

Genetic determinants of diabetes are similarly associated with other immune-mediated diseases

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Purpose of review

I discuss the increasing number of genes discovered to exert pleiotropic action on susceptibility to diabetes and simultaneously to other immune-mediated diseases. While a genetic correlation between type 1 diabetes and autoimmunity is not surprising, the mechanism of a relationship to other conditions such as atopy is less obvious. The recent wave of genome-wide association studies offers confirmation of previously recognized risk loci, but also novel loci that also are likely to act via multiple pathogenetic pathways. I will review this material more in a genetical than an immunological way.

Recent findings

Identification of *IFIH1*, an RNA helicase involved in the innate immune response to viral infection as a risk factor for type 1 diabetes and rheumatoid arthritis. Confirmation of the roles of *CTLA4* and *PTPN22* as general immune function modulators with a nonlinear dose–response effect on autoimmunity, and confirmation of the role of *IL2RA*, which may act via a regulatory T cell subset on immune disease risk. Expansion of the role of *PPARG* in immunity.

Summary

The wave of genome-wide association studies already experienced in the last 2 years has solidified what we thought we knew and added a list of genes in new pathways. The association of *IFIH1* with type 1 diabetes may offer a real window into early events in the development of that disease.

Keywords

CLEC16A, human leukocyte antigen, *IFIH1*, *IL2RA*, *PTPN22*, tumor necrosis factor

Abbreviations

GWAS	genome-wide association study
HLA	human leukocyte antigen
SNP	single nucleotide polymorphism
T1D	type 1 diabetes
T2D	type 2 diabetes
TNF	tumor necrosis factor
WTCCC	Wellcome Trust Case Control Consortium

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Introduction

That a number of other autoimmune diseases co-occur with type 1 diabetes (T1D) both within the individual and in families has been recognized for many years. From the 1970s onward, the genetic basis of this correlation has been uncovered, starting with the role of human leukocyte antigen (HLA). This gene discovery has accelerated in recent years. The genetic association studies published in 2006–2007 are characterized by their very large sample sizes, representing many years of patient recruitment, plus the availability of high-throughput genotyping technologies. For example, the study of multiple sclerosis reported by Hafler *et al.* [1] involved genotyping of 12 360 individuals and the Wellcome Trust Case Control Consortium (WTCCC) [2•] genotyped 18 000 individuals.

There have been a number of genome-wide association studies (GWASs) of both T1D and type 2 diabetes (T2D) published recently. In the case of T2D, the novel associated genes (or sequence far from any known gene) have been in surprising (or uncharacterized) pathways and some may be of relevance to inflammation. The roles of previously identified T2D genes, notably *PPARG*, in immunity have also been clarified. With the wealth of publicly available GWAS data, one can now quickly cross-classify loci associated with different immune phenotypes. For example, the asthma-associated single nucleotide polymorphisms (SNPs) in *ORMDL3* reported by Moffatt *et al.* [3] that are in common with those utilized by the WTCCC [2•] or the Diabetes Genetics Initiative [4] do not show association to T1D, T2D, rheumatoid arthritis or Crohn's disease.

Descriptive genetic epidemiological studies

A number of authors have presented evidence that atopic individuals are less likely to develop T1D, a finding interpreted as placing these two conditions at either end of a (simplistic) global T helper 1–T helper 2 activity

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continuum. Thus, a study of 488 841 Israeli conscripts [5[•]] found that asthmatics were less likely to develop a broad range of autoimmune diseases: T1D, rheumatoid arthritis, immune thrombocytic purpura and inflammatory bowel disease.

Molecular genetics of type 1 diabetes and autoimmunity

The online database <http://t1dbase.org> [6[•]] was set up by a consortium of institutions and laboratories to integrate genetic information about T1D. It is an excellent bioinformatic resource and lists 30 T1D candidate regions, many of which will be familiar to researchers studying other immune-related diseases.

The most important paper this year in T1D genetics must be the WTCC GWAS [2^{••}]. The consortium recruited approximately 8000 cases (50% of the UK T1D population), although only 2000 of these were genotyped in this particular study. These were compared to 3000 controls. The study easily replicated the strong associations to *HLA-DRB1* (*IDDM1*), *INS* (*IDDM2*), *CTLA4* (*IDDM12*), *PTPN22*, *IL2RA* and *IFIH1* (Table 1). There were three novel regions implicated purely with T1D, association to which was subsequently replicated using other datasets: 12q13, 12q24 and 16p13 [7]. In addition, there were two regions, 10p15 and 18p11, where the evidence for association to T1D by itself did not reach genome-wide significance, but did when the T1D cases were combined with the rheumatoid arthritis and Crohn's disease cases. The 18p11 association (*rs6679677*) has also been replicated in other datasets [8[•]].

Only slightly smaller, another GWAS for T1D was reported by Hakonarson *et al.* [8[•]], who studied 1046 cases and 2112 controls (the latter including 966 parents of cases). This again detected the HLA region (including epistatic action of a HLA-DRB1 tagging SNP *rs2647044* with *rs3117098* within the *BTNL2* locus), *INS* and *PTPN22*. The novel loci achieving genome-wide signifi-

cance in this first stage were *COL1A2*, *LPHN2* and *KIAA0350*, but the former two could not be replicated in the replication stage. *KIAA0350* (official name *CLEC16A*) is the 16p13 locus also discovered by the WTCCC.

Human leukocyte antigen

The HLA region harbors loci explaining 50–60% of the total genetic risk of T1D [9[•]] and see <http://www.ncbi.nlm.nih.gov/mhc>). Aside from DRB1-DQB1, there seem to be several other risk loci, but the DR4-DQB1*0302/DR3-DQBG1*0201 genotype gives a risk 15–20 times higher than any other HLA or non-HLA locus in Caucasian samples [9[•],10]. This specific haplotype also increases risk of celiac disease, but generally, of course, there is immense haplotypic and locus (class I–III) heterogeneity for the causative alleles for other immune diseases.

Tumor necrosis factor

The tumor necrosis factors (TNFs) are key cytokines involved in innate immunity, inflammation, apoptosis, metabolism and development. The size of the literature on the genetics of this system published in 2006–2007 alone would require a separate review (124 publications for the PubMed search 'TNF promoter polymorphism' alone; <http://www.ncbi.nlm.nih.gov/sites/entrez>).

Owing to the strength of linkage disequilibrium of the class II HLA region to TNF and lymphotoxin- α , despite many studies it is still not clear whether TNF promoter polymorphisms, such as the $-308G>A$ promoter variant (*rs1800629*), have an independent role in predisposition to T1D [9[•]] (it is known that this variant does not directly influence transcript levels of TNF- α). In the WTCCC T1D scan [2^{••}], the only TNF promoter SNP included (*rs1799964*, $-1031T>C$, in strong linkage disequilibrium with *rs1800629*) gave an allelic association $P = 7.9 \times 10^{-8}$, a demonstration of the strength of the association signal for this gene. Aminkeng *et al.* [11] report no association of

Table 1 Type 1 diabetes susceptibility loci associated with autoimmune and other immune-mediated diseases

Type 1 diabetes susceptibility gene(s)	Chromosomal location (name assigned via linkage analysis)	Other autoimmune diseases associated with locus	Other inflammatory diseases associated
<i>DQA1</i> , <i>DQB1</i> , <i>DRB1</i>	6p21 (<i>IDDM1</i>)	Gluten enteropathy, rheumatoid arthritis, multiple sclerosis, etc.	Manifold, but allelic heterogeneity
<i>CTLA4</i> (<i>CD28</i> , <i>ICOS</i>)	2q33.2 (<i>IDDM12</i>)	Autoimmune hypothyroidism, Graves' disease	Atopy
<i>CASP7</i>	10q25 (<i>IDDM17</i>)	Rheumatoid arthritis	
<i>IFIH1</i>	2q24 (<i>IDDM19</i>)	Graves' disease	
<i>IL12B</i> (?)	5q33.3 (<i>IDDM18</i>)		Atopy?, tuberculosis
<i>IL2RA</i> (<i>CD25</i>)	10p15 (<i>IDDM10</i>)	Multiple sclerosis, Graves' disease	
<i>PTPN22</i>	1p13 (<i>Idm10</i>)	Rheumatoid arthritis, Graves' disease, Hashimoto thyroiditis, systemic lupus erythematosus, Addison's disease, myasthenia gravis, vitiligo	Endometriosis?

rs1800629 to T1D in a sample of 1029 Belgian cases and 575 controls, but did find a strong association to a TNF microsatellite marker that persisted after adjustment for HLA-DQA1-DQB1 genotype. Specifically, in cases and controls who were DQA1*0501-DQB1*201 homozygotes, the *TNFA1* allele was twice as common in cases ($P=0.0008$). They note that they still cannot exclude that this effect is due to other HLA haplotypes.

So many studies of *rs1800629* have been published that there are recent meta-analyses validating associations with psoriasis [12], rheumatoid arthritis (significant in Latin America, but not Europe) [13], systemic lupus erythematosus (in Europeans) [14] and asthma [15]. Meta-analysis found no role for TNF promoter polymorphisms in premature birth [16].

TNFRSF1A/B

A number of association studies have attempted to implicate genetic variation in the TNF receptor subtypes with complications of T1D and T2D diabetes, notably atherosclerosis. Nishimura *et al.* [17] is the only report I am aware of that describes association to T1D itself (Japanese T1D patients, $P=0.003$), rather than to disease complications. The WTCCC GWAS did not detect any association to T1D risk using three SNPs within the gene [2**].

The TNF receptor-associated periodic syndrome is an autosomal dominant Mendelian disorder characterized as auto-inflammatory and is due to mutations with *TNFRSF1A* (12p) (reviewed in [18]). The *TNFRSF1A* R92Q mutation has been associated both with TNF receptor-associated periodic syndrome, carotid atherosclerosis and myocardial infarction, and is present at 2–4% allele frequency in Caucasian populations. Kumpfel *et al.* [19] also found it to be common in a subset of multiple sclerosis patients who had suggestive symptoms.

IL2RA

The interleukin-2 receptor α gene (*IL2RA*) lies on chromosome 10p15.1. It was first implicated in T1D in 2005 [20]. In addition to the replication by the WTCCC [2**], Qu *et al.* [21] were able to replicate an association between *IL2RA* SNPs and T1D using 949 triad families and the transmission–disequilibrium test (where the parental alleles not transmitted to the affected child are utilized as matched controls). Two SNPs in intron 1 were implicated. Similarly, Lowe *et al.* [22] describe fine mapping of putative causative variants also within the 5' end of *IL2RA* and in the neighboring RBM17. They showed that these T1D risk genotypes were also associated with low serum levels of soluble interleukin-2 receptor α , which they interpreted as a marker of overall immune responsiveness. Hafler *et al.* [1] implicated two

IL2RA variants as risk factors for multiple sclerosis and Brand *et al.* [23] with Graves' disease.

Whether these variants are direct causes of autoimmunity or whether the association is due to linkage disequilibrium is still not completely certain. The interleukin-2 receptor (CD25) is a marker of the regulatory helper T cell subset involved in regulating tolerance. This class is being intensively studied in a range of immune diseases including T1D and impairments of regulatory T cell function are seen in the IPEX syndrome (due in some cases to FOXP3 mutations), a severe autoimmune lymphoproliferative syndrome (T1D, autoimmune thyroid disease, eczema, hyperimmunoglobulinemia E).

PTPN22 (Lyp)

Variants in this gene were first shown to increase risk of diabetes in 2004 [24] and a wide of variety of autoimmune diseases subsequently [25,26*]. Ammendola *et al.* [27] presented evidence that the R620W variant increases risk of endometriosis (odds ratio = 2.78, 95% confidence interval = 1.21–6.43), but this needs replication. Given the broad range of diseases already associated with *PTPN22*, a number of studies in the last year have been performed that exclude association with aplastic anemia [28], asthma [29], inflammatory bowel disease [2**,30], systemic sclerosis [31,32] and trypanosomiasis [33].

The R602W variant is surprisingly common in European populations (6–12%) and so has a population attributable fraction of 1–7% for autoimmune disease [25,26*]. The pattern of autoimmune and inflammatory diseases *not* affected by *PTPN22* variation is potentially instructive, but not yet fully comprehended. *PTPN22* encodes a hematopoietic-specific protein tyrosine phosphatase that acts to negatively regulate T cell receptor signaling via dephosphorylation of the Lck tyrosine kinase, ZAP-70, CD3 and the T cell receptor [34*]. The R620W allele that is most strongly associated with autoimmunity in Caucasians seems to be a gain-of-function mutation [35]. This leads to reduced T cell activation and presumably decreased deletion of autoreactive T cells within the thymus. Murine *N*-ethyl-*N*-nitrosurea-induced mutations in ZAP-70 (W163C, I367F and W504R) seem to increase autoimmunity in this fashion and, interestingly, the latter two mutations are also characterized by high serum levels of IgE ([36] and C. Goodnow, unpublished).

Caspase-7

Caspase-7 was first flagged as a positional candidate for *IDDM17* (10q25) in 2003 within a single large pedigree [37]. More recently, Garcia-Lozano *et al.* [38] found *rs2227309* in this gene to confer a 1.3-fold relative risk of rheumatoid arthritis in a study of 906 cases and 528 controls. The G/G genotype was found to increase expression of the procaspase-7 β -isoform ($P=2 \times 10^{-4}$).

IL12B

In 2002–2004, there was some excitement about variants in the 3'-untranslated region of the gene encoding the interleukin-12 p40 chain that affected expression levels, and risk of both T1D and to allergic disease [39,40]. These do not seem to have held up, although Morahan *et al.* [41] replicates association [42] of the same variants with tuberculosis (high-expression genotypes) and leprosy (low expression genotypes). The immune response in both these diseases has been linked to that seen in atopy. No SNPs in or around this gene exhibited significant association in the WTCCC T1D GWAS [2**].

ILIH1

Smyth *et al.* [43*] first described association of the interferon-induced helicase gene to T1D found in the 'pilot' nonsynonymous coding SNP GWAS for T1D (6500 SNPs tested) performed as part of the WTCCC. The initial P value of 4×10^{-5} for *rs1990760* was improved upon by genotyping a further 2470 cases and 4590 controls, and then 2134 European parent–case triads. This was (unsurprisingly) subsequently replicated in the main WTCCC T1D GWAS [2**]. The *major* allele (an alanine at position 946) increases risk of T1D 1.2-fold. Sutherland *et al.* [44] also tested the same coding variant *rs1990760* for association to autoimmune thyroid (646 cases) and adrenal disease (214 cases). The alanine allele increased the odds of Graves' disease 1.47-fold ($P = 2 \times 10^{-5}$). By contrast, Marinou *et al.* [45] found no association with rheumatoid arthritis using 965 cases and 988 controls at the same SNP.

ILIH1, initially named melanoma differentiation-associated gene-5 (*MDA-5*), encodes a RNA helicase specialized for the recognition of cytoplasmic viral double-stranded RNA (specifically picornaviruses, but also activated in measles and influenza A infection [46–48]) leading to interferon- β production via activation of interferon regulatory factor-3 and nuclear factor- κ B [46]. Smyth *et al.* [43*] presumed that the T1D association might therefore be via the response to viral infection thought to underlie the production of anti-islet immunity. Other plausible candidates acting via the same pathway might include the other major RNA helicase RIG-1 and negative regulator LGP2 [46].

CLEC16A (KIAA0350)

As noted above, association to this 16p13.2 locus was replicated in stage 2 (follow-up) studies by Hakonarson *et al.* [8*], with a combined P value of 7×10^{-11} for the

peak SNP *rs2903692*. This SNP did not affect transcript levels of the gene product, which encodes a C-type lectin receptor. No other genes are nearby, and this gene is mainly expressed in dendritic cells and lymphocytes, so it is the most plausible candidate.

C-type lectin receptors are widely expressed on dendritic cells, are specialized to recognize specific self or pathogen antigens, and are suspected of involvement in tolerance and autoimmunity [49]. Using the downloadable WTCCC data [2**], we can see that none of the other six diseases show association to any T1D associated SNPs on 16p (best $P = 0.02$), so in this case the association is disease specific.

SOD2

The genes encoding the various superoxide dismutases are popular candidates for a variety of diseases, especially diabetes, where reactive oxidation species are believed to underlie many complications of the disorder [50]. The MnSOD gene (*SOD2*) does lie within the broad *IDDM5* linked region and Mollsten *et al.* [51], for example, found that the *SOD2* V16A (*rs4880*) polymorphism was associated with diabetic nephropathy, most impressively in smokers.

Molecular genetics of type 2 diabetes and inflammation

There have been more T2D than T1D GWASs published so far (see the nice but already outdated review by Frayling [2**,52*,53,54]). A number of the recently uncovered T2D susceptibility loci tend to be more implicated in differentiation and development (and thus often oncogenesis). These include *TCF2* (one variant involved in susceptibility to diabetes and prostate cancer [55]), *TCF7L2*, *IGF2BP2* (*IMP2*), *ANRIL/CDKN2A/CDKN2B* and perhaps *FTO*. *WFS1* mutations lead to Wolfram syndrome and nonsyndromic sensorineural deafness.

PPARG

Association of variants of *PPARG* (encoding peroxisome proliferator-activated receptor- γ) and T2D was first reported in 1998 and this was confirmed in several of the recent GWASs [2**] (see Table 2). In the immunological literature, the recent interest in this receptor has been on its effects on immune function in general. Activation of *PPARG* was shown in 2000 by Yang *et al.* [56] to suppress T cell activity and similar strong inhibitory effects on monocyte lineage cells (including

Table 2 Type 2 diabetes susceptibility loci associated with other immune-mediated diseases

Type 2 diabetes susceptibility gene(s)	Chromosomal location (prior evidence of linkage)	Other inflammatory diseases associated
<i>PPARG</i>	3p25 (no)	Psoriasis, asthma, metabolic syndrome

dendritic cells) invoked as an additional mechanism for an antidiabetic effect [57]. More recently, Wohlfert [58] has shown that one subclass of immune cells is upregulated by activation of *PPARG*, i.e. the regulatory T cells implicated in tolerance. Several papers suggest that *PPARG* agonist therapy may have a role in the treatment of diseases such as psoriasis and asthma [59,60], respiratory syncytial virus infection [61], as well as Alzheimer's disease [62].

Thus, it is not surprising that studies of the effects of the *PPARG* T2D-associated polymorphisms on other diseases continue to be performed. Palmer *et al.* [63] studied 569 asthmatics, and found homozygosity at the P12A (*rs1801282*) and 1431C>T sites was increased in patients with more frequent exacerbations of asthma ($P=0.002$). There is no association of serum IgE level with any of 10 SNPs in *PPARG* in the British 1958 Birth Cohort GWAS dataset, although this is a 'normal' population sample and so may lack power in comparison with a disease-centered study. (See <http://www.b58cgene.sgul.ac.uk>; with little fanfare, this website also makes freely available GWAS data for IgE level, systolic blood pressure, BMI, height, lung function, hearing, cholesterol, hemoglobin A1c, fibrinogen and birth weight vs. 1 million SNPs.)

In psoriatic arthritis, Butt *et al.* [64] found the *rs1801282**P allele to be weakly associated with increased disease risk. The earlier study of Mossner *et al.* [65] did not detect any association with psoriasis *per se*.

Conclusion

Of necessity, this review has been brief. A first point to emphasize is the huge amount of genetic data that is now freely available for download. Now that the main papers have been published by these groups, which concentrated on only the most extreme significant results, others can combine datasets and trawl for multidisease associations, and compare SNP allele frequencies in cases with different diseases. We must presume that risk loci of lesser effect are among the association P values that did not reach the strict thresholds used to declare genome-wide significance in the GWASs and these may be uncovered by testing the same candidates vs. related diseases, as pointed to by the title of this paper, as well as by the relatively crude approach taken by the WTCCC of simply pooling cases with different diseases.

In the case of T1D, most of the significant associations arising from the GWASs were replications of loci known by linkage or candidate gene association. The clear exceptions are *ILIH1* and *CLEC16A* (*KIAA0350*), although with hindsight the former might have eventually been flagged as a candidate, given the rich findings in other genes of the innate immune system. We know

little about *CLEC16A*, but the role of other C-lectin-binding receptors in immunity is tantalizing [66]. In the case of T2D (and the other diseases studied by the WTCCC and others), the associations have been to unexpected loci, but it remains to be seen how many of these will impact diseases outside of the metabolic syndrome.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 576–577).

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