Clinical Paper Summary 4/11/25 ciT1zen science
Stage- and Subgroup-Specific Impact of Non-HLA Polymorphisms on Preclinical Type 1 Diabetes Progression

Source: Vandewalle et al., "The stage- and subgroup-specific impact of non-HLA polymorphisms on preclinical type 1 diabetes progression," 11 (2025) e42156.
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Explanation of HLA in Type 1 Diabetes Prediction:

The **Human Leukocyte Antigen (HLA)** gene complex is crucial for predicting Type 1 diabetes (T1D) because it significantly influences immune function. Variations in these HLA genes determine an individual's susceptibility to autoimmune conditions by influencing how the immune system recognizes self and non-self antigens. Specific HLA variants, like **HLA-DQ2 and HLA-DQ8**, greatly increase the risk of developing T1D by predisposing individuals to autoimmune attacks on insulin-producing beta cells. Thus, HLA genotyping is often used to identify individuals at heightened risk for developing T1D.

Summary of the Abstract:

This study explored how genetic variations (**SNPs**) in genes **outside of the HLA region** (**non-HLA loci**) impact the progression of preclinical Type 1 diabetes (T1D) in people already showing early signs of autoimmunity. Researchers analyzed genetic data from 448 individuals who were relatives of T1D patients and persistently tested positive for autoantibodies. Further, this research article investigates the influence of **17 non-HLA** single nucleotide polymorphisms (SNPs) on the progression of preclinical type 1 diabetes (T1D) in persistently autoantibody-positive first-degree relatives (FDRs).

Key findings include:

- **Early stage (single autoantibody positivity) progression to T1D**:
  - **FUT2 and CTSH** gene variations accelerated the progression from having a single autoantibody to developing multiple autoantibodies. This effect depended specifically on having insulin autoantibodies (for FUT2) or the presence of HLA-DQ2/DQ8 genotypes (for CTSH).
- **Later stage progression to T1D (multiple autoantibody positivity to clinical diabetes)**:
  - Variants in **GLIS3, CENPW, IL2, GSDM, MEG3A, and NRP-1** independently predicted faster progression to clinical diabetes.

- Other genes (**CLEC16A, NRP-1, TCF7L2**) interacted with HLA class I alleles, **CTSH** interacted with maternal diabetes history, and **CD226** interacted with having a high-risk autoantibody profile to further influence progression rates.

The study emphasizes that the predictive power of specific non-HLA genetic markers significantly varies based on disease stage and individual context (like autoantibody type and HLA genotype). The findings suggest that incorporating stage- and subgroup-specific effects of **non-HLA SNPs can refine existing T1D prediction models** and is crucial for personalizing risk assessment, estimating the timing of diabetes onset, and designing and interpreting prevention trials.

GENES discussed

- **FUT2**: A gene involved in determining secretor status, influencing immune interactions and gut microbiome composition.
- **CTSH**: A gene encoding a lysosomal protease involved in immune responses and antigen processing.
- **GLIS3**: A transcription factor gene crucial for pancreatic beta-cell development and function.
- **CENPW**: A gene important for chromosome stability and cell division processes.
- **IL2**: An immune regulatory gene critical for T-cell activation and maintaining immune tolerance.
- **GSDM**: A gene family involved in immune responses through regulation of inflammation and cell death.
- **MEG3A**: A gene encoding a non-coding RNA involved in gene regulation and cellular growth.
- **NRP-1**: A gene encoding a protein involved in immune signaling and inflammation pathways.
- **CLEC16A**: A gene influencing autophagy and immune cell function, associated with autoimmune conditions.
- **TCF7L2**: A gene regulating insulin secretion and beta-cell function, commonly associated with diabetes risk.
- **CD226**: An immune receptor gene important in regulating T-cell activation and autoimmune responses.