Shared genetic factors between type 1 diabetes (T1D) and co-occurring autoimmune diseases

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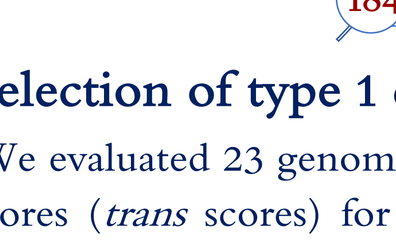
Aim

- To investigate if genetic factors of T1D are associated with the risk of autoimmune diseases frequently co-occurring with T1D.
  - People with type 1 diabetes have a higher frequency of other autoimmune diseases, of which causal mechanisms underlying this co-occurrence is unclear.
  - The genetic overlap between T1D and other autoimmune diseases has previously been studied in independent cases of each trait.
  - Here, we analyzed the presence of other autoimmune diseases in people with T1D.

Methods

1. Type 1 diabetes study cohort - SDRNTIBIO

- 4,964 Scottish people with T1D from the Scottish Diabetes Research Network Type 1 Bioresource (SDRNTIBIO).
- Included only co-occurring autoimmune diseases with >100 cases in this study.



- 915 Hypothyroidism (HTD)
- 355 Pernicious anemia (PA)
- 197 Psoriasis
- 189 Celiac disease
- 187 Inflammatory bowel disease (IBD)
- 184 Rheumatoid arthritis (RA)

2. Selection of type 1 diabetes genetic markers

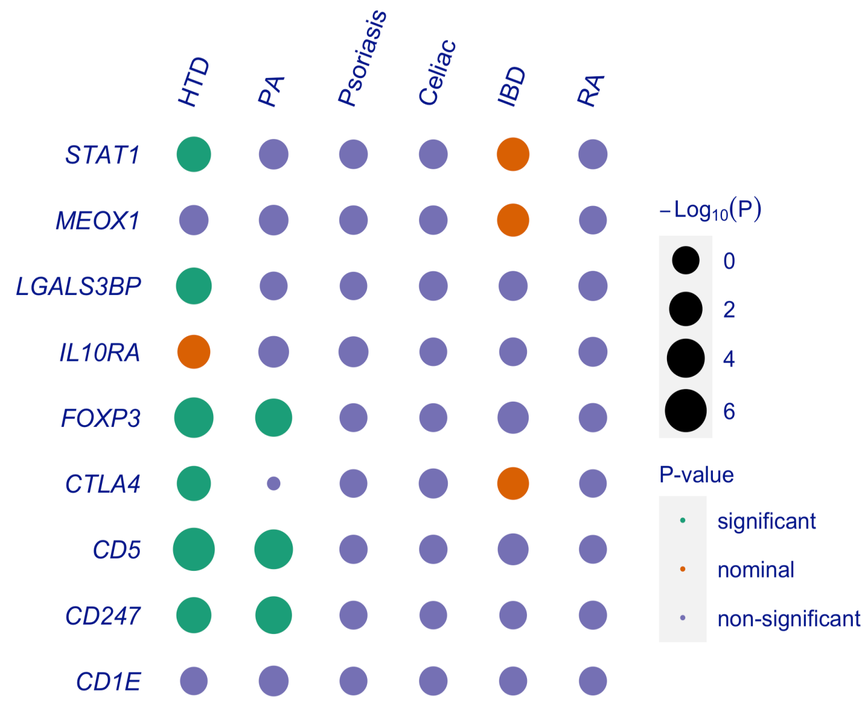
- We evaluated 23 genome-wide aggregated *trans*-QTL genotypic scores (*trans* scores) for whole-blood gene expression (9) and circulating protein level (14), which we consider as "core" genes of T1D using the omnigenic model nomenclature:
  - These *trans* scores showed strong association with T1D risk, and these associations were supported by other lines of evidence.[1]
  - The *trans* scores aggregate polygenic *trans*- effects of common SNPs on gene expression and on protein level.
  - Omnigenic model hypothesis: these *trans*- effects coalesce on a relatively sparse set of "core" effector genes for a disease.

3. Statistical Analysis

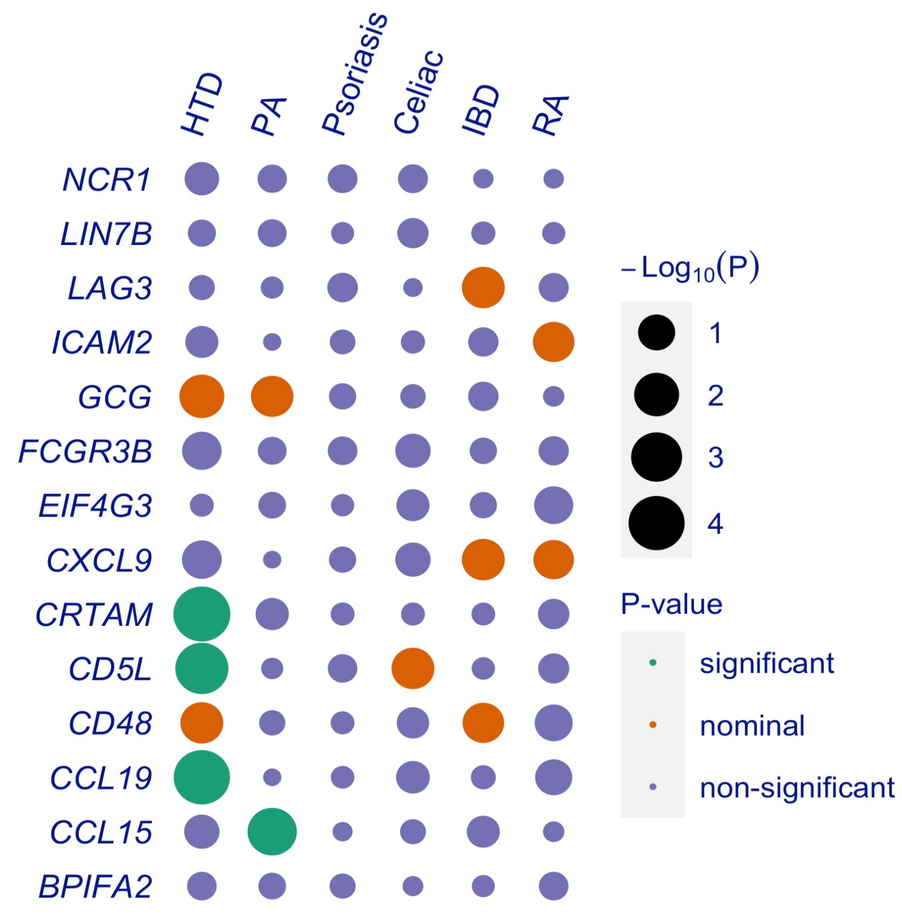
- Logistic regression was used to test association of these *trans* scores with the risk of other autoimmune diseases.
- For each of these autoimmune disease, the remaining T1D cohort was used as controls.
- *Trans* scores of 9 and 14 eQTL and pQTL core genes, respectively were evaluated at Bonferroni corrected threshold of $P < 5.5 \times 10^{-3}$ for eQTLs and $P < 3.5 \times 10^{-3}$ for pQTLs.

Results

A. eQTL *trans* scores analysis for T1D core genes



B. pQTL *trans* scores analysis for T1D core genes



- Genes *FOXP3*, *CD5* and *CD247* were associated with hypothyroidism and with pernicious anaemia.
- Genes *LGALS3BP*, *STAT1*, *CRTAM*, *CCL19* and *CD5L* were associated only with hypothyroidism.
- Gene *CCL15* was associated only with pernicious anaemia.
- All significant genes conferred the same effect direction as T1D
- Besides *CD247* and *LGALS3BP*, which play other significant roles in the immune system, these genes are involved in the induction and activity of CD4+ regulatory T cells (Tregs).
- Non-significant associations for some autoimmune diseases could be attributed to having moderate sample sizes.

Conclusion

- We showed that aggregated *trans* scores for genes and proteins previously identified for T1D are also associated with the risk of co-occurring hypothyroidism and pernicious anaemia in people with T1D.
- This suggests shared immune system pathways between these autoimmune diseases and highlights possible causal mechanisms underlying this co-occurrence.
- The detected genes could serve as potential targets for drug development.

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References:
1. Iakovliev et al. AJHG 2023. https://doi.org/10.1016/j.ajhg.2023.04.003

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