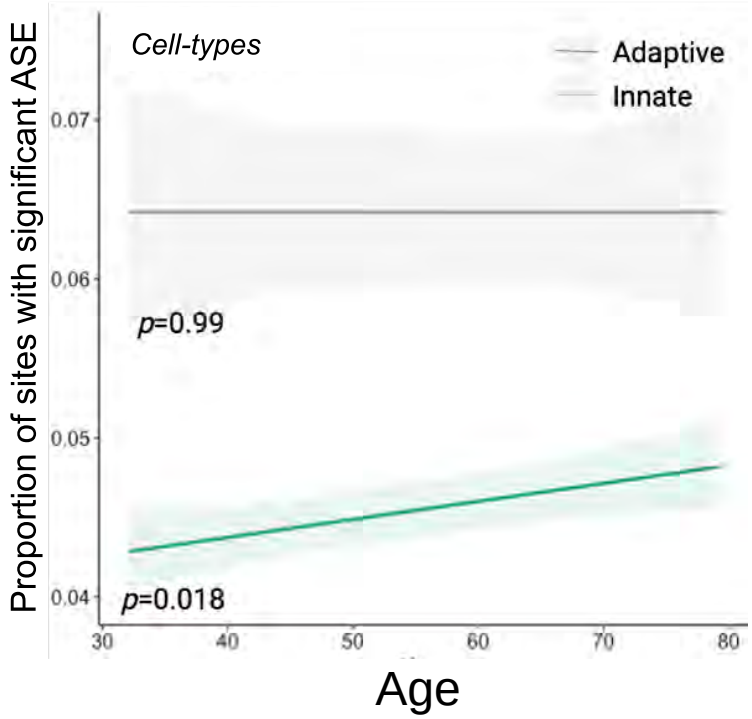
Binomial regression:

Proportion ASE ~ Age

Aged individuals have larger proportion of ASE

OHS





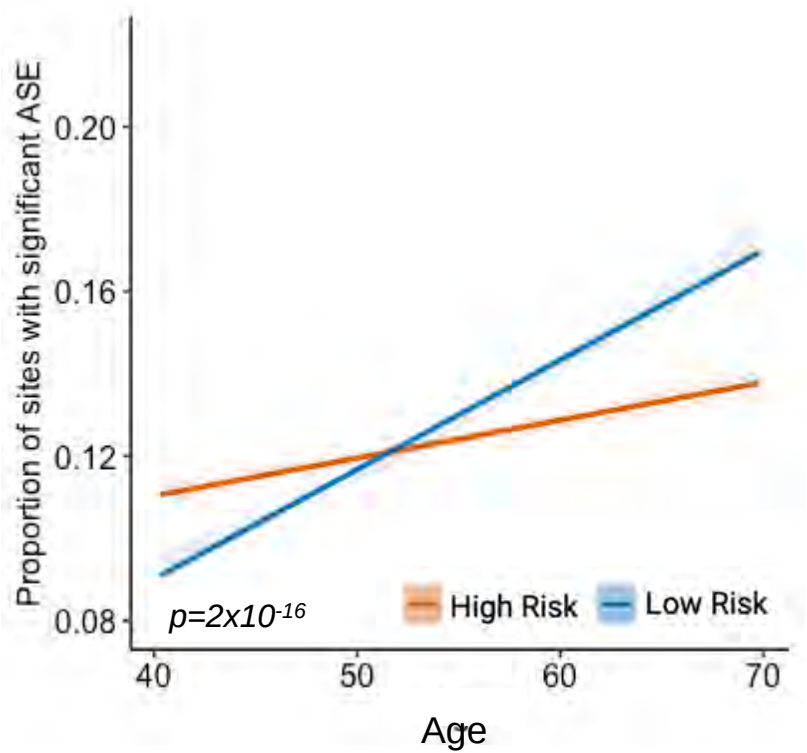
- Confirmed that ASE **increases with age** (Balliu et al. 2019)
- Replicated in OHS pseudo-bulk and **adaptive** immune cells

Binomial regression:

Proportion ASE ~ Age

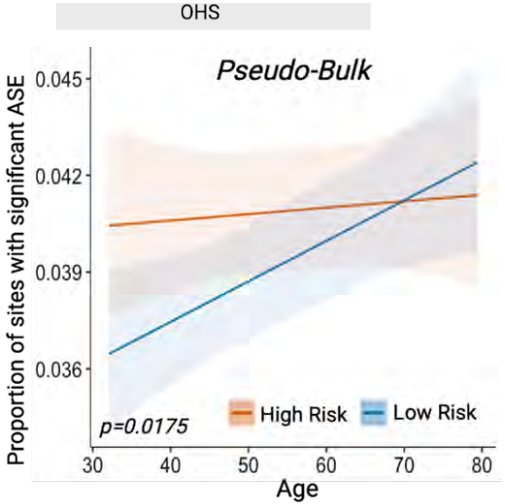
Increased proportion of ASE in aged individuals is stronger in individuals who have a low health risk

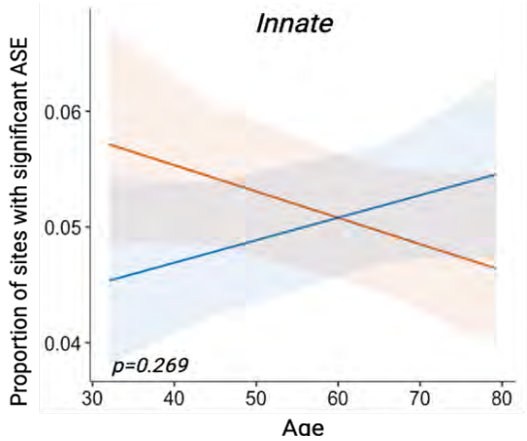
CARTaGENE

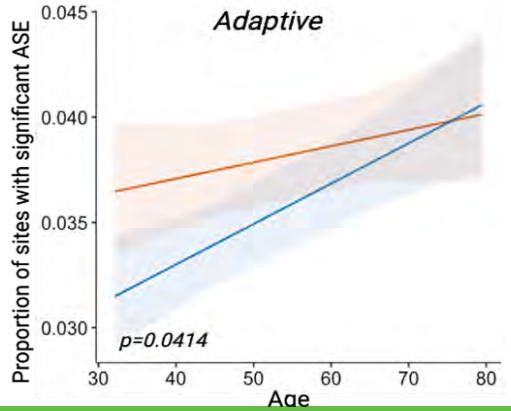


- Low risk individuals experience **larger increases** in ASE with age

Increased proportion of ASE in aged individuals is stronger in individuals who have a low health risk

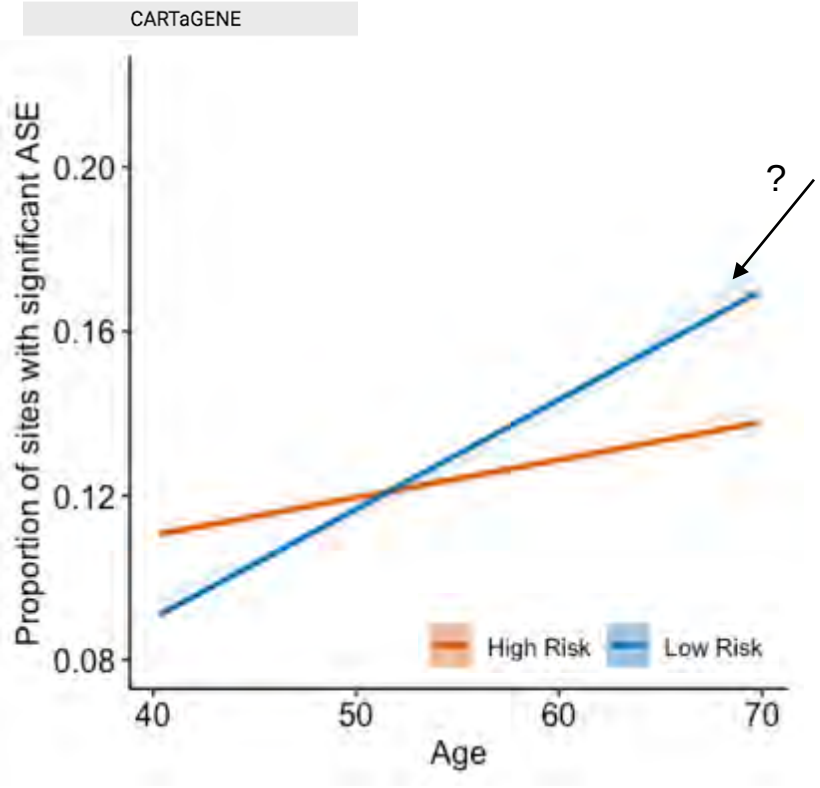






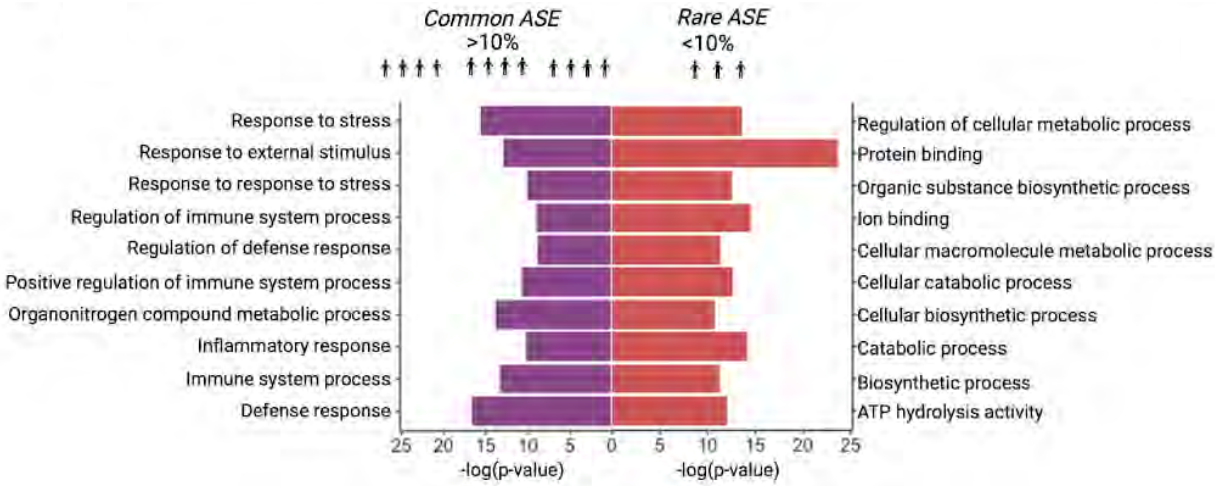
- Low risk individuals experience **larger increases** in ASE with age
- Replicated in OHS pseudo-bulk and **adaptive** immune cells

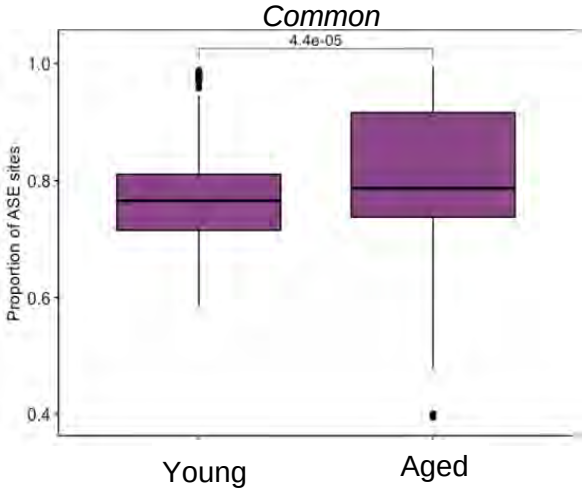
What genes could be driving this?



Older individuals have more common ASE events in genes involved in immune response

CARTaGENE

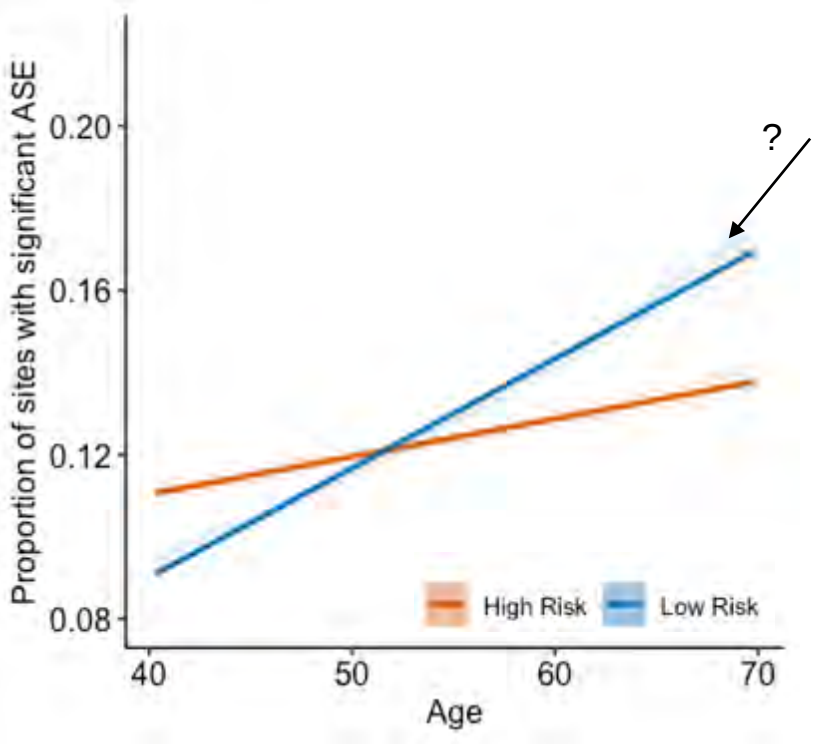




- **Aged** individuals have **more common** ASE events, which are involved in i**mmune response**

Are immune genes driving this pattern?

CARTaGENE



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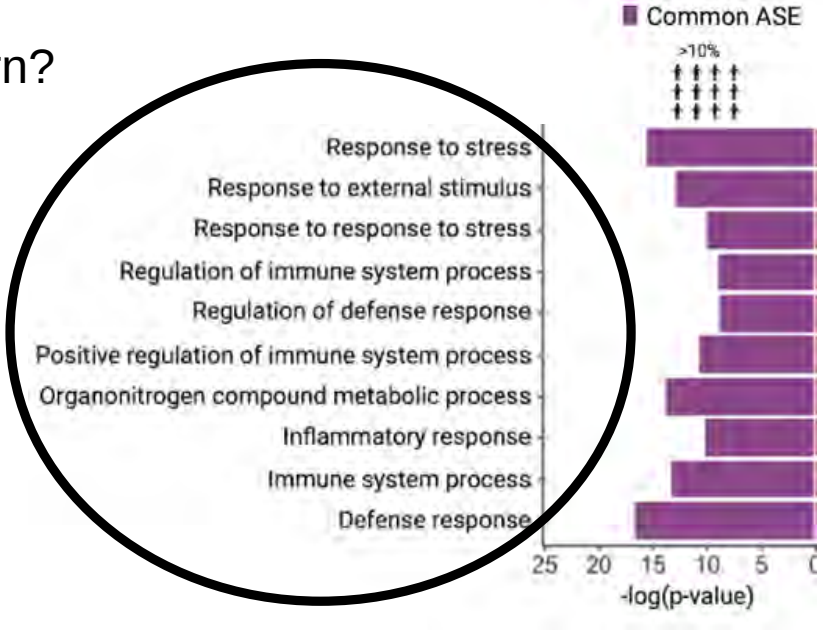


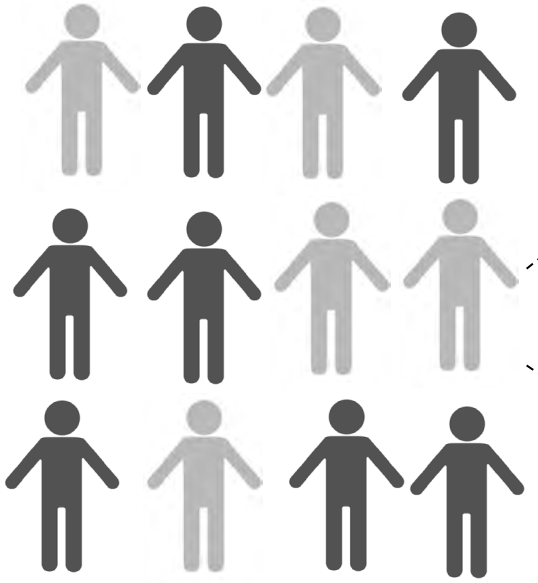
RESULTS

Increased ASE in immune genes demonstrates lower health risk in aged individuals

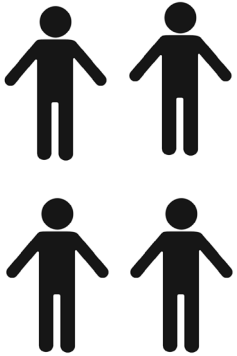
CARTaGENE

Immune gene set (534 genes)

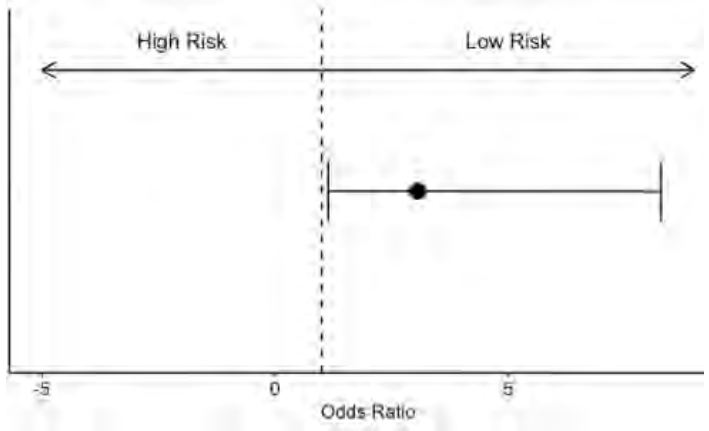
$$\frac{\#\ significant\ sites\ in\ immune}{\#\ heterozygote\ sites\ in\ immun}$$



High proportion of ASE in immune genes (>3rd quartile)



- Aged individuals with **high proportion of ASE in immune genes** are more likely to be **low risk**

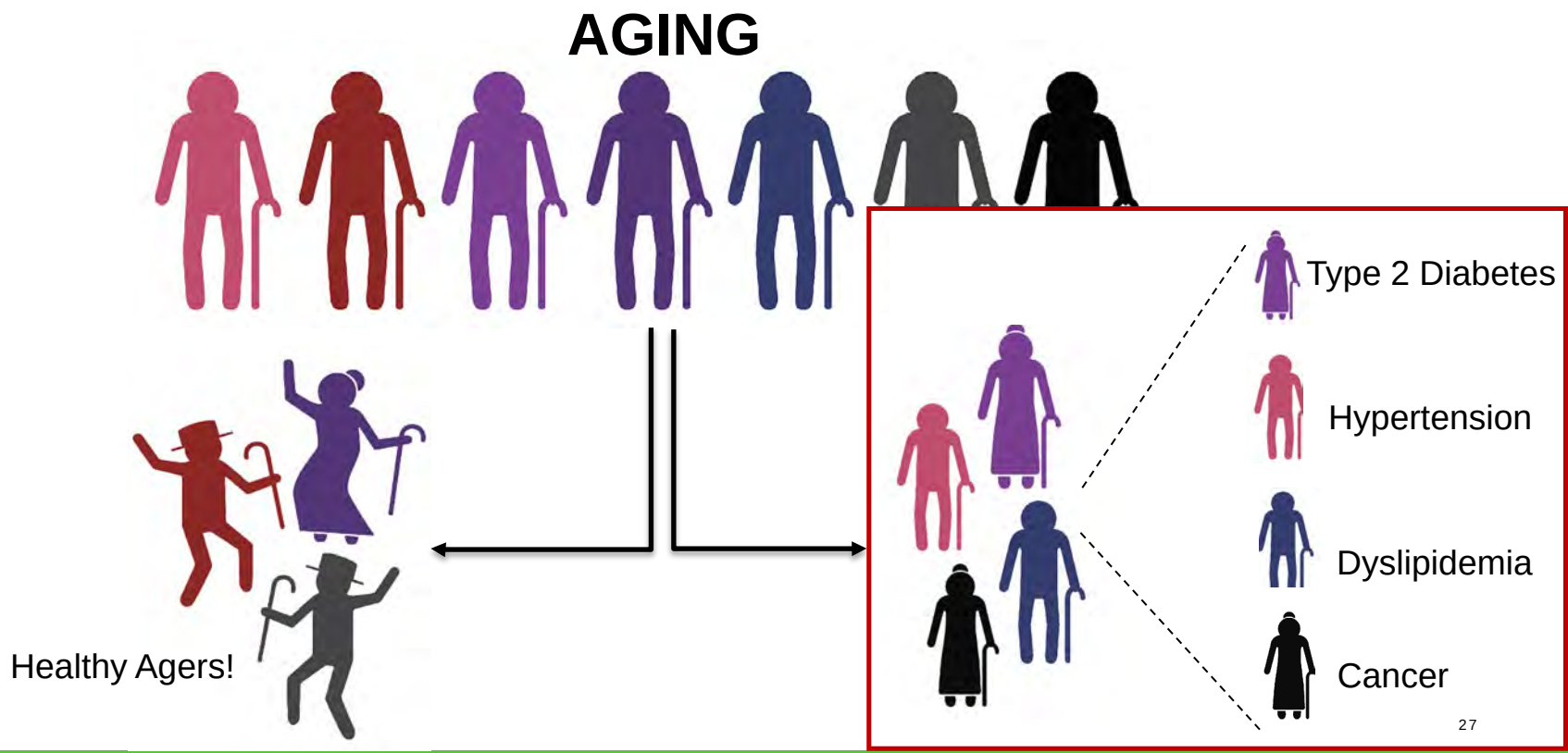


Are they more likely low risk?

logistic regression model:

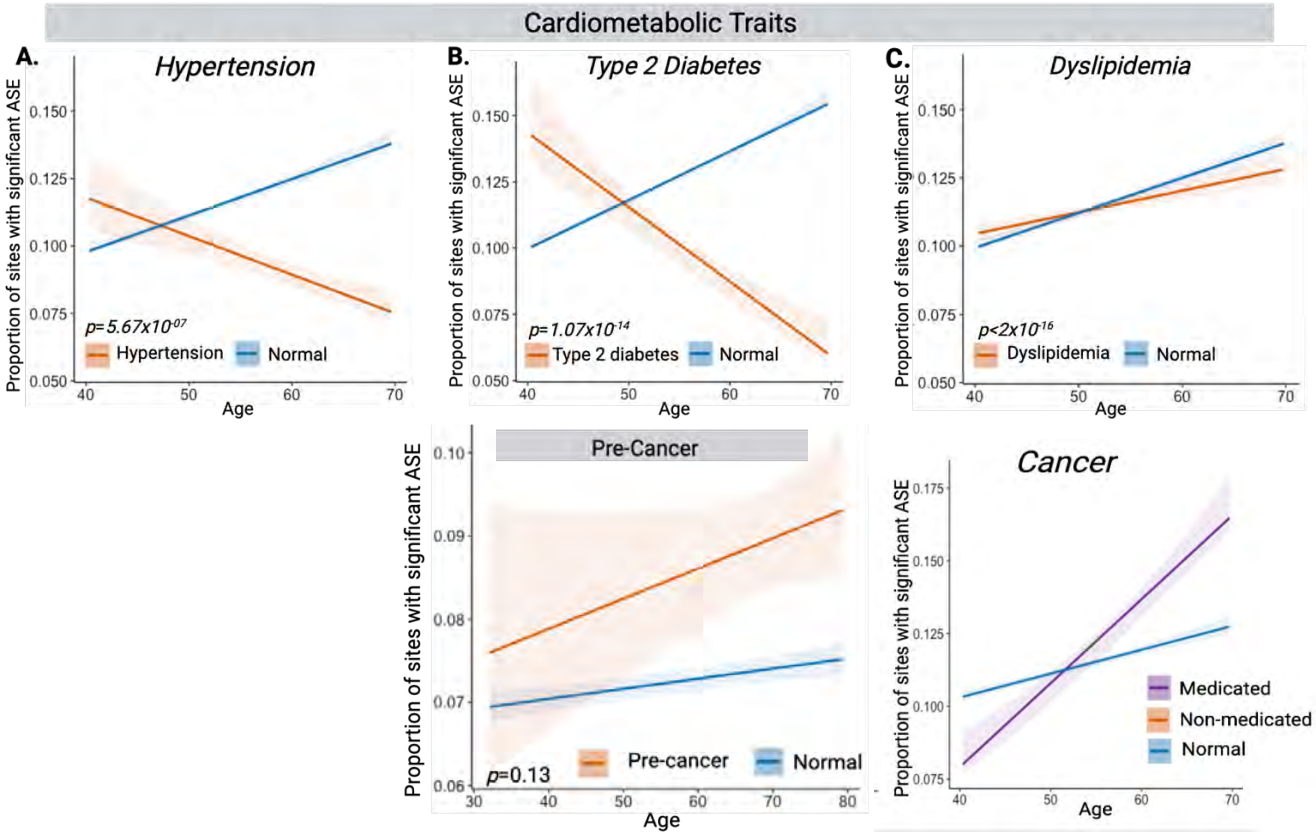
log(odds) = RiskScore ~ ASE in immune

Do individuals with a known disease show consistent results with the risk score?



Increased ASE during aging may reduce risk of cardiometabolic traits

CARTaGENE

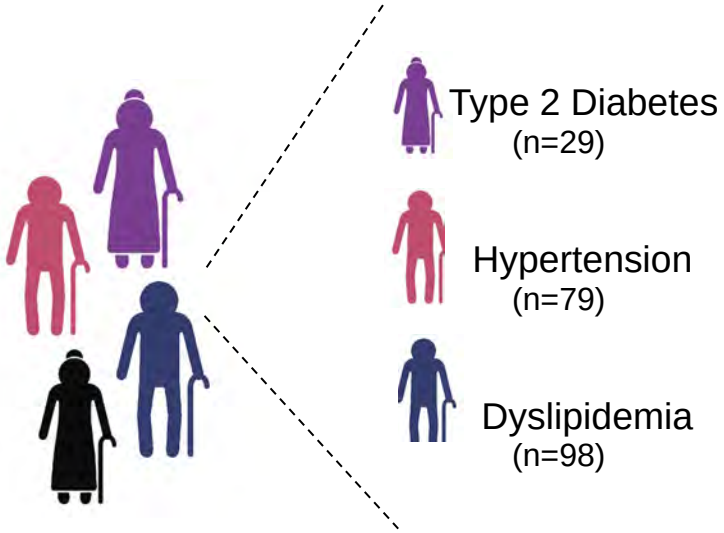


- **Hypertension and T2D** individuals experience a **decrease** of ASE with age

- **Pre-cancer** individuals have increases of ASE with age- possible **tissue specificity or immune involvement**?

- **Consistent in cancer samples**, but individuals are treated and have no information on remission status

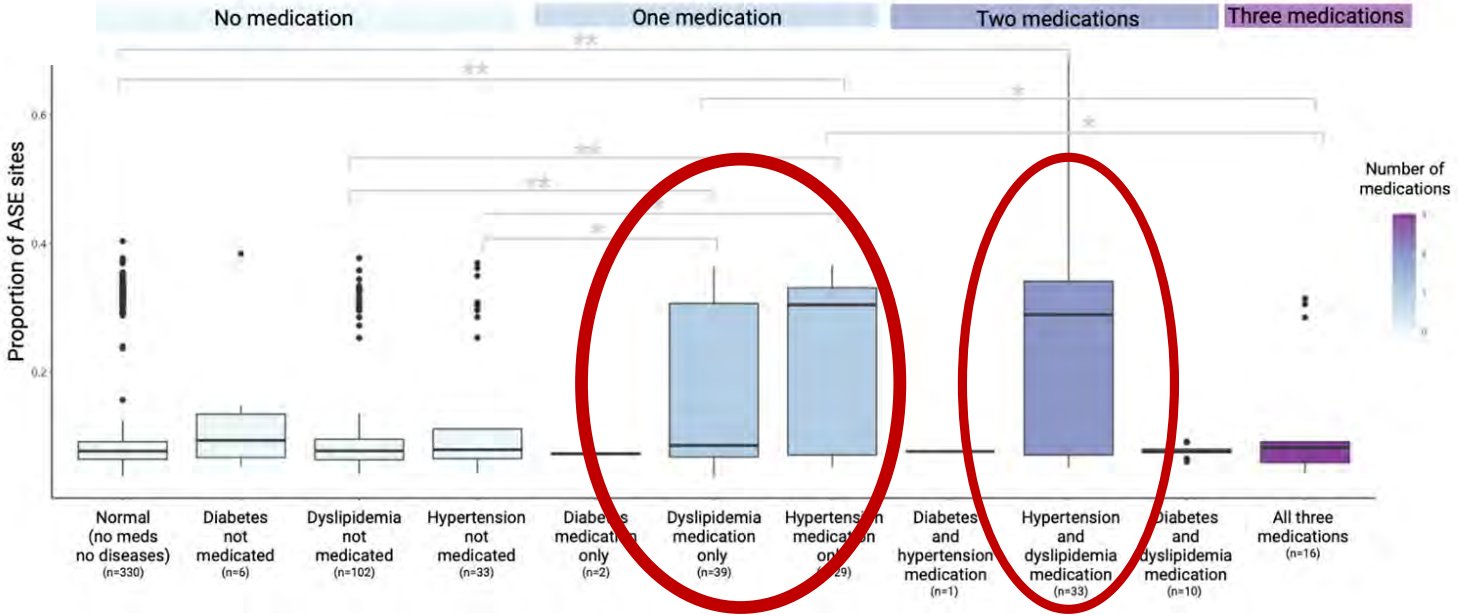
Many studies exploring ASE with disease may ignore impact from medication



- CARTaGENE cohort has t**reatment information for cardiometabolic disease**
- Overlapping disease/treatments, and different drug classes cause challenges with testing for associations
- **Response to treatment estimated** based on lab reported blood measurements

Medication associated with increased ASE for hypertension and dyslipidemia

CARTaGENE



- **Hypertension and dyslipidemia** medications associated with **increased** ASE levels

Medication associated with increased ASE for hypertension and dyslipidemia

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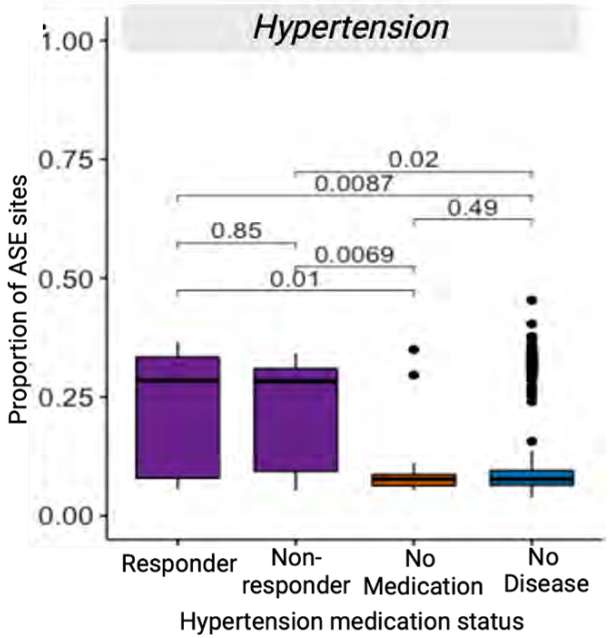
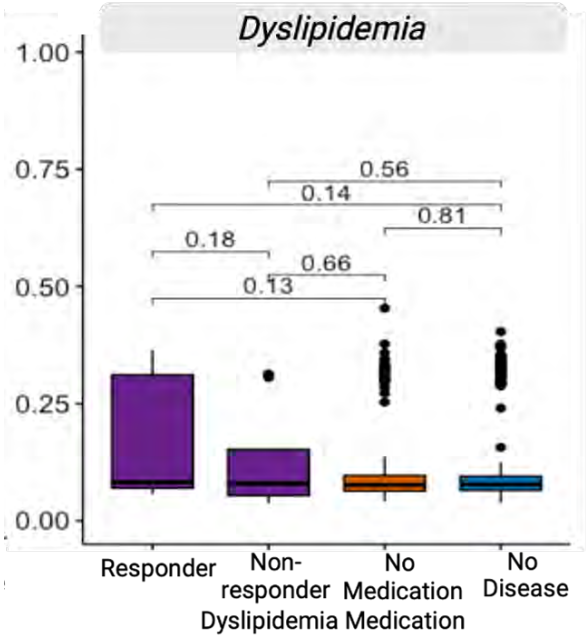
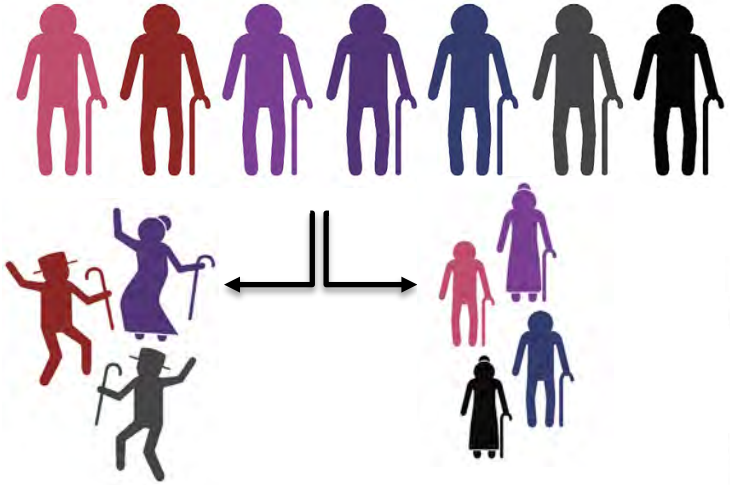


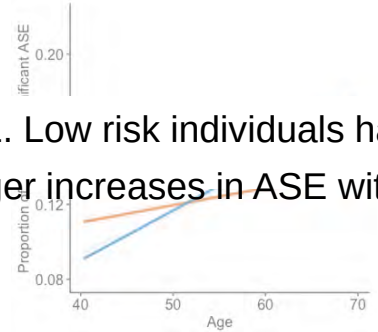


- **Hypertension and dyslipidemia** medications associated with **increased** ASE levels
- Increases in ASE observed in **both responders and non-responders**
- Identified genes with ASE differences specifically in non-responders

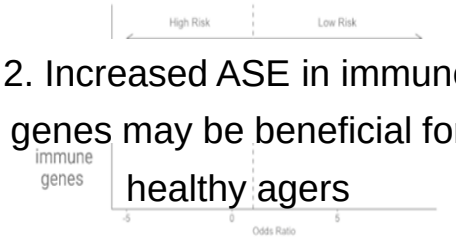
Summary

Does ASE contribute to phenotypic variation during aging?

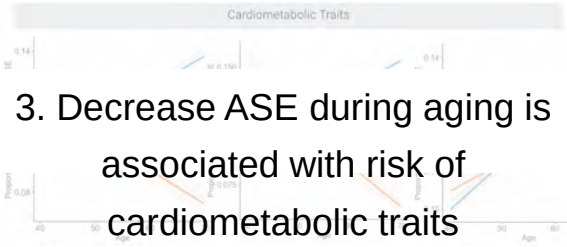




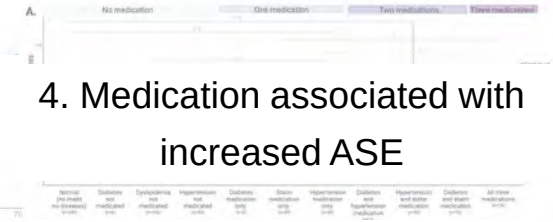
1. Low risk individuals have larger increases in ASE with age



2. Increased ASE in immune genes may be beneficial for healthy agers



3. Decrease ASE during aging is associated with risk of cardiometabolic traits



4. Medication associated with increased ASE

@mp_harwood

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- **Kimberly Skead**
- **Dr. David Soave**
- Jasmina Uzunović

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