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TYPE 1 DIABETES AND AUTOIMMUNE THYROIDITIS: THE GENETIC CONNECTION

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Genetic studies have transformed our understanding of autoimmune diseases. As new genes and loci are being identified, novel mechanisms underlying autoimmunity are being unravelled. For example, with the mapping of NOD2 as a major Crohn's disease gene, it became clear that the innate immune response is critical for the development of Crohn's disease, and the entire field moved in this direction (1). Similarly, the identification of HLA-DR (2) and 5 additional non-MHC genes (3) as major susceptibility genes for autoimmune thyroid diseases (AITD) highlighted the central role of the immunological synapse (i.e. the interface between antigen presenting cells and T-cells during antigen presentation (4;5)) in the etiology of thyroid autoimmunity (6).

In recent years it has become apparent that genetic susceptibility is shared between several autoimmune diseases (7–9). Indeed, clinically distinct autoimmune diseases cluster in families (10;11), suggesting the existence of joint autoimmunity susceptibility genes (7;8). Of all autoimmune conditions, the familial clustering of autoimmune diseases is most pronounced for type 1 diabetes (T1D) and AITD (12;13)(reviewed in (14;15)). In fact, the prevalence of thyroid autoimmunity in relatives of T1D patients is as high as 48%, compared with a general population prevalence of only 3–10% (12;16–18). Moreover, T1D and AITD frequently occur within the same individual (14;19). Up to 50% of T1D patients were reported to be positive for thyroid antibodies (TAb) (reviewed in (15)), and approximately 50% of them progress to develop clinical AITD (20). Conversely, 2.3% of children with AITD have been reported to have islet cell antibodies, compared with 0% of controls (21). When T1D and AITD occur in the same individual, the phenotype is classified as one of the variants of autoimmune polyglandular syndrome type 3 (APS3 variant [abbreviated here as APS3v]) (13;22;23).

Despite the strong genetic association between T1D and AITD, up until recently little was known about the shared susceptibility genes for T1D and AITD. Most previous studies focused on the HLA locus (23–31). More recently, we have shown that, in addition to HLA class II, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is a major gene associated with joint risk for T1D and AITD (29). These data were confirmed by two recent studies from Japan (32) and the UK (33).

In the current issue of *Thyroid* another important autoimmunity susceptibility gene was examined in APS3v (T1D+AITD) patients, the protein tyrosine phosphatase-22 (PTPN22) gene (34). Dultz et al report a significant association between APS3v (T1D+AITD) and PTPN22, suggesting that PTPN22 is an important susceptibility gene for APS3v (34). A coding SNP at nucleotide 1858 of PTPN22 that causes an arginine to tryptophan substitution at position

620 (R620W) was found to be strongly associated with several autoimmune diseases (35) including systemic lupus erythematosus (36), rheumatoid arthritis (37), as well as T1D (38; 39), and GD (40). Therefore, it was not surprising that the PTPN22 gene was shown to be associated with APS3v. However, the role of PTPN22 in Hashimoto's thyroiditis (HT) is unclear. Studies of the PTPN22 gene in HT have been inconsistent (35;41), suggesting only a minor (or no) role in susceptibility to HT. Intriguingly, Dultz et al found a strong association of PTPN22 with HT in the context of APS3v (34). The association with HT was even stronger than the association with GD when it constituted part of the APS3v phenotype (the odds ratios were 6.14 and 2.79, respectively). The data of Dultz et al. support the notion that APS3v (T1D +AITD) is a unique syndrome with distinct genetic susceptibility. Moreover, it demonstrates the power of subset analysis to detect associations (42). When all HT patients were tested for association with PTPN22 there was weak association (41), but when the subset of HT patients that also have T1D were tested the association became very significant (34).

What could be the mechanism by which PTPN22 causes autoimmunity? The PTPN22 gene encodes the lymphoid tyrosine phosphatase (LYP) protein which belongs to a family of protein tyrosine phosphatases that are expressed in both immature and mature B and T lymphocytes. LYP is a powerful inhibitor of the T-cell receptor signaling pathway (43). LYP binds to the C terminal of the protein kinase, Csk, thus restricting the response to antigens by disrupting protein tyrosine phosphorylation events that control cell activation and differentiation (44; 45). Studies suggest that the disease associated tryptophan variant makes the protein an even stronger inhibitor of T cells, as it is a gain-of-function change (46). This is surprising because one would expect the associated allele to increase T-cell activation, as has been shown for CTLA-4 (47–49). One possible explanation for this paradox is that a lower T cell receptor signaling could result in self-reactive T cells to escaping thymic deletion. Clearly, there is need for further studies to clarify the mechanisms underlying the association of PTPN22 with autoimmunity.

In summary, a picture of the genetic architecture of T1D and AITD is emerging where some susceptibility genes are shared by both conditions and predispose to APS3v, while other susceptibility genes are specific for each phenotype (Figure 1). These genes interact with each other, as well as with other genes, and epigenetic and environmental factors. Interestingly, the four APS3v susceptibility genes identified so far (15) all participate in the immunological synapse and T-cell activation (Figure 2). These include the HLA-DR molecules presenting peptide antigens to T-cells; CTLA-4, an important costimulatory molecule; PTPN22, a gene regulating TCR signaling pathways; and FOXP3, considered the master regulator of Treg development and function (50). This suggests that, similar to AITD, APS3v is also influenced by abnormalities of the immunological synapse enabling presentation of self peptides to T-cells and augmenting their responses to the presented peptides. Identifying the major genetic variants predisposing to APS3v (T1D+AITD) and the functional consequences of these variants will lead to a better understanding of the molecular mechanisms causing the association between T1D and AITD.

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***These genes are specific
for Graves' disease**

Figure 1.

Summary of confirmed susceptibility genes for autoimmune thyroid diseases (AITD) and type 1 diabetes (T1D). These include genes specific for AITD (Tg, TSHR and CD40) and genes specific for T1D (HLA-DQ2/DQ8, VNTR [a tandem repeat polymorphism located approximately 600 bp 5' of the insulin gene], MICA [MHC class I polypeptide-related sequence], IL2RA/CD25 [interleukin 2 receptor alpha], and IFIH1/MDA5 [interferon induced with helicase C]). Four genes are common to both diseases (HLA-DR3/DR4, CTLA-4, PTPN22, and FOXP3 [forkhead box P3, which controls regulatory T-cell differentiation]).

Figure 2.

The immunological synapse or the interface between an antigen presenting cell and a T-cell. The four confirmed APS3v susceptibility genes participate in the immunological synapse. These include the HLA-DR genes which present the autoantigens to T-cells, the CTLA-4 gene, an important co-stimulatory molecule which suppresses T-cell activation, the PTPN22 gene which negatively regulates the T-cell receptor signaling pathway, and the FOXP3 gene which is the key regulator of the differentiation of regulatory T cells.