SHEFFIELD INSTITUTE of GLUTEN RELATED DISORDERS

Sheffield Gastroenterology

ISSCD

A genome-wide association study of celiac disease identifies novel risk variants in the 5p15.33 locus: results from a population-based screening of adults, the HUNT4 study.

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Introduction

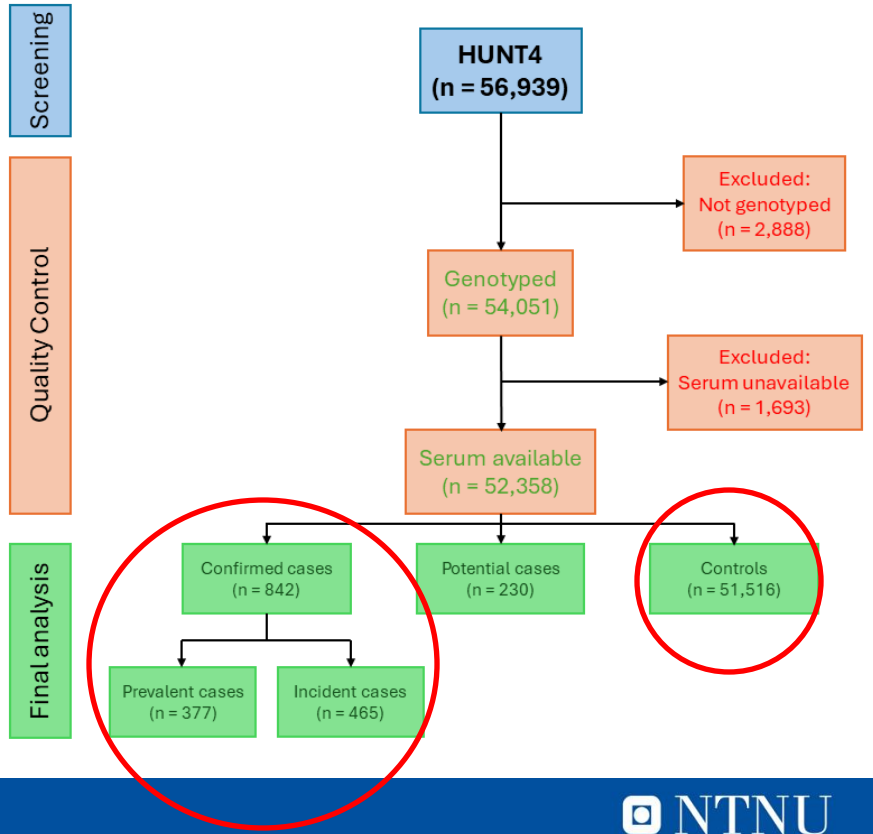
- Conditions:
  - Genetically susceptible
  - Environmental factors
- Screening revealed:
  - 55% carry the HLA-DQ risk heterodimers
  - 1-2% of the risk carriers develop the disease
- Genetic variation:
  - HLA + Non HLA: 50%
  - Unknown: 50%

Methods - Cohort

- Study:
  - HUNT4 (2017-2019)
  - Participation:
    - Sample size = ~57,000
    - Participation rate = ~54%
    - Female proportion = ~54%

Methods - CeD screening

- Inclusion and exclusion:
  - Seropositivity cutoff:
    - TG2-IgA ≥0.7 mg*/L or
    - TG2-IgG ≥1 mg*/L
  - Biopsy:
    - Marsh grade 3
  - Ruling out *H pylori* and NSAIDs
- Final analysis:
  - ~51,000 controls
  - 842 cases (465 incident, 377 prevalent)



Methods - Genetics

- Genotyping:
  - ~360,000 SNPs
  - Panels:
    - Illumina HumanCore Exome
    - UM HUNT Biobank
- Imputation:
  - IMPUTE5 tool
  - Haplotype Reference Consortium
  - 24.9 mill variants ≥ 0.3 imputation score

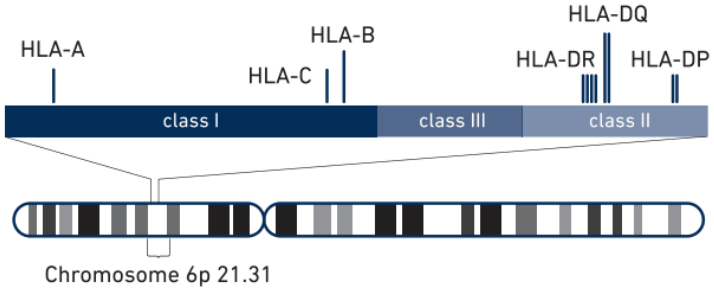
Methods - GWAS and validation

- SAIGE
  - Case-control imbalance
  - Relatedness

- Six randomly selected population subsets

Methods – HLA and downstream

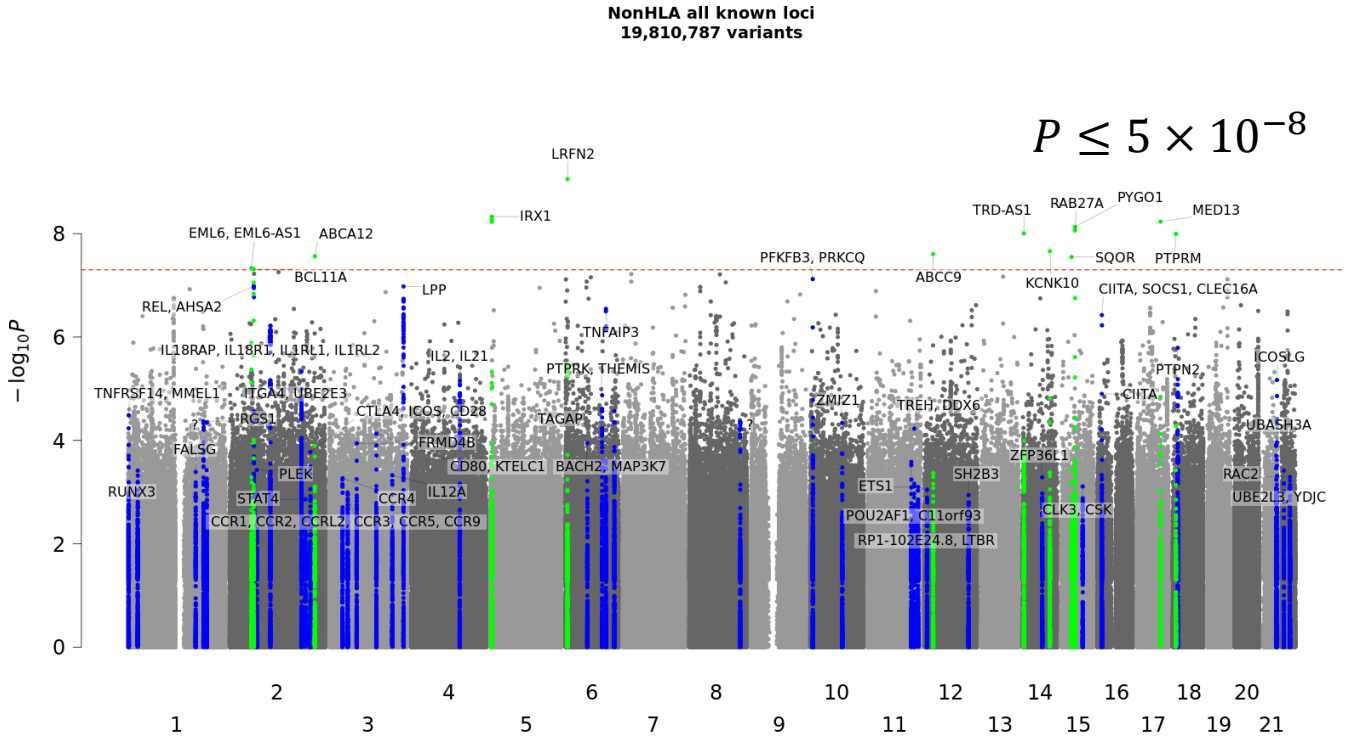
- HLA:
  - CHR6: 29MB – 34MB [hg19]
  - ~12,000 variants ≥ 0.8 imputation score
  - Conditional analysis



- FUMA:
  - SNP2GENE
  - GENE2FUNC

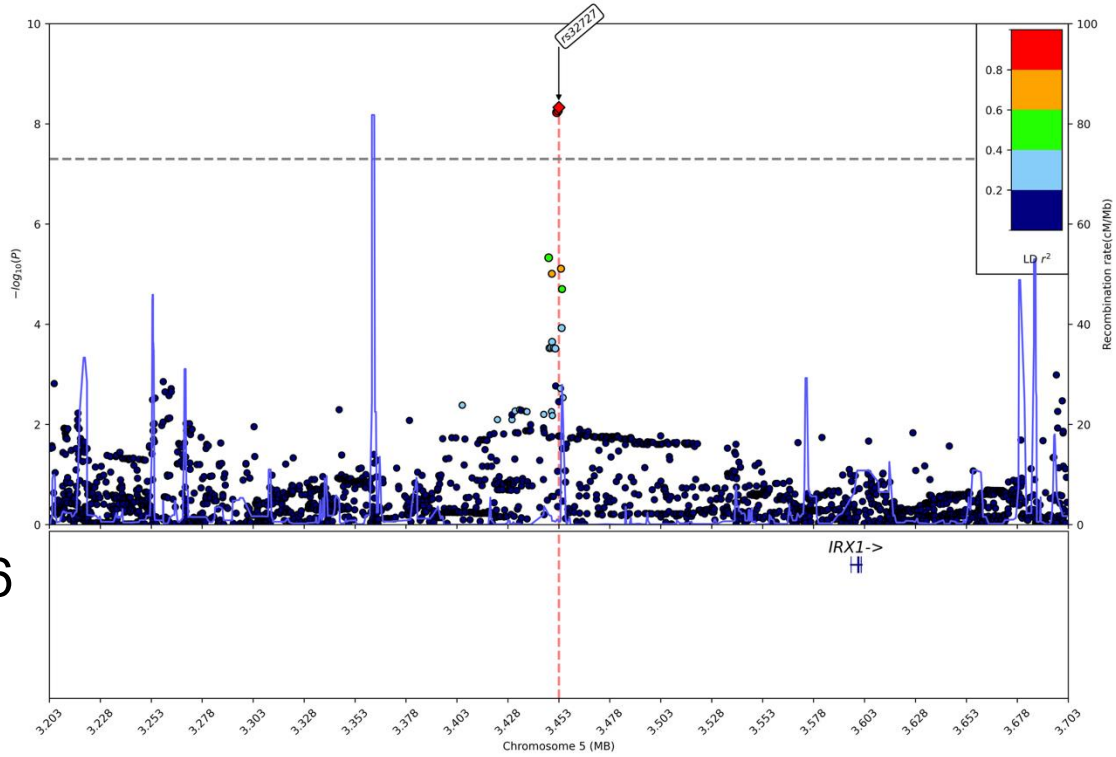
Results

- Novel findings:
  - 13 SNPs (Green)
- Replicated observation:
  - 38 out of 42 autosomal loci (blue)



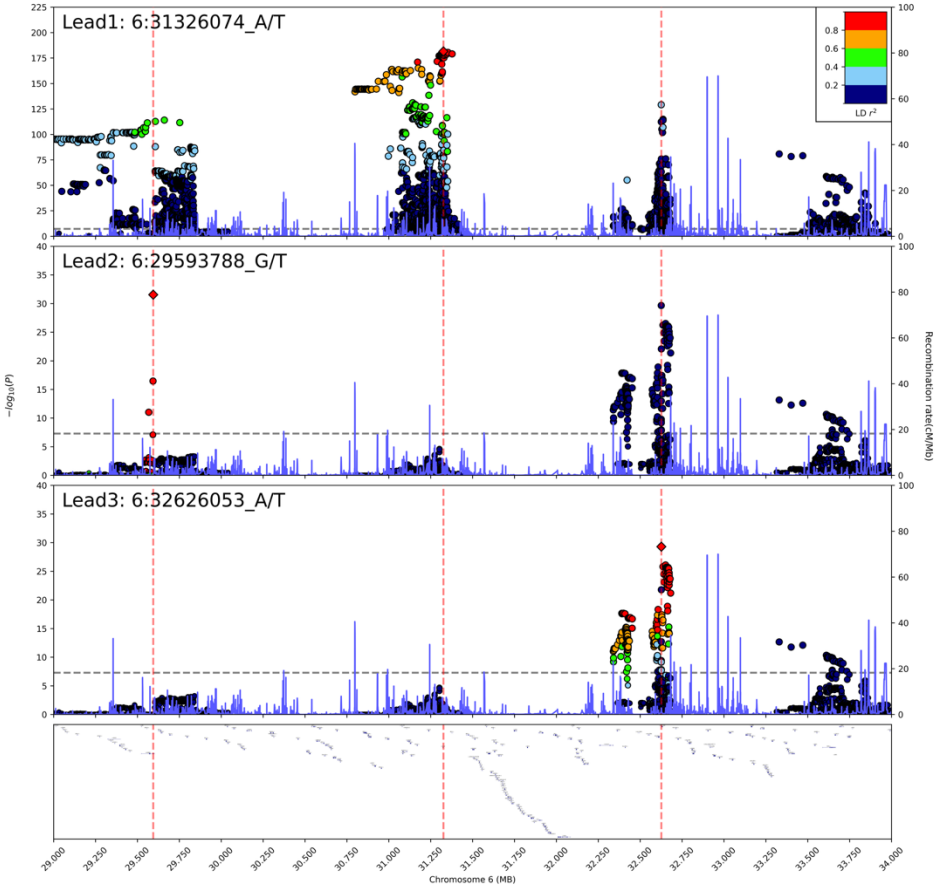
Results (contd.)

- Locus post filtering:
  - MAF ≥ 5%
  - MAC ≥ 10
    - **5p15.33**
- SNPs
  - Lead: rs32727
  - In LD: rs32723, rs32726
- Heritability of non-HLA region = 23%



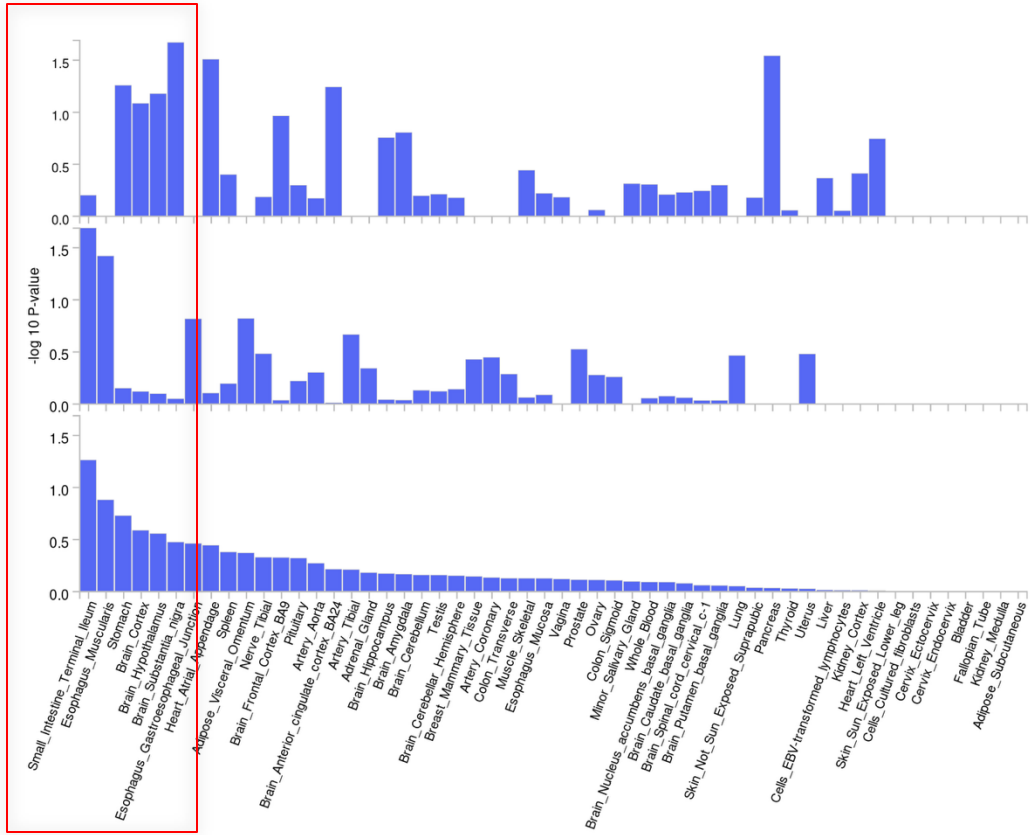
Results (contd.)

- Lead SNP in HLA region:
  - rs28633132 (HLA-DQB1)
  - rs2853999 (HLA-B)
  - rs715044 (GABBR1)



Results (contd.)

- Gene expression:
  - Small intestine
  - Esophagus
  - Stomach
  - Brain
- Validation results:
  - Post filtering
  - 5p15.33 consistent
  - attained $P \leq 5 \times 10^{-7}$



Discussion

- 5p15.33 locus:
  - rs32737 is a long non-coding RNA SNP
  - reached significance in validation subsets too
  - closest gene *IRX1*, also associated with rheumatoid arthritis
- Strengths:
  - Screening: inclusion of histologically confirmed incident cases
  - SAIGE: controlling relatedness and imbalanced dataset
- Limitations:
  - Missing young cohort, limited cases, European ancestry only

Conclusion

- The lncRNA might be involved in key gene regulations
- Close to *IRX1* linked to RA
- RA is known to share loci with CeD

<u>The 5p15.33 is a novel locus associated with CeD</u>

Thank you for your attention!

HUNT4
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