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GENETICS (AP MORRIS, SECTION EDITOR)

The Genetic Contribution to Type 1 Diabetes

Marina Bakay[1] · Rahul Pandey[1] · Struan F.A. Grant[1,2,3,4] · Hakon Hakonarson[1,2]

Abstract

Purpose of Review To provide an updated summary of discoveries made to date resulting from genome-wide association study (GWAS) and sequencing studies, and to discuss the latest loci added to the growing repertoire of genetic signals predisposing to type 1 diabetes (T1D).

Recent Findings Genetic studies have identified over 60 loci associated with T1D susceptibility. GWAS alone does not specifically inform on underlying mechanisms, but in combination with other sequencing and omics-data, advances are being made in our understanding of T1D genetic etiology and pathogenesis. Current knowledge indicates that genetic variation operating in both pancreatic β cells and in immune cells is central in mediating T1D risk.

Summary One of the main challenges is to determine how these recently discovered GWAS-implicated variants affect the expression and function of gene products. Once we understand the mechanism of action for disease-causing variants, we will be well placed to apply targeted genomic approaches to impede the premature activation of the immune system in an effort to ultimately prevent the onset of T1D.

Keywords Type 1 diabetes (T1D) · Genome-wide association study (GWAS) · Susceptibility loci · Autoimmunity · C-type lectin-like domain family 16A (*CLEC16A*) gene

Introduction

Type 1 diabetes (T1D) is a chronic multifactorial disease with a strong genetic component. It arises as a consequence of autoimmune destruction of pancreatic β cells. The resulting insulin deficiency requires exogenous insulin for survival, and long-term complications can cause substantial disability and shorten lifespan. The prevalence of diabetes is increasing worldwide with populations of European ancestry having the highest presentation rate [1]. According to the International Diabetes Federation, the worldwide prevalence of diabetes mellitus in 2018 was 425 million, and is predicted to reach 629 million by 2045 (https://diabetesatlas.org). T1D represents approximately 10% of these patients [2, 3]. The incidence of T1D is increasing 3–4% annually, most notably in children and adolescents [4]. T1D is a heritable polygenic disease with monozygotic twin concordance of 30–70% [5–8] and sibling risk of 6–7%, which is approximately 10 times greater than in the general population [9].

T1D develops at all ages. In addition to genetic predisposition, environmental and epigenetic factors impact disease susceptibility [10–12]. Studies in human and animal models have revealed that both innate and adaptive immune responses participate in disease pathogenesis. It is well understood that there are extensive interactions between immune cells during T1D onset, including T cells ($CD4^+$ and $CD8^+$), B cells, natural killers (NK), macrophages, dendritic cells (DC), and antigen-presenting cells (APCs).

Here, we review recent progress in the genetics of T1D and its complications resulting from genome-wide association study (GWAS). In addition, we discuss strategies being used to further validate GWAS findings and to enhance our

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✉ Hakon Hakonarson
hakonarson@email.chop.edu

[1] The Center for Applied Genomics, Division of Human Genetics, The Children's Hospital of Philadelphia, 3615 Civic Center Boulevard, Abramson Research Center, Suite 1216B, Philadelphia, PA 19104-4318, USA

[2] Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

[3] Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

[4] Center for Spatial and Functional Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

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functional understanding to improve our interpretation of the genetic component of T1D pathogenesis.

Genetic Component of Type 1 Diabetes

T1D risk is strongly influenced by multiple genetic loci and poorly understood environmental factors. Studies of T1D genetics started in the 1970s and revealed the key contribution of the human leukocyte antigen (HLA) region to T1D susceptibility. Family and candidate gene approaches discovered an additional five loci to be associated with T1D. Starting in 2007, GWAS have dramatically increased the number of loci associated with T1D to over 60 as depicted in Fig. 1A. These loci harbor many novel genes that were not previously thought to be obvious candidates for T1D susceptibility prior to the GWAS era.

Before the Genome-Wide Association Study

Only six loci were shown to be associated with T1D prior to GWAS. It has been long established that approximately half of the genetic risk for T1D is conferred by the human leukocyte antigen (HLA) region on chromosome 6p21 [13–15]. HLAs are homologous proteins that present antigens to T cells. Class I HLAs (A, B, C) consist of a single chain and are ubiquitously expressed. Class II HLAs (DP, DQ, RD) are composed of A and B chains and expressed by APCs, such as dendritic cells, B cells, monocytes, and the thymus epithelium. However, the exact biological mechanisms by which alleles of HLA-encoding genes contribute to T1D risk remain elusive. The highly polymorphic HLA locus makes association analyses complicated, and the strong linkage disequilibrium (LD) in the region makes assessment of individual risk variants very challenging. In fact, the HLA region is the most polymorphic section of the human genome, with 22,362 unique alleles reported as of May 2019 (http://www.ebi.ac.uk/imgt/hla/stats.html). The genetic risk for T1D is conferred mainly by combinations of HLA class II DR and DQ loci, especially in genes that encode highly polymorphic β chains (*DRB* and *DQB*) [16]. All four chains are encoded by genes (*DQB*, *DQA*, *DRB*, and *DRA*) that are both physically close and in tight LD, making it near-impossible to dissect their relative

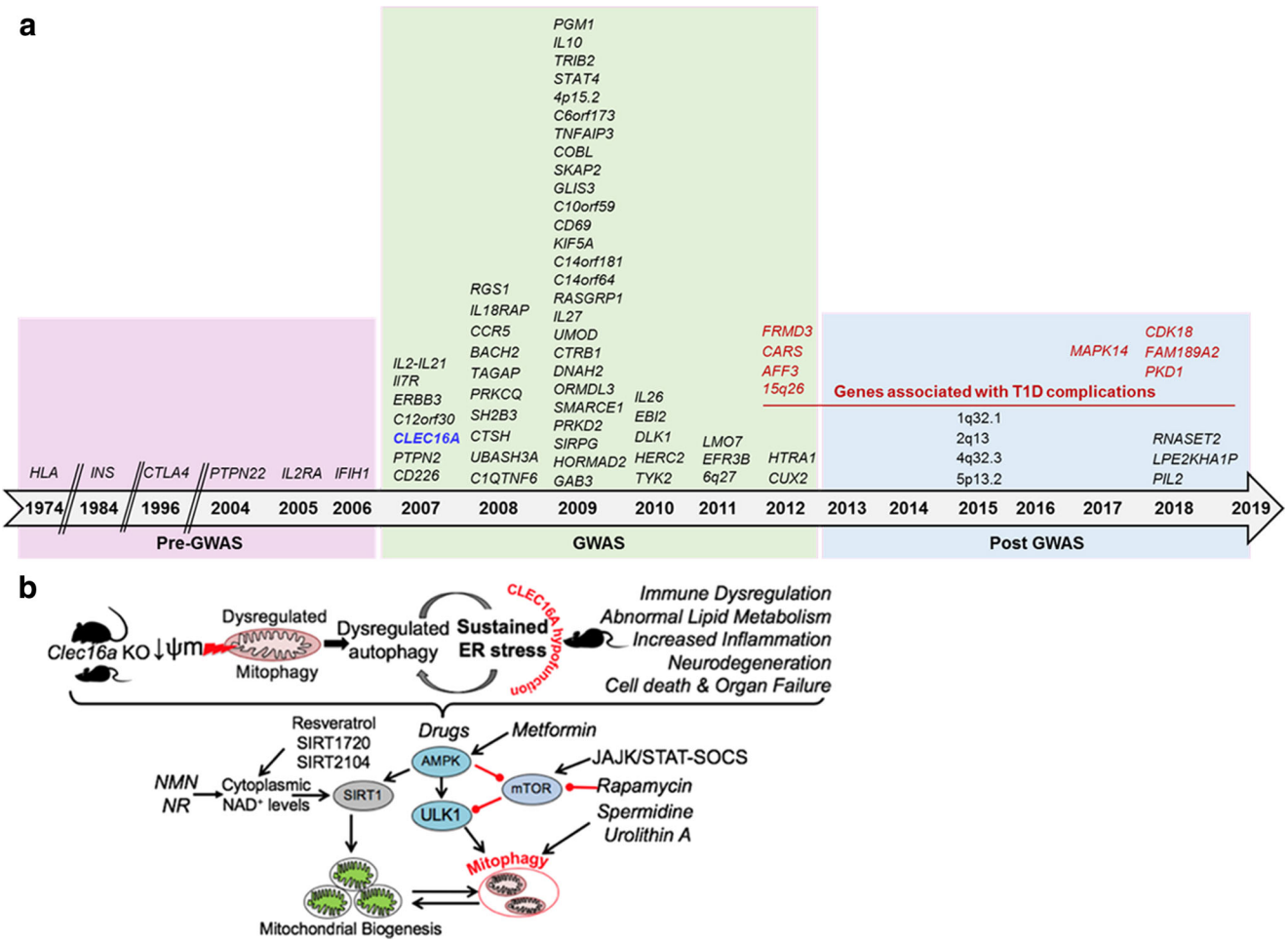

Fig. 1 The type 1 diabetes (T1D) susceptibility loci. **a** Timeline of discovery: the loci are presented by a year when first implicated in T1D. Genes depicted in red are associated with specific T1D complications. **b** Representation of the CLEC16A gene biology

importance by genotyping. Risk is assigned instead to *DR–DQ* haplotypes [17]. In 1984, the insulin (*INS*) gene was identified as the second locus associated with T1D [18]. In 1996, the "cytotoxic T lymphocyte–associated protein 4 (*CTLA4*)" gene was recognized as the third locus [19]. Another case-control study in 2004 reported the protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) gene to be associated with susceptibility to T1D [20]. Vella et al., 2005 reported the interleukin 2 receptor alpha (*IL2RA*) gene as the fifth T1D locus [21], with the sixth candidate being the interferon-induced with helicase C domain 1 (*IFIH1*) gene. *IFIHI* was identified through genotyping of only 6500 non-synonymous single-nucleotide polymorphisms (SNPs) genome-wide [22]. As such, this was the state of the understanding of T1D genetics prior to GWAS.

GWAS and Meta-analyses of T1D GWAS

The advent of GWAS in the mid-2000s has changed the state of complex common disease genetics dramatically, increasing the pace and efficiency of discovering T1D loci by a factor of 10. As GWAS allows a large number (up to millions) of variants to be tested in a hypothesis-free context, this technology has enabled scientists to search for additional T1D loci, the outcomes of which are briefly reviewed and referenced below.

The first full-scale GWAS for T1D was published simultaneously by our group [23] and the Wellcome Trust Case-Control Consortium (WTCCC) [24]. In addition to confirming previously identified loci [14, 16, 18, 20, 25], significant association was uncovered with variation near the *KIAA0350* gene, which was independently replicated [23] and confirmed by others [26]. In separate efforts, associations with genetic variation at the 12q13 locus and the *UBASH3A* locus on 21q22.3 were discovered and replicated [24, 26, 27]. In subsequent meta-analyses of 3561 T1D cases and 4646 controls, using GWAS from different investigative groups, including the WTCCC [24] and the Genetics of Kidneys in Diabetes (GoKinD) study [28, 29], followed by genotyping the most significant SNPs in additional 6225 cases, 6946 controls, and 2828 families, four previously unknown loci were reported [30]. The genome-wide meta-analysis by the Type 1 Diabetes Genetics Consortium (T1DGC) [31], reported in 2009, provided evidence of T1D association with 41 distinct genomic locations, confirming a number of previously reported associations [32–34] in addition to discovery of 22 novel loci. Of these novel loci, 18 were replicated (with standard genome-wide significance threshold of $P < 5 \times 10^{-8}$) and four regions had nominal evidence of replication ($P < 0.05$) (reviewed in [35]). Our in silico replication of the T1DGC results [36] and comparative genetic analysis of inflammatory bowel disease and type 1 diabetes [37] further confirmed these associations. The novel susceptibility loci from the 2009 T1DGC study [31] were also replicated in 2012 [38] by genotyping of 3108 families, which excluded the possibility of false-positives due to population stratification. In the search for additional T1D susceptibility loci, we performed a meta-analysis of ~ 2.54 million SNPs in a combined cohort of 9934 T1D cases and 16,956 controls. This approach allowed us to discover three new signals residing at chromosomal locations 2p23, 6q27, and 13q22. We successfully replicated these findings in an independent collection of 1120 affected trios [39]. The three novel T1D loci were (i) an intronic region of the *LMO7* (LIM domain only 7) gene on 13q22; (ii) an intronic region of the *EFR3B* (protein EFR3 homolog B) gene on 2p23; and (iii) a gene-rich region that harbors *WDR27*, *C6orf120*, *PHF10*, *TCTE3*, *C6orf208*, *LOC154449*, *DLL1*, *FAM120B*, *PSMB1*, *TBP*, and *PCD2*. Additional studies are needed to confirm both the causative variants and the corresponding effector genes for these loci. Table 1 summarizes all T1D-associated loci and some loci associated with diabetic complications reported to date.

Genetics of T1D Complications

T1D is a chronic disorder that can result in many long-term complications. Diabetes (types 1 and 2) is a leading cause of end-stage renal disease, blindness, foot and leg amputation, and cardiovascular disease. Loci for diabetic complications have been reported [50]. The identification of genetic variants explaining individual predisposition to T1D complications is important for a mechanistic understanding of these disorders. However, no firm progress has been made on defining genetic susceptibility to complications.

Diabetic kidney disease (DKD) is a major complication of diabetes and the leading cause of end-stage renal disease (ESRD). The first application of GWAS to DKD was published in 2009; however, no significant associations were identified [51]. A further meta-analysis reported promising associations at the *FRMD3* and *CARS* loci; however, neither signal reached genome-wide significance, nor were the results widely replicated [52]. The GEnetics of Nephropathy: an International Effort (GENIE) consortium performed another meta-analysis of GWAS for DKD. This effort revealed two new loci significantly associated with ESRD: the *AFF3* gene locus and an intergenic region on 15q26 between the *RGMA* and *MCTP2* genes. A SNP in *ERBB4* gene showed a strong association with DKD, but did not reach genome-wide significance [53]. GWAS performed to determine sex-specific genetic risk factors for ESRD discovered an intergenic region on 2q31.1 to be associated in women, but not in men [54]. The locus is located between the *SP3* and *CDCA7* genes.

In 2012, a pilot GWAS attempted to find risk loci for erectile dysfunction in T1D, but no candidate genes reached the genome-wide significance [55]. Diabetic foot ulcer (DFU) is a devastating complication of diabetes. A recent GWAS in a Scottish cohort of patients with diabetes discovered a skin-

Table 1 Loci associated with T1D susceptibility loci and diabetic complications identified to date

Reference	Study type	Main findings	Sample size and phenotype	Replication sample size and phenotype	Ethnic group
Hakonarson et al., 2007 [23]	GWAS	*HLA-DRB1*, *HLA-DQA2*, *CLEC16A*, *INS*, *PTPN22*	467 T1D trios, 561 T1D cases, 1143 controls	2350 T1D cases in 549 T1D families; 390 T1D trios	European ancestry
WTCCC 2007 [24]	GWAS	*HLA-DRB1*, *INS*, *CTLA4*, *PTPN22*, *IL2RA*, *IFIH1*, *PPARG*, *KCNJ11*, *TCF7L2*	1963 T1D cases, 2938 controls	See Todd et al., 2007	European, British
Todd et al., 2007 [26]	GWAS	*PHTF1-PTPN22*, *ERBB3*, *CLEC16A*, *C12orf30*	see WTCCC 2007	2997 T1Dtrios, 4000 T1D cases, 5000 controls	European, British
Hakonarson et al., 2008 [40]	GWAS	*SUOX–IKZF4*	467 T1D trios, 561 T1D cases, 1143 controls	549 families, 364 trios	European ancestry
Concannon et al., 2008 [27]	GWAS	*INS*, *IFIH1*, *CLEC16A*, *UBASH3A*	2496 T1D families	2214 T1D trios, 7721 cases, 9679 controls	European ancestry
Cooper et al., 2008 [30]	GWAS meta-analysis	*PTPN22*, *CTLA4*, *HLA*, *IL2RA*, *ERRB3*, *C12orf30*, *CLEC16A*, *PTPN2*	3561 T1D cases, 4646 controls	6225 T1D cases, 6946 controls, 3064 T1D trios	European ancestry
Grant et al., 2009 [41]	GWAS	*EDG7*, *BACH2*, *GLIS3*, *UBASH3A*, *RASGRP1*	563 T1D cases, 1146 controls, 483T1D trios	636 T1D families, 3303 T1D cases, 4673 controls	European ancestry
Awata et al., 2009 [42]	TaqMan genotyping	*ERBB3*, *CLEC16A*	735 T1D cases, 621 controls	–	Japanese
Zoledziewska et al., 2009 [43]	TaqMan genotyping	*CLEC16A*	1037 T1D cases, 1706 controls	–	European, Sardinian
Fung et al., 2009 [33]	TaqMan genotyping	*STAT4*, *STAT3*, *ERAP1*, *TNFAIP3*, *KIF5A/PIP4K2C*	8010 T1D cases, 9733 controls	–	European, British
Wu et al., 2009 [44]	TaqMan genotyping	*CLEC16A*	205 T1D cases, 422 controls	–	Han Chinese
Barrett et al., 2009 [31]	GWAS meta-analysis	*MHC*, *PTPN22*, *INS*, *C10orf59*, *SH2B3*, *ERBB3*, *CLEC16A*, *CTLA4*, *PTPN2*, *IL2RA*, *IL27*, *C6orf173*, *IL2*, *ORMDL3*, *GLIS3*, *CD69*, *IL10*, *IFIH1*, *UBASH3A*, *COBL*, *BACH2*, *CTSH*, *PRKCQ*, *C1QTNF6*, *PGM1*	7514 T1D cases, 9045 controls	4267 T1D cases, 4670 controls, 4342 T1D trios	European
Wallace et al., 2010 [45]	GWAS meta-analysis	*DLK1*, *TYK2*	7514 T1D cases, 9045 controls	4840 T1D cases, 2670 controls, 4152 T1D trios	European ancestry
Wang et al., 2010 [37]	GWAS	*PTPN22*, *IL10*, *IFIH1*, *KIAA0746*, *BACH2*, *C6orf173*, *TAGAP*, *GLIS3*, *L2R*, *INS*, *ERBB3*, *C14orf181*, *IL27*, *PRKD2*, *HERC2*, *CLEC16A*, *IFNG*, *IL26*,	989 T1D cases, 6197 controls	–	European ancestry
Reddy et al., 2011 [46]	TaqMan genotyping	*PTPN22*, *INS*, *IFIH1*, *SH2B3*, *ERBB3*, *CTLA4*, *C14orf181*, *CTSH*, *CLEC16A*, *CD69*, *ITPR3*, *C6orf173*, *SKAP2*, *PRKCQ*, *RNLS*, *IL27*, *SIRPG*, *CTRB2*	1434 T1D cases, 1864 controls	–	European ancestry, southeast USA
Bradfield et al., 2011 [39]	GWAS meta-analysis	*LMO7*, *EFR3B*, *6q27*, *TNFRSF11B*, *LOC100128081*, *FOSL2*	9934 T1D cases, 16,956 controls	1120 T1D trios	European ancestry
Asad et al., 2012 [47]	Genotyping and sequencing	*HTR1A*, *RFN180*	424 T1D families, 3078 T1D cases, 1363 controls	–	European, Scandinavians
Huang et al., 2012 [48]	Genomes-based imputation	*CUX2*, *IL2RA*	16,179 individuals	–	European ancestry
Williams et al., 2012 [52]	GWAS meta-analysis	*FRMD3*, *CARS*	2966 T1D with DN[@] (cases), 3399 T1D without DN[@] (controls)	–	European ancestry

Table 1 (continued)

Reference	Study type	Main findings	Sample size and phenotype	Replication sample size and phenotype	Ethnic group
Onengut-Gumuscu et al., 2015 [59]	Dense genotyping on the ImmunoChip	*1q32.1*, *2q13*, *4q32.3*, *5p13.2*	6670 T1D cases, 12,262 controls, 2601 T1D sibling pairs, 69 T1D trios	–	European ancestry
Meng et al., 2017 [56]	GWAS	*MAPK14*	699 DFU[#] (cases), 2695 T1D without DFU[#] (controls)	–	European, Scottish
Sharma et al., 2018 [49•]	Dense genotyping on the ImmunoChip	*RNASET2*, *PLEKHA1*, *PPIL2*	Prospective cohort of 5806 subjects followed for T1D	–	European ancestry
Charmet et al., 2018 [57]	GWAS meta-analysis	*CDK18*, *FAM189A2*, *PKD1*	434 T1D with CAD[‡] (cases), 3123 T1D without CAD (controls)	585 T1D with CAD[‡] (cases), 2612 T1D without CAD (controls)	European ancestry

CAD, coronary artery disease
[‡] Diabetic foot ulcer (DFU)
[@] Diabetic nephropathy (DN)

related gene, *MAPK14*, to be associated with DFU [56]. Patients with T1D are more at risk of coronary artery disease (CAD) when compared to the general population. A GWAS aimed at identifying loci associated with CAD in T1D resulted in three novel candidate loci: *CDK18*, *FAM189A2*, and *PKD1* [57]. Analyses also suggested that genetic variation at the *ANKS1A*, *COL4A2*, and *APOE* loci, previously found to be associated with CAD in the general population, could have stronger effects in T1D [57]. All these associations need to be validated in independent studies/populations before they can be accepted as genuine susceptibility loci for complications in T1D.

The Post-GWAS Era

The completion of the human genome sequence in 2003 and the development of high-throughput technologies to detect genetic variation and measure gene expression have enabled identification of thousands of loci and genetic variants (mainly SNPs) that contribute to complex diseases in humans. However, the underlying mechanisms of action of these loci in disease development and progression are largely unknown, which limits the clinical application of GWAS findings. Thus, functional characterization and mechanistic elucidation of these loci, pinpointing causal SNPs and the genes through which their effects are mediated is the next major challenge. Analytical strategies in the post-GWAS era should typically include the following: fine-mapping of susceptibility regions to identify both the putative causal variants and the corresponding susceptibility effector genes for elucidating the biological mechanism of action; joint analysis of susceptibility genes in diseases with similar underlying biology; integration of GWAS, transcriptome, and epigenetic data to incorporate expression and methylation quantitative trait loci (eQTL and mQTL) at the whole-genome level.

Fine-Mapping of Susceptibility Regions The vast majority of disease-associated variants are located in non-coding regions. It was common to annotate these GWAS regions with the gene mapping closest to the strongest associated variant or to genes with biological significance for the disease. However, the causal gene(s) is not necessarily the one closest to the associated SNP. In addition, the majority of T1D GWAS-associated loci harbor multiple genes and it is therefore essential to narrow down the causal variants and genes. The development of fine-mapping methods proved to be efficient in detecting multiple independent association signals for the disease at the same locus. In 2015, Wallace et al. applied this approach to re-analyze the *IL2RA* region and showed that there were four independent signals associated with T1D, specifically SNPs located in intron 1 of *IL2RA*, the intergenic region between *IL2RA* and *RBM17*, at the 5′ of *RBM17*, and in the region spanning the 5′ of *RBM17* to intron 2 of *PFKFB3* [58]. The most extensive T1D fine mapping effort was performed in

2015 using the ImmunoChip, which is a custom Illumina high-density genotyping array designed for immunogenetics studies. This genotyping confirmed and narrowed down most GWAS-implicated susceptibility loci, and identified four new T1D-associated regions: 1q32.1, 2q13, 4q32.3, and 5p13.2 [59]. However, additional studies are needed to fully confirm the causative variants and corresponding effector genes for these loci.

Joint Analysis of Susceptibility Genes in Different Diseases Over 50% of genome-wide significant autoimmune disease associations are shared by at least two distinct autoimmune diseases [60, 61]. Several studies have combined data from multiple diseases in order to increase power to detect novel loci. To investigate if genetic variation may similarly affect the risk of ten clinically distinct pediatric-age-of-onset autoimmune diseases (pAIDs), we performed a meta-analysis of GWAS on a combined cohort of 6035 cases and 10,718 population-based controls [62]. We identified 27 loci-associated, at genome-wide significance, with at least one pAID, mapping them to autoimmune-associated genes (including *IL2RA*) and new candidate loci with established immune-regulatory functions such as *ADGRL2*, *TENM3*, *ANKRD30A*, *ADCY7*, and *CD40LG*. We also identified biologically correlated, pAID-associated candidate gene sets on the basis of immune cell expression profiling and found that 22 of the 27 loci (81%) were shared across multiple pAIDs. Knowledge of shared genetic etiologies may help pinpoint common therapeutic mechanisms, especially since certain pAIDs exhibit high rates of comorbidity [62]. In adults, GWAS of the autoimmune polyglandular syndrome type 3 (APS3v) enabled identification of genes causing co-occurrence of T1D and autoimmune thyroid diseases (AITD) [63]. T1D and AITD frequently occur in the same individual and are classified as a variant of APS3v, pointing to a strong shared genetic susceptibility. A small discovery set of 346 patients of European ancestry with APS3v and 727 matched healthy controls identified multiple signals within the HLA region and variants in the *GPR103* gene at genome-wide significance. Findings were replicated in an independent dataset of 185 patients and 340 healthy controls. The novel *GPR103* locus was unique to the APS3v phenotype, and had not been suggested by previous studies of APS3v, T1D, or autoimmune thyroid diseases. The *GPR103* gene encodes a G protein–coupled receptor that is expressed primarily in brain, but also in human pancreatic islets; and it may have an effect on insulin secretion. The ligand for GPR103 (P518) is expressed in thyroid cells. Taken together, these expression data suggest a role for GPR103 and its signaling pathway in APS3v [63]. Recently, another group jointly fine-mapped loci for rheumatoid arthritis and T1D and found putative causal missense variants at *DNASE1L3*, *PTPN22*, *SH2B3*, and *TYK2*, as well as noncoding variants at *MEG3*, *CD28–CTLA4*, and *IL2RA* [64]. Thus, joint analyses of GWAS data for multiple autoimmune diseases may help to localize shared causal variants and elucidate the common molecular mechanism(s) and establish therapies and/or prevention measures.

Combined Analysis of GWAS and Transcriptional or Epigenetic Data Resources In recent years, high-throughput sequencing techniques have been developed and widely applied to generate "big data" at the genome, transcriptome, and epigenome levels. The explosion of such data has made it possible to perform comprehensive integrative analyses of these multi-omics to better understand molecular signatures of disease and to elucidate potential causative changes that impact development and progression.

A variety of eQTL studies have emerged to bridge the gap between genetic variation and phenotype. The association between a genetic variant and the disease could be strengthened through eQTL analysis as it can help pinpoint causal variants within GWAS loci and the genes through which their effects are mediated. It has been demonstrated that complex trait loci are enriched for eQTLs in T1D that are cell type–specific. Thus, cell type is important in characterizing the function of SNPs associated with T1D susceptibility [65]. Identification of differential gene expression profiles in cases of T1D and controls and/or in T1D model systems may suggest disease mechanisms for follow-up studies [66, 67]. It was also demonstrated that GWAS loci, including those for T1D, are enriched for SNP mapping to regulatory elements [68, 69].

Implementation of single-cell RNA sequencing (scRNA-seq) has revolutionized our ability to study the immune system. A recent single-cell exploratory study on peripheral blood of individuals with T1D and controls demonstrated that islet antigen (Ag)-reactive $CD4^+$ memory T cells with unique antigens are expanded during disease progression [70]. Further studies are needed before these findings could impact on T1D treatment. It is likely that therapeutics involving islet Ag-reactive T cells could be personalized, as there was no clonotype sharing between individuals with T1D, indicating a predominance of "private" T cell receptors (TCR) [70].

Leung et al. [71] combined scRNA-seq and a *NOD* mouse model to interrogate regulatory T cells (Treg) during immune rejection or tolerance of transplanted pancreatic islets. Analysis of 12,964 $CD4^+$ T cells, derived from rejecting and tolerated grafts, uncovered two functionally distinct groups of $CD4^+FOXP3^+$ Treg. One group of Treg mainly promotes chemotactic and ubiquitin-dependent protein catabolism during transplant rejection. The other group acts in case of transplant tolerance and these Treg utilize their proliferative and immunosuppressive function via programmed cell death protein-1 (PD-1) signaling. PD-1 blockade with a neutralizing anti-PD-1 antibody caused reduced Treg proliferation and graft rejection. As Treg are indispensable for maintaining peripheral

self-tolerance, these findings could be useful in clinical development of human embryonic stem cell (hESC)–derived pancreatic tissues when searching for sustainable alternative treatments for T1D [71].

Mastracci et al. [72] attempted to investigate mechanisms underlying T1D susceptibility by directly analyzing human donor pancreatic islets. High-depth RNA sequencing of pancreatic islets from patients with short- and long-duration of T1D and controls identified several inflammatory pathways that were upregulated in short-duration disease [72]. While the sample size was small, it is a proof-of-principal study, which demonstrates that the direct analysis of human islets provides a greater understanding of human disease. Recently, the combination of scRNA-seq and bioinformatics approaches allowed discovery and characterization of previously unknown lymphocytes that clonally expand in patients with T1D [73••]. These rare cells are dual expressers (DEs) of TCR and B cell receptor (BCR) and bear lineage markers of both B and T cells. Clonally expanded DEs encode a potent autoantigen (x-autoantigen). Its peptide forms functional complexes with DQ8 molecules and robustly stimulates $CD4^+$ T cells from T1D, but not healthy individuals [73••]. These rare unique TCR- and BCR-positive lymphocytes could be pathophysiologically important due to their expansion in T1D. Future studies will determine if x-autoantigen serves as a T1D-risk biomarker. The study also highlighted the importance of using primary cells from patients and controls for finding a mechanistic explanation for those cell types that promote the onset of T1D. In the future, well-characterized large cohorts and extensive scRNA-seq could result in the identification of promising novel targets for effective therapeutic interventions for T1D.

An approach gaining increasing traction to identify potential and novel risk genes for T1D performs a network analysis of genomics and disease-relevant transcriptomics data. Recently, Lu et al. carried out a novel system network analysis of GWAS summary statistics and transcriptomic gene expression data to reveal some of the missing heritability for T1D using weighted gene co-expression network analysis (WGCNA). Systematic consideration of gene-gene interactions through network analyses identified 45 interconnected genes, including several core genes (*TPP1*, *RAC2*, and *PTPN11*), to be significantly associated with T1D [74]. Another study integrated genetic variation, 3D genome organization, and functional data (eQTLs) to better understand the downstream effects of SNPs associated with T1D [75]. The study identified 246 spatially regulated genes and showed that T1D-associated variants interconnect through networks that form part of immune regulatory pathways, including immune-cell activation, cytokine, and PD-1 signaling [75].

Recently performed epigenomic profiling of primary type 1 helper T cells (Th1) and Treg isolated from patients with T1D uncovered a large number of deregulated enhancers and altered transcriptional signatures in both cell types that were not observed in healthy controls [76]. Four SNPs (rs10772119, rs10772120, rs3176792, and rs883868) proven to alter enhancer activity and expression of immune genes were identified. Of note, none of these SNPs are lead GWAS SNPs (i.e., the SNP with the strongest association at a locus); rather, they are in LD with lead SNPs. This highlights the challenge of finding risk variants in the background of LD and adds to increasing reports of genetic variants that can disrupt 3D genome organization and gene expression [76].

Large Longitudinal/Prospective Cohorts With a few exceptions, previous genetic studies of T1D have used a retrospective case-control or family-based design. However, cohorts with longitudinal data could have more power to identify genetic factors associated with disease susceptibility [77]. A time-to-event analysis includes information over time for all subjects in the study population, whereas a case-control study is only a snapshot in time for the selected cases and controls. A recent study assessed genetic associations for islet autoimmunity (IA) and T1D in prospective cohorts using a time-to-event analysis approach. A total of 5806 individuals from the TEDDY (The Environmental Determinants of Diabetes in the Young) study were genotyped for 176,586 SNPs on the ImmunoChip to discover the loci associated with risk for IA, T1D, or both. The analysis of T1D identified one region already known to be associated with disease susceptibility (*INS*) and three novel regions (*RNASET2*, *PLEKHA1*, and *PPIL2*) [49•]. These latest associations add to the growing repertoire of loci predisposing to T1D.

Overlap with Loci for Latent Autoimmune Diabetes in Adults

Latent autoimmune diabetes in adults (LADA) shares common genetic, clinical, and pathophysiological features with both type 1 (T1D) and type 2 (T2D) diabetes, and for this reason, it is often referred in medical literature as "type 1.5 diabetes." Despite showing many features of autoimmune diabetes, LADA is commonly misdiagnosed as T2D because patients do not initially require insulin; indeed the misdiagnosis rate, where LADA is incorrectly classified as T2D, can be as high as 10%. To date, the relatively limited candidate gene studies carried out for LADA have supported a role for both T1D and T2D risk loci, in particular the MHC and *TCF7L2* [78]. Despite these initial observations, a deep understanding of the genetic basis of LADA has been lacking. To at least partially address this paucity in understanding, we recently performed the first GWAS of clinically defined LADA in individuals of European ancestry [79•] and confirmed the hypothesis that the strongest genetic risk loci for LADA are shared with T1D, albeit with a somewhat ablated effect;

nevertheless, by correlating genome-wide genetic effects on T1D, T2D, and LADA using LD-score regression, it is clear that there is also a marked contribution of T2D loci to LADA susceptibility [79•, 80]. Our results further highlight the need for a novel diabetes classification system, especially as there is even disagreement over whether LADA is a truly distinct disease entity [81], a point that is reinforced by the results of our GWAS. Furthermore, it has now been shown that there is a role for T2D loci in the pathogenesis of T1D, especially where patients present with positivity for just a single autoantibody [82, 83], which complicates the picture further.

Insights from Specific T1D Susceptibility Loci

Four decades of investigations have uncovered over 60 T1D susceptibility loci. However, the precise mechanisms by which associated loci confer T1D susceptibility remain elusive and require in-depth characterization. In this regard, several novel T1D susceptibility loci are discussed below.

CLEC16A (16p13)

Since 2007, when we first identified the region mapping to *KIAA0350* (now called C-type lectin-like domain family 16A (*CLEC16A*)) as a novel T1D susceptibility locus within a 233-kb LD block on chromosome 16p13 [23], its association to the disease was confirmed in in populations of European descent [26, 30] and several others: Sardinian [43], Spanish [84], south-east USA [46], Chinese [44, 85], and Japanese [86]. Later, *CLEC16A* was also associated with adult-onset autoimmune diabetes [87]. To date, GWAS have identified associations of SNPs at the 16p13 locus harboring the *CLEC16A* gene with several autoimmune diseases including multiple sclerosis [43, 88, 89], primary adrenal insufficiency [90], systemic lupus erythematosus [91, 92•], celiac disease [93], Crohn's disease [94], selective immunoglobulin A deficiency [95], alopecia areata [95], juvenile idiopathic arthritis [96], rheumatoid arthritis [84, 96], and primary biliary cirrhosis [97, 98]. The shared impact of *CLEC16A* in these diverse inflammatory and autoimmune diseases suggests that *the gene* could be a critical regulator of aberrant autoimmune responses. Of note, while GWAS have indicated a primary association in T1D and other autoimmune diseases to intronic *CLEC16A* SNPs, many of them are in strong LD [89], which makes it difficult to identify the causal variant(s) in this gene region. At present, it is widely accepted that there is more than one effector gene at the 16p13 region, the so called the *CIITA-DEXI-CLEC16A-SOCS1* gene complex [99]. The MHC class II transactivator (*CIITA*) gene [100], the dexamethasone-induced gene (*DEXI*) and the suppressor of cytokine signaling 1 (*SOCS1*) gene [101, 102] are all immune-regulatory genes of potential interest for autoimmunity. Also, it was shown that intron 19 of *CLEC16A* behaves as a regulatory sequence, affecting the expression of a neighboring gene, *DEXI* [103]. Taken together, these reports highlight the importance for further fine-mapping and functional studies of the 16p13 region in relation to T1D pathogenesis.

The first evidence of CLEC16A function came from studies on its *Drosophila* ortholog, *Ema*, which is required for endosomal trafficking, as well as for normal autophagosomal growth and autophagy [104]. Later, we showed that CLEC16A regulates mitophagy in β cells. A pancreas-specific deletion of *Clec16a* leads to an increase in Parkin, the master regulator of mitophagy. Islets of mice with this pancreas-specific deletion had abnormal mitochondria with reduced oxygen consumption. Patients with the *CLEC16A* T1D risk allele, rs12708716 G, have reduced expression of CLEC16A in islets and attenuated insulin secretion [105], providing further evidence that CLEC16A could control β-cell function and contribute to diabetes risk. Another study reported that CLEC16A, NRDP1, and USP8 form an ubiquitin-dependent protein complex to regulate β-cell mitophagy [106]. It was also reported that CLEC16A may control the HLA-II antigen presentation pathway via late endosomal maturation in antigen-presenting cells [107] and that CLEC16A expression impacts thymic selection playing a role in thymic epithelial cell (TEC) autophagy [108]. To further investigate the role of CLEC16A in autoimmunity, we generated an inducible global knockout (KO), *Clec16a* KO mice. We demonstrated the loss of CLEC16A in immune cells that leads to an abnormal mitophagy and upregulated inflammatory cytokine response that increases the risk of autoimmunity [109]. We also found that CLEC16A expression restrains NK cell functions in human and mouse, highlighting that a delicate balance of CLEC16A is needed for NK cell function and homeostasis [110].

Of note, our *Clec16a* ubiquitous, inducible-knockout mouse develops not only autoimmune dysfunction but also a severe neurologic phenotype, including impaired gait and dystonic postures. Examined regions of the central nervous system (CNS) and peripheral nervous system (PNS) showed dysregulated mitophagy (Hain, unpublished data). These results confirm and extend the recent observations that homozygous mice carrying a gene-trap insertion in *Clec16a* (*Clec16a*$^{GT/GT}$) developed an overt neurological phenotype at 7–8 weeks of age, ascribed to the loss of cerebellar Purkinje cells. *Clec16a*$^{curt/curt}$ mice, which have a 4-nucleotide deletion allele in exon 21, resulting in a frameshift mutation, also lose cerebellar Purkinje cells [111, 112]. Figure 1B shows the consequences of CLEC16A loss in our *Clec16a* ubiquitous inducible-knockout mouse.

In summary, our published [105, 109, 110] and unpublished data suggest reduced CLEC16A expression that leads to dysregulated mitophagy/autophagy and endoplasmic reticulum (ER) stress, which predisposes to development of an

inflammatory autoimmune phenotype and neurodegeneration. *CLEC16A* is genetically linked with many distinct autoimmune disorders, which makes it an attractive candidate to explore the pathogenic mechanisms involved and potential therapeutic focus for autoimmune disorders. As proposed in Fig. 1B, the use of experimental and FDA-approved drugs to rescue autophagy/mitophagy defects in the context of *Clec16a* KO could prevent or ameliorate the induced phenotype. Additional functional studies are required to elucidate the pathogenic mechanism(s) and options in treating and preventing autoimmunity in individuals with risk-associated *CLEC16A* variants.

22q11.21

The 22q11.21 locus is associated with development of IA and T1D [49•]. The nearest gene to the most strongly associated variant is *PPIL2* (peptidylprolyl isomerase (cyclophilin)-like 2). This gene is a member of the cyclophilin, family of peptidylprolyl isomerases. Cyclophilins are a highly conserved ubiquitous family, members of which play an important role in protein folding, immunosuppression by cyclosporin A, and infection of HIV-1 virions. The highest expression levels of PPIL2 were observed in the thymus, testis, and islet cells in the pancreas. A recent proteome-scale profiling study identified PPIL2 as a novel T1D-associated autoantigen [113]. Other genes mapping to the locus are *UBE2L3*, *MAPK1*, *YDJC*, *YPEL1*, *CCDC116*, *SDF2L1*, and two microRNAs (*MIR301B* and *MIR130B*). The role of UBE2L3 in the ubiquitination of the NF-κB precursor implicated it in autoimmune diseases including rheumatoid arthritis, celiac disease, Crohn's disease, and systemic lupus erythematosus (SLE) [114]. MAPK1 (ERK2) acts as an integration point for multiple biochemical signals, including signaling pathways required for $CD8^+$ T cell proliferation and survival; these cells are associated with β cell destruction in T1D. T cells from non-obese diabetic (NOD) mice exhibit strongly impaired phosphorylation of ERK1/2 resulting in signal transduction defects. Stromal cell-derived factor 2-like 1 (SDF2L1) is an endoplasmic reticulum (ER)-localized protein that involved in ER-associated degradation of misfolded proinsulin in β cells. Two microRNAs (MIR301 and MIR130) at the 22q11.21 locus have been implicated in inflammatory response and autoimmunity [49•].

6q27

The 6q27 locus includes *RNASET2*, *CCR6*, *RPS6KA2*, *GPR31*, *TCP10L2*, *FGFR1OP*, and microRNA *MIR3939* [49•]. *RNASET2* (ribonuclease T2) encodes a member of the Rh/T2/S-glycoprotein class of extracellular ribonucleases and was associated with Grave's disease and vitiligo. *CCR6* (C-C chemokine receptor type 6) is involved in trafficking of autoimmune lymphocytes during an immunological response. In NOD mice, reduced CCR6 expression upon resveratrol treatment resulted in inhibited migration of inflammatory cells [115]. RPS6KA2 is associated with inflammatory bowel disease. Genome-wide DNA methylation analysis revealed *RPS6KA2* as a gene with decreased methylation in cases with proliferative diabetic retinopathy comparing with controls [116]. G protein–coupled receptor 31 (GPR31) is implicated in the 12 lipooxygenase (LO) pathway in the pancreatic islets. 12-LO plays a proinflammatory role in the β cell. Its major product is 12-HETE. GPR31 interacts with 12-HETE. Activation of GPR31 results in decreased antioxidant production, increased oxidative stress, and finally β cell death [49•].

10q26.13

The 10q26.13 locus resides nearby *PLEKHA1* and microRNA MIR3941 genes [49•]. Other nearby genes in the region are *BTBD16*, *ARMS2*, *HTRA1*, and *DMBT1*. *PLEKHA1* encodes a protein shown to regulate B cell activation and autoantibody production [49•]. DMBT1 is a marker of precursor cells and cells in early stages of endocrine differentiation in the pancreas [117].

Conclusion

This review provides a summary of recent advances in the identification of loci associated with T1D. GWAS has revolutionized the discovery approach for autoimmune-mediated disorders. Prior to GWAS, only six genomic regions were well known for T1D, while in the GWAS era the number reached 60. The discoveries of genetic factors involved in T1D through GWAS present the first step in a long process leading to cure.

The biggest challenge in T1D, and many other complex disorders, is prioritizing and characterizing variants in introns and intergenic regions, and establishing their roles in the pathology of the disease. Large-scale sequencing technology, including scRNA-seq analysis, has opened new avenues to elucidate the role of coding and noncoding RNAs in health and disease, and is accelerating the identification of causative genes in T1D. In the future, large cohorts and the use of scRNA-seq might result in the identification of promising novel targets for effective therapeutic interventions for T1D.

There is no doubt that the in vitro and in vivo biology of the candidate effector genes is an area of exploration and interest for many scientists, and implementation of techniques such as CRISPR/Cas9 and hiPSCs will be critical in understanding cell-intrinsic screening and validation of GWAS-implicated variants. Integration of multiomics in the functional interpretation of T1D-associated SNPs has already identified novel pathways and tissue-specific functionality in the genes of

interest, assisting scientists with prioritization of targets for clinical investigation in the future. Systemic analysis of data at multiple levels simultaneously, including the genome, transcriptome, and epigenome, is likely to provide the most comprehensive understanding of T1D, and help to develop strategies for early diagnosis, development of personalized treatment, and ultimately prevention of disease onset.

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Compliance with Ethical Standards

Conflict of Interest Marina Bakay and Rahul Pandey report they have a patent pending on new innovative weight reduction therapies targeting CLEC16A.

Struan F.A. grant reports he has a patent issue on genetic alterations and methods of use thereof for the diagnosis and treatment of type I diabetes issued (patent number 10125395); a patent issued on genetic alterations on chromosome 16 and methods of use thereof for the diagnosis and treatment of type 1 diabetes (patent number 10266896); and a patent issued on genetic alterations on chromosomes 21Q, 6Q, and 15Q and methods of use thereof for the diagnosis and treatment of type 1 diabetes (patent number 10066266).

Hakon Hakonarson reports he has a patent issued on genetic alterations and methods of use thereof for the diagnosis and treatment of type I diabetes issued (patent number 10125395); a patent issued on genetic alterations on chromosome 16 and methods of use thereof for the diagnosis and treatment of type 1 diabetes issued (patent number 10266896); a patent issued on genetic alterations on chromosomes 21Q, 6Q, and 15Q and methods of use thereof for the diagnosis and treatment of type 1 diabetes (patent number 10066266); and a patent pending on new innovative weight reduction therapies targeting CLEC16A.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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