Biobank Norway | Nordic Biobank Conference | Nordic Biobank Network | NSHG-PM

HUNT4

Assessing the susceptibility of celiac disease by **polygenic risk scores**: analysis of a population-based cohort, the HUNT study.

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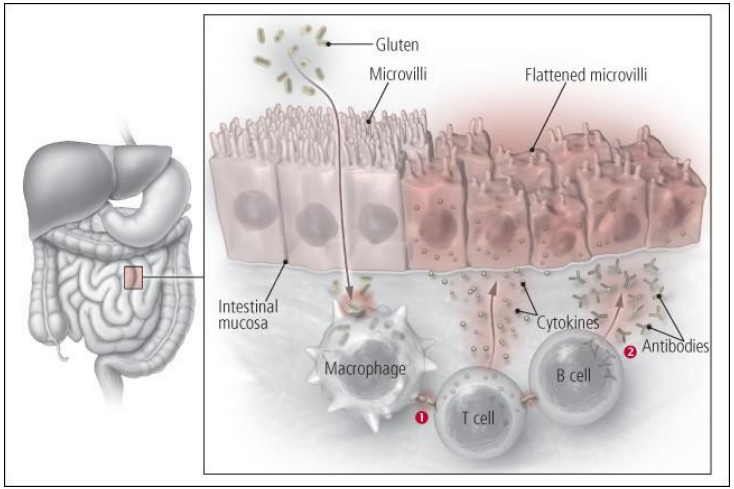
Background

- Celiac disease
  - what is it?
  - conditions required?
  - why does it needs to be studied?

- Chronic disease of gut
- Atrophy of villi upon gluten intake



https://www.health.harvard.edu/diseases-and-conditions/celiac-disease

Background

- Celiac disease
  - what is it?
  - conditions required?
  - why does it needs to be studied?

- Genetic susceptibility (HLA DQ risk haplotypes)
  - 55% carry it
  - 1-2% develop it
- Gluten as driver
- Exposomic factors (All factors outside the genome) as triggers

Background

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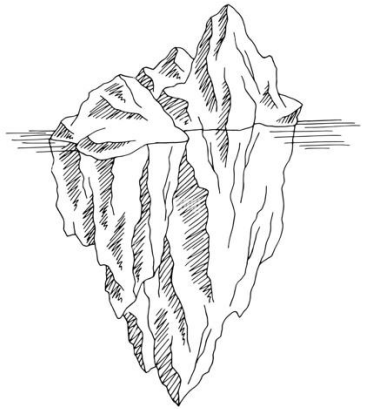
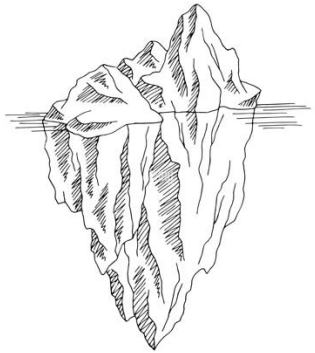
  - 1 in every 100 persons suffer from CeD
  - Celiac iceberg



Hypothesis

The genetic make of known group and unknown group were different from one another.



Methods

- HUNT4
  - When?
  - Where?
  - Who?

- Conducted between **2017-2019**
- In the **Nord Trondelag** County
- All adults (≥ **20 years** old) were invited
- **~57,000** participated
- **54%** participation rate
- **54%** women

Methods

- HUNT4 - CeD
  - Screening
  - Genetics

- Serological screening
- Endoscopy
- Medical searches

- 842 cases [465 incident; 377 prevalent]
- ~370,000 genotyped SNPs
- ~24.9 mil imputed SNPs
- HLA haplotypes were imputed and validated

Methods

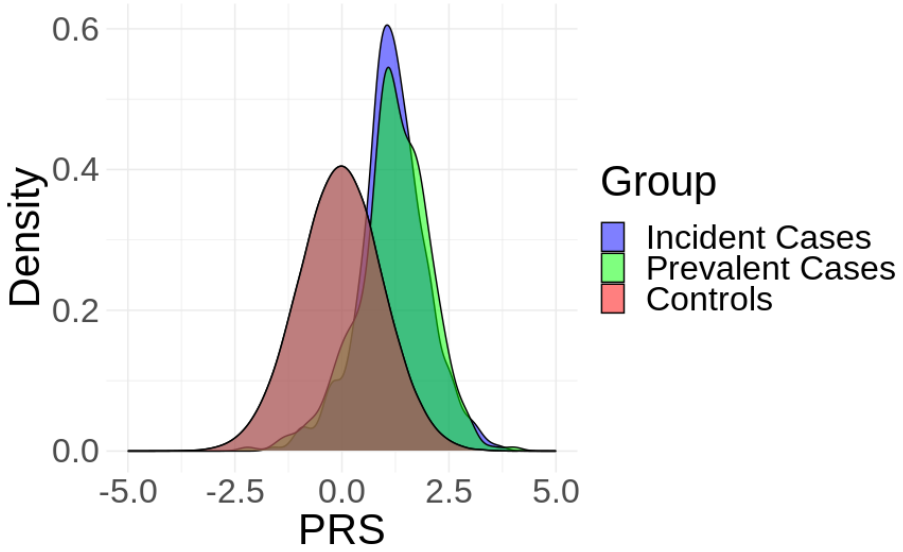
- Analysis
  - PLINK1.9
  - Accuracy metric
  - Reclassification metric

- Reproduced the 228 SNP based PRS[1]
- Accuracy assessment through AUROC
- Comparision of HLA vs PRS risk net reclassification index

1 Abraham, Gad, et al. "Accurate and robust genomic prediction of celiac disease using statistical learning." *PLoS genetics* 10.2 (2014): e1004137.

Results

- PRS
  - Distribution of PRS
  - Risk among groups
  - Accuracy
  - Reclassification



Results

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Risk among median groups	
Prevalent cases	1.7
Incident cases	1.47

PRS > 90th percentile	
Prevalent	2.73
Incident	1.63

Results

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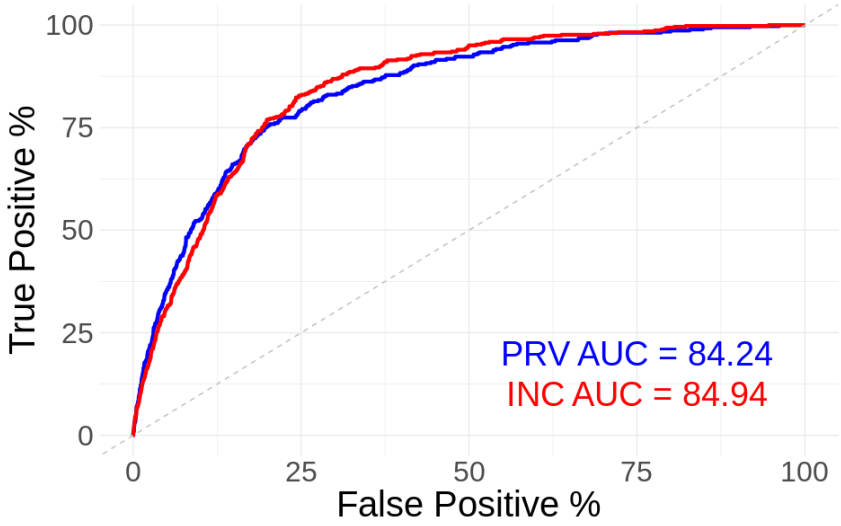

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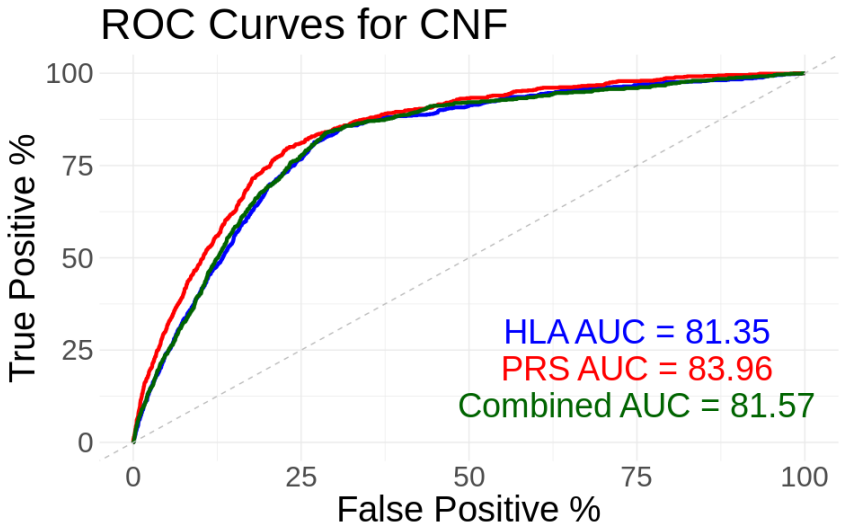

Results

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  - Distribution of PRS
  - Risk among groups
  - Accuracy
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NRI	2.70%	PRS		
IDI	-0.80%	Low	Medium	High
HLA	Low	8930	2612	4146
	Medium	8458	36	7033
	High	3123	1402	16618

Next Steps

- Downstream

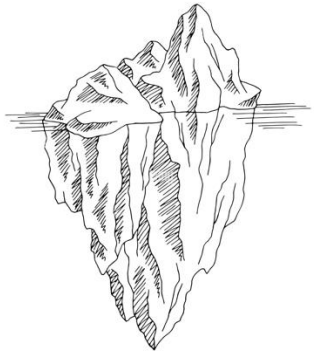
  - Perform sensitivity analysis
  - Possibly explore some other more recent PRS
  - Check for Non-HLA SNP effect difference among the groups

Discussion

- Higher accuracy of PRS vs HLA only
- 1 SD ↑ => ↑ risk by ~1.5 times
- Higher risk for prevalent vs incident
- Larger difference between median and top decile prevalent cases compared to incident case.
- ~3% reclassified

Take home message

- PRS better than HLA only
- We actually see a higher genetic load in prevalent than incident cases, possibly explaining why prevalent cases are already diagnosed and the incident cases are not.



Thank you for your attention!

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