Milestone 3

The genetic underpinnings of T1D

By the 1970s, researchers recognized that type 1 diabetes (T1D) was strongly driven by genetic factors. Their studies suggested a polygenic pattern of inheritance; however, the genes associated with disease development were not known. Defining the underlying genetic factors was not a straightforward task in the absence of a map of the human genome and the technologies available today.

Understanding that the development of T1D had an immune component (Milestones 7 and 8) pointed the way to identifying the first genes associated with the disease. The HLA system had been shown to be genetically linked to antigen-specific, cell-mediated immunity. HLA-mediated immunity was associated with the susceptibility to viral infections, as well as autoimmune diseases.

In 1974, Nerup et al., writing in *The Lancet*, clarified previous contradictory reports by demonstrating that HL types A8 and W15 were found more frequently on white blood cells from individuals with T1D and were associated with anti-pancreatic, cell-mediated immunity. Although how HLA variants controlled disease development was not known, the researchers hypothesized that these flavours of the histocompatibility complex somehow triggered the autoimmune reaction that destroyed pancreatic cells.

"HL types A8 and W15 were found more frequently on white blood cells from individuals with T1D"

Later, genome-wide studies shed light on other genomic regions associated with T1D. In 2009, in an untargeted analysis, Barrett et al. listed single-nucleotide polymorphisms in the genomes of individuals from the UK with and without T1D and combined these data with other similar studies. The researchers found additional genomic locations, many linked to immune functions, that had a possible relevance to T1D.

Another notable discovery followed in 2015 when Onengut-Gumuscu et al. compared the genetic profile of 15 autoimmune diseases and demonstrated that T1D was genetically similar to other diseases characterized by the occurrence of autoantibodies.

Further studies untangled the relative importance of genetic variants to T1D risk and pinpointed the exact locations that constituted important disease alleles. It became evident that variants within the HLA locus represent half of the genetic risk in T1D. In particular, positions coding for amino acids within the region of the HLA proteins where antigenic peptides are bound and presented to immune cells, the so-called antigen-binding grooves, strongly conferred risk. Hu et al. found that three amino acid positions in the antigen-binding grooves of HLA genes together showed a notable effect. The demonstration that the critical locations for amino acid variations in HLA proteins were on the face of the protein that immune cells interacted with helped explain the occurrence of autoimmunity.

While the HLA genes were strongly associated with the occurrence of autoimmunity, it was less clear whether they were also driving the progression to clinical T1D. In fact, the progression from producing autoantibodies to insulin insufficiency is variable and the genetic risks were unclear. Beyerlein et al. clarified that genetic risk scores could indicate the rate of progression to clinical T1D and that the most prominent HLA genotypes were not the main drivers in this equation.

Based on the recognition that an integrated genetic risk score would capture the likelihood to develop the disease more accurately than focusing on the main HLA genotypes alone, Sharp et al. developed an updated genetic risk score for T1D in 2019 to predict future T1D in infants.

Although studies of T1D genetics over the past 50 years have advanced our understanding of important genetic risk loci and informed research on disease mechanisms, they are not broadly useful. Previous studies have mainly focused on individuals with European ancestry, and thus genetic risk scores based on this research fail to accurately capture genetic susceptibility for the majority of the population. Onengut-Gumuscu et al. (2019) demonstrated the improved performance of an ancestry-specific T1D risk score that included HLA alleles from individuals with African ancestry. Inclusion of ancestry-specific disease-associated variants is needed to accurately calculate genetic risk.

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Milestone study

Nerup, J. et al. HL-A antigens and diabetes mellitus. *Lancet* **304**, 864–866 (1974)

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