

Can the Genetics of Type 1 and Type 2 Diabetes Shed Light on the Genetics of Latent Autoimmune Diabetes in Adults?

Struan F. A. Grant, Hakon Hakonarson, and Stanley Schwartz

Departments of Pediatrics (S.F.A.G., H.H.) and Medicine (S.S.), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104; and Center for Applied Genomics (S.F.A.G., H.H.), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104

The pathophysiology of latent autoimmune diabetes in adults (LADA) is considered less understood than its much better characterized counterparts of type 1 and type 2 diabetes (T1D and T2D), where its clinical presentation exhibits some features of each of these two main diseases, earning it a reputation as being "type 1.5 diabetes". The etiology of LADA remains unknown, but a genetic component has been implicated from recent reports of T1D and T2D genes playing a role in its pathogenesis.

One way to shed much needed light on the classification of LADA is to determine the discrete genetic factors conferring risk to the pathogenesis of this specific phenotype and to determine to what extent LADA shares genetic similarities with T1D and T2D. For instance, no conclusive support for a role of the T1D-associated *INS* gene has been reported in T2D; conversely, but similarly, no evidence has been found for the role of the T2D-associated genes *IDE/HHEX*, *SLC30A8*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, *FTO*, and *TCF7L2* in T1D. However, and somewhat at odds with current thinking, *TCF7L2*, the most strongly associated gene with T2D to date, is strongly associated with LADA, a disorder considered by the World Health Organization to be a slowly progressing form of T1D.

In this review, we address recent advances in the genetics of T1D and T2D and how such discoveries have in turn shed some light on the genetics of LADA as being potentially at the "genetic intersection" of these two major diseases. (*Endocrine Reviews* 31: 0000–0000, 2010)

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I. Introduction

Type 1 and type 2 diabetes (T1D and T2D) both result from the metabolic consequences of suboptimal insulin action, with similar complications, but appear to be due to distinct biological mechanisms. An overlap in genetic predisposition to these two diseases has been

previously proposed (1), but none of the genes identified to date in each of these given disorders has been shown to be associated with the other disease (2, 3).

The pathophysiology of latent autoimmune diabetes in adults (LADA) is considered less understood than its much better characterized counterparts of T1D and T2D, where its clinical presentation exhibits some features of each of these two main diseases, earning it a reputation as being "type 1.5 diabetes" (2). Although LADA patients often present with a clinical picture similar to T2D, with an adult age at onset and insulin independence at diagnosis, they are characterized by circulating islet autoantibodies similar to those found in T1D (4). Indeed, on average, 8–10% of patients diagnosed with T2D are in fact misdiagnosed LADA cases.

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Abbreviations: GADab, Glutamic acid decarboxylase antibodies; GWA, genome-wide association; HLA, human leukocyte antigen; LADA, latent autoimmune diabetes in adults; MHC, major histocompatibility complex; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes.

gies has enabled investigators to perform high-density genome-wide association (GWA) studies in search of T1D and T2D loci. Combined with the well-established genes known for many years, at least 20 loci each have now been uncovered to date for T1D (5–11, 13) and T2D (14–26). Conversely, non-hypothesis-driven genetic studies of LADA are sorely lacking, with no novel loci described to date; however, the newly gained knowledge of the genetics of T1D and T2D does shed some much needed light on this somewhat mysterious phenotype.

II. Epidemiology of Latent Autoimmune Diabetes in Adults

To fully understand the epidemiology of LADA, one must first put it in the context of diabetes in general. Diabetes mellitus affects an estimated 194 million adults worldwide and more than 18 million in the United States, with the chronic complications including microvascular disease and accelerated development of cardiovascular disease. Approximately 90 to 95% of those affected with diabetes have the T2D form of the disease. Typically T2D is a late-onset disease (>40 yr), and it is on the increase due to an aging population and increasing rates of obesity. Hyperglycemia is a key feature of T2D and occurs through the combination and interaction of two mechanisms: 1) abnormal insulin secretion due to pancreatic β -cell defects; and 2) insulin resistance in skeletal, muscle, liver, and adipose tissue.

Unlike T2D, T1D typically presents in childhood and has a much stronger genetic component. It primarily arises as a consequence of autoimmune destruction of pancreatic β -cells, resulting in insufficient production of insulin; in addition, syndromes of insulin-requiring β -cell failure in the absence of clinically evident autoimmunity also fall under the definition of T1D. This disorder accounts for approximately 10% of all cases of diabetes and is most prevalent in populations of European ancestry, with approximately 2 million people affected in total across Europe and North America. It is well recognized that there is an approximately 3% increase in the incidence of T1D globally per year (27), at least partly due to a decreasing average age of onset, and it is expected that the incidence will be 40% higher in 2010 than in 1998 (28). T1D in children is mostly caused by an autoimmune process, characterized by T cell-mediated destruction of pancreatic β -cells. Common allelic variants at the human leukocyte antigen (HLA) class II loci account for the major T1D genetic risk in children and young adults.

In addition to T1D and T2D, maturity-onset diabetes of the young is a relatively rare autosomal dominantly inherited form of diabetes without insulin dependency

that is characterized by β -cell dysfunction and diagnosed at a relatively young age (less than 25 yr old); it is made up of subtypes defined on the basis of genetic etiology.

Glutamic acid decarboxylase antibodies (GADab), along with islet cell antibodies, IA-2-protein tyrosine phosphatase-like protein antibodies, insulin autoantibodies, and ZnT8 antibodies, are well recognized autoimmune markers of T1D; however, it remains unclear whether they actually identify the same disease in both young and adult diabetic patients (29–31). Indeed, a subgroup of patients diagnosed with T2D have circulating levels of GADab (32–34) and islet cell antibodies (35–38), so they are in fact LADA cases; these individuals are generally considered indistinguishable from the early stages of T2D.

It is widely accepted that autoantibody-positive diabetes in adults presents with no insulin requirements at the point of diagnosis and has a slower progression toward insulin deficiency than T1D. These observations led to the definition of LADA (32, 39, 40) as its own subgroup in the World Health Organization (WHO) criteria for diabetes (4), but LADA is still considered a subdivision of T1D based on the rate of disease progression. Despite the recognition of this specific phenotype, there is still little agreement on the diagnostic criteria for LADA, including what is considered the “adult” age of onset, which has varied from 25 to 40 yr (34, 41). As such, this clinical phenotype is still fraught with a lack of a clear definition; for instance, older patients who appear to have a form of T2D but present with circulating autoantibodies may have one of several phenotypes, *e.g.*, the more benign LADA phenotype that does not require insulin at presentation or the more severely decompensated A-B+ ketosis-prone diabetes phenotype presenting with diabetic ketoacidosis (42).

Apart from the U.K. Prospective Diabetes Study (UKPDS) (34), studies on LADA have been small and underpowered, with the majority of them based on data from hospital outpatient clinics where more serious cases tend to be selected. Despite these limitations, many of these studies have shown that GADab (32–34, 43, 44) or islet cell antibodies (29, 37, 38) positivity tracks strongly with insulin deficiency and/or relative insulin requirement in both Caucasians and the Japanese (45, 46). In one such study, 50% of newly diagnosed GADab-positive patients developed relative insulin deficiency after 10 yr compared with only 3% of GADab-negative patients (44), whereas the UKPDS reported that 52% of GADab-positive patients required insulin therapy after 6 yr (34).

One Finnish study investigated the prevalence of GADab-positive patients among a cohort of local T2D patients (39). Within this group, they observed that GADab-positive T2D patients differed from patients with T1D in that they had higher C-peptide concentrations and generally more meta-

bolic syndrome symptoms. Because only 3% of the T2D patients were diagnosed before the age of 35 yr, compared with the fact that 70% of T1D patients are diagnosed before that age and only 5% of LADA patients are diagnosed before the age of 35 yr (with the median age of diagnosis being 58.5 yr), they considered a reasonable definition of LADA to be GADab positivity in patients who were older than 35 yr at onset of diabetes and who do not require insulin at the least in the first 6 months of diagnosis.

Another Finnish investigation, from the Botnia study group, found that 9.4% of their T2D patients were GADab positive (47); however, GADab positivity was substantially higher among diabetes patients with an age at onset of diabetes between 28 and 45 yr (19%), whereas it was stable at around 8.2% after 45 yr of age. These proportions were similar in the UKPDS, where they reported that for GADab positivity, 34% of patients were diagnosed under the age of 35 yr, 14% were between 35 and 44 yr old, and approximately 8% were in the 45 yr and older age bracket (34).

III. Evidence for a Genetic Component

Diabetes is a classic example of a set of complex traits resulting from the interplay between behavioral, environmental, and genetic factors influencing individual outcome. There is now clear evidence of a strong genetic component to diabetes.

With respect to a genetic component of T2D, evidence comes from prevalence differences between ethnic groups, the markedly higher concordance rate among monozygotic twins compared with dizygotic twins, and family studies demonstrating risk ratios among siblings of T2D patients being approximately 3.5 (48).

T1D risk is also strongly influenced by multiple genetic loci and environmental factors. Notably, T1D is most prevalent in populations of European ancestry compared with other ethnic groups. The disease is also highly heritable, with first-degree relatives of cases being at 15 times greater risk than the general population and concordance in monozygotic twins being as much as 50%. However, the majority of new T1D cases arise from the general population, and therefore this group should remain a major focus of predictive studies.

Maturity-onset diabetes of the young is a genetic disease and is considered a monogenic form of diabetes, with seven genes already identified to date, the most common forms resulting from mutations in the genes encoding the glycolytic enzyme, glucokinase, and the transcription factor, hepatic nuclear factor-1 α .

There is substantially less genetic epidemiology available for LADA, with the focus in the literature being pri-

marily on T1D and T2D. However, as outlined below, the roles of both the T1D major histocompatibility complex (MHC) locus and the T2D *TCF7L2* gene have been strongly implicated in the phenotype, suggesting that LADA lies somewhere at the genetic intersection of these two diseases.

IV. Previous Genetic Studies

The “candidate gene” approach was for many years the only option to approach the genetics of complex disease and was the most logical because it was grounded in biological reasoning. However, such studies have been plagued with the “winner’s curse” (49), where an initial report of association does not hold up under the rigor of subsequent replication attempts by independent investigators.

Overall, linkage studies using family-based designs have also only achieved very limited success in identifying genetic factors underpinning complex disease primarily because this approach is generally poor in identifying the types of variants modern geneticists are now looking for, *i.e.*, common genetic variants with modest effects.

The International HapMap project, a large-scale effort aimed at understanding human sequence variation, has provided many new insights into genetic diversity in the human genome (50, 51). This in turn has facilitated genome-wide genotyping of over 500,000 prespecified tag-SNPs, together with detecting variations in copy number (52) throughout the genome that can now be readily assayed in parallel using new technologies. Advances in single-base extension biochemistry and hybridization/detection to synthetic oligonucleotides now make it possible to carry out these assays in a rapid and highly reliable fashion (53). As a consequence, the GWA approach has served the critical need for a more comprehensive and unbiased strategy to identify genes related to a given disease phenotype in the last 4 yr. Already with this technology, compelling evidence for genetic variants involved in many diseases has been revealed; indeed, a catalog of these studies is now available at the National Institutes of Health web site (<http://www.genome.gov/gwastudies>).

T1D and T2D appear to be due to distinct biological mechanisms, with none of the genes identified to date in each of these given disorders having an association with the other disease (2, 3). If we are indeed to consider LADA as being at the genetic intersection of these two phenotypes, one must have a comprehension of the discrete genetic factors uncovered in either T1D or T2D (reviewed in *Sections IV.A and IV.B*) and how they might also operate in the other counterpart and in LADA. Some work has already been carried out in this regard, as reviewed below; however, to have a much better picture of any genetic

commonality or specificity between and across the main diabetes phenotypes and LADA, a full-scale GWA study of LADA is still required.

A. Type 1 diabetes

Before the era of the GWA approach, a handful of genetic regions for T1D had already in fact been established through the candidate gene and linkage methodologies; the relative success of these classical approaches in T1D could be put down partially to the relatively high genetic component to the disease compared with other complex disorders. The major locus is at 6p21, where variation in the region accounts for approximately half of the genetic risk for T1D; this region coincides with the HLA class II genes (primarily *HLA-DRB1*, *-DQA1*, and *-DQB1* genes) which encode the highly polymorphic antigen-presenting proteins. The other established loci confer more modest effects: the insulin locus (*INS*) VNTR on 11p15 (54–56), the cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*) locus on 2q31 (57–60), and the protein tyrosine phosphatase-22 (*PTPN22*) gene on 1p13 (61, 62). More recently, a fifth T1D susceptibility locus has been uncovered at the IL-2 receptor α (*IL2RA*) locus on chromosome 10p15 utilizing noncoding SNPs (63).

The sixth T1D gene, interferon-induced with helicase C domain 1 (*IFIH1*) on chromosome 2q24, was the first locus uncovered using an early genome-wide SNP genotyping approach leveraging just 6500 nonsynonymous SNPs (5). However, the first full-scale GWA studies published for T1D came later from both our group (8) and the Wellcome Trust Case-Control Consortium (WTCCC) (6, 15).

Our GWA study was published in *Nature* (8) where we described a scan of a large pediatric cohort of European descent. In addition to clearly observing the previously identified loci, we found and replicated highly significant association with noncoding variants in the *KIAA0350* gene. The nomenclature of the gene indicated that its protein product was not assigned a function at the time; however, public annotations based on predictive models suggest that this gene encodes a protein with a C-type lectin binding domain structure with a sugar binding function; as such, the gene has recently been renamed “C-type lectin domain family 16, member A” (*CLEC16A*). The WTCCC (6, 15) study also reported the 16p13 signal, along with other loci on 12q24, 12q13 [also described by our group (7)], and 18p11.

To ensure maximum use of the GWA data we had generated, we elected to carry out a meta-analysis approach to uncover additional novel loci impacting the risk of T1D (11). By leveraging a combination of our genotyping data generated on our cases and controls plus T1D family trios, we took forward 1000 SNPs that met the criteria of both not residing in the MHC and being at least nominally significantly associated with T1D, *i.e.*, $P < 0.05$. Through

subsequent rounds of testing in an independent cohort of nuclear T1D families from Montreal, Children’s Hospital of Philadelphia and the Type 1 Diabetes Genetic Consortium, followed by the WTCCC dataset and the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study cohort, signals were consistently observed in the genes encoding ubiquitin-associated and SH3 domain-containing protein A (*UBASH3A*) (an association signal that reached genome-wide significance in its own right when all data were combined) and broad complex-tramtrack-bric-a-brac (BTB) and cap ‘n’ collar (CNC) homology 2 (*BACH2*). Because such a large sample was required to detect such signals, it is of no surprise that the risks conferred by these loci were very modest compared with those described in the first studies (11). Independent of our finding, association was also recently uncovered between the *UBASH3A* locus and T1D through the utilization of SNP genotyping data from a linkage study of affected sib pairs in nearly 2500 multiplex families (9).

An additional meta-analysis (10) involving the datasets generated on the WTCCC (15) and the Genetics of Kidneys in Diabetes (GoKinD) study (65, 66) plus control data derived from the National Institute of Mental Health reported strong nominal significant association with the previously observed loci *PTPN22*, *CTLA4*, MHC, *IL2RA*, 12q13, *C12orf30* on 12q24, *CLEC16A* and *PTPN2* on 18p11 but less compelling evidence for the *IFIH1* and *INS* loci. Although they found no evidence of new T1D loci reaching the threshold for genome-wide significance, they did find additional evidence for the role of the *IL2-IL21* locus, which was suggestive in the original WTCCC follow-up study (6). They took forward the most associated SNPs by genotyping them in an independent British cohort of approximately 6000 cases, 7000 controls, and 2800 families. In addition to the *IL2-IL21* association strengthening further, they found compelling evidence of four additional loci, namely *BACH2* [as we had described previously (11)], 10p15 harboring the “protein kinase C, theta” gene (*PRKCC*), 15q24 harboring nine genes including cathepsin H (*CTSH*), and 22q13 harboring the C1q and TNF-related protein 6 (*C1QTNF6*) and somatostatin receptor 3 (*SSTR3*) genes.

The latest, largest meta-analysis reported to date (13) again involved samples derived from the WTCCC (15), the GoKinD study (65), and the National Institute of Mental Health study (67) but also brought in a further large set of cases, controls, and trios from the T1DGC families. In addition to uncovering previously observed loci, they reported novel association to 1q32.1 (which harbors the IL genes *IL10*, *IL19*, and *IL20*), Glis family zinc finger protein 3 (*GLIS3*) [also suggested by us (11)], *CD69*, and *IL27*.

In summary, approximately 20 T1D loci have now been established, with approximately 50% of the genetic contribution coming from the MHC. However, the genetics of T1D has not been completely solved, with a component still to be explained that may well be due to rare single base and copy number variants.

B. Type 2 diabetes

T2D has been the focus of more GWA studies than any other disorder studied to date. Indeed, the repertoire of genes already established for a number of years in the pathogenesis of T2D, primarily *PPARG* (68), *CAPN10* (69), and *KCNJ11* (70), now have new bedfellows as a consequence of results from recent GWA studies of the disease. The first batch of such studies, published in *Nature* (14, 15) and *Science* (16–18), revealed an additional nine genes [CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*), homeobox hematopoietically expressed (*HHEX*), *LOC387761*, Exostosin 2 (*EXT2*), IGF-II mRNA-binding protein 2 (*IGF2BP2*), cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), and an intragenic region on 11p12], with the strongest association by far being with a gene established in 2006 by Dr. Struan F. A. Grant as playing a role in the disease, namely the Wnt-signaling pathway member, transcription factor 7-like 2 (*TCF7L2*) (71). The variant within the *TCF7L2* gene is approximately 1.5 times more common in patients than in controls; this corresponds to an approximately 50% increase in risk of T2D per copy carried. Other investigators have already independently replicated the association of variation in *TCF7L2* with T2D in individuals of European, Asian, and African descent; a recent meta-analysis of published studies of the *TCF7L2* association with T2D worldwide estimated a pooled odds ratio of 1.46 ($P = 5.4 \times 10^{-140}$) (72); this is now considered the most significant genetic finding in T2D to date (73), and functional studies are beginning to suggest that it exerts its primary impact on T2D in the pancreatic islet (74, 75).

Obesity is also an important risk factor for T2D. The discovery of the fat mass and obesity associated gene (*FTO*) (76) was made indirectly as a consequence of T2D GWA studies but turned out to be operating through insulin resistance and has been consistently observed by others (77–80).

With a recent meta-analysis of T2D genome-wide SNP genotype data (24) producing another six loci [juxtaposed with another zinc finger gene 1 (*JAZF1*), cell division cycle 123 homolog/calcium/calmodulin-dependent protein kinase ID (*CDC123-CAMK1D*), tetraspanin 8/leucine-rich repeat-containing G protein-coupled receptor 5 (*TSPAN8-LGR5*), thyroid adenoma associated (*THADA*), ADAM metal-

lopeptidase with thrombospondin type 1 motif, 9 (*ADAMTS9*) and *NOTCH2*], there are now more than 15 genes established in the disease, plus most recently potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) from T2D GWA studies specifically in China and Japan (25, 26).

In addition, multiple GWA studies of fasting glucose concentrations have revealed the melatonin receptor 1B gene (*MTNR1B*) as a key locus for this trait, which has also gone on to be associated with T2D (20–22). Even more indirectly, a GWA study of prostate cancer revealed transcription factor 2 (*TCF2*) as a key locus, and the same study went on to establish this gene as a key player of T2D as well (23).

In summary, there are now in excess of 20 T2D loci established; however, collectively they explain less than 10% of the genetic component to the disease, so further work is required to uncover the other 90%, which is most likely going to be primarily made up of rare single base and copy number variants.

The more recent loci uncovered for T2D through consortia-based analyses have revealed them all to have very small effect sizes (24); however, the fact that such a study did not account for LADA cases, which will invariably be present in the study populations, begs the question: could some of these association signals be due to the genetics of LADA rather than the genetics of T2D?

C. Role of T1D genes in T2D and vice versa

An overlap in genetic predisposition has been proposed for T1D and T2D (1). No conclusive support for a role of the insulin gene (*INS*) has been reported in T2D (81); more data are required on more recently uncovered T1D loci in the context of T2D. Conversely, but similarly, no evidence has been found for the role of the major T2D gene, *TCF7L2* (71), in T1D (82, 83). We went on to investigate other T2D loci uncovered in GWA studies in the context of T1D: *IDE/HHEX*, *SLC30A8*, *CDKAL1*, *CDKN2A/B*, and *IGF2BP2*; again, no evidence of association with T1D was found (3).

Raj *et al.* (84) subsequently went further by testing 12 T2D-associated gene regions in T1D, namely *PPARG*, *CDKAL1*, *HNF1B*, *WFS1*, *SLC30A8*, *CDKN2A-CDKN2B*, *IGF2BP2*, *KCNJ11*, *TCF7L2*, *FTO*, *HHEX-IDE*, and *THADA*. Apart from an association with the *PPARG* Pro12Ala variant (85), which came of no surprise due its known function in inflammation, no convincing genetic link between T1D and T2D was made in this study.

FTO has been shown to exert its influence through body mass index (76) as opposed to insulin secretion, and because it has been suggested that childhood weight gain accounts for the trend toward an earlier age of onset observed in T1D (86), it is highly notable, despite what one

would anticipate, that we and others do not observe association to variation at this locus with respect to T1D (3, 87).

As such, there has been very little overlap in the genes identified to date in each of these given disorders.

D. Latent autoimmune diabetes in adults

One way to shed light on the classification of LADA is to determine to what extent LADA shares genetic similarities with T1D and T2D with respect to the other genes that have been uncovered previously from candidate gene and large-scale association studies.

It is widely believed that LADA shares susceptibility genes with T1D; however, there are only a small number of studies that have been powered enough to sufficiently address this issue (39, 88–90), with two further studies supporting the conclusions drawn (91, 92). The HLA locus, which confers approximately 50% of the genetic susceptibility to T1D (93), has also shown similar associations with LADA (88, 90), but with some specific differences, *e.g.*, DQB1 *0201/*0302 is a more common genotype in T1D than in LADA, whereas the protective genotypes *0602/X and 0603/X are more common in LADA than in T1D (39). However, the *INS* short class I variable number of tandem repeats has been shown to confer equally strong susceptibility to both T1D (94) and LADA (89).

Another study attempted to compare genetic variation within the HLA locus, the *INS* VNTR, plus the *PTPN22* and *TCF7L2* genes among patients with T1D, LADA, or T2D and healthy control subjects (95) [the relatively recent identification of the *TCF7L2* gene as the strongest locus for T2D (71) has allowed, for the first time, the possibility to test whether LADA also shares genetic features with T2D]. Interestingly, they found association to all the tested variants in LADA, including, oddly to the *TCF7L2* gene that has conclusively not been shown be associated with T1D (83). The *PTPN22* association with LADA was substantially weaker with LADA than with T1D, but the LADA patients showed the same magnitude of increased frequency of the *TCF7L2* risk allele as in T2D patients. They, therefore, concluded that the data from this study positions LADA genetically as an admixture of T1D and T2D, rather than as a subgroup of T1D. Added to this, they later showed that they could leverage the *TCF7L2* observation to distinguish middle-aged antibody-positive patients from young antibody-positive patients (64).

More recently, in a Polish study of 68 newly diagnosed patients with LADA and 195 healthy controls, it was found that the *TCF7L2* risk allele was again overrepresented in LADA patients compared with controls but also found that fasting C-peptide serum concentration was significantly lower in the group of patients with LADA homozygous for the T2D risk allele (12).

V. Summary

Despite a large body of data supporting the role of genetic factors in T1D and T2D, there is still relatively little known about the genetics of LADA, which has been considered to be at the genetic intersection of these two disorders. The key issues that still need to be fully resolved in the genetics of LADA are: does LADA represent 1) a late manifestation of T1D; 2) the genetic intersection of T1D and T2D; or 3) a unique disease entity?

Although the findings are highly notable, it is clear that GWA studies have not uncovered the entire genetic architecture of either T1D or T2D. As such, further attempts and finding the missing pieces are under way through copy number variation and sequencing approaches plus larger and larger meta-analyses.

One obvious way to approach the challenge in this review would be to carry out a GWA study of LADA itself. However, the reason such approaches have not already been carried out is due because LADA is relatively difficult to empirically ascertain, involving expensive GADab-related assaying, with the definition of the phenotype varying considerably between investigators. However, such a study would uncover major genetic factors involved in the pathogenesis of LADA. We already predict from previous studies that at least *TCF7L2* and the MHC will be significantly associated with LADA in any such study; however, it is likely that additional signals would be novel, as has been the case with the outcome of GWA studies of other complex phenotypes. These genetic variants could then be cross-referenced in publicly available genome-wide genotyped datasets for both T1D and T2D to figure out what is common to these phenotypes and what is discrete. Genes that are uncovered in any such association studies could be fundamental to diabetes biology and would define key molecular pathways that influence LADA.

Irrespective of the technique used, better understanding of the genetic basis of LADA is needed to more accurately place this disorder in the spectrum of diabetes phenotypes. Such characterization would shed light on how to more specifically treat this sizeable fraction of the diabetes community and also aid in identifying “true” T1D and T2D cases. In addition, diabetes genetics has not been totally resolved, with additional breakthroughs in T1D and T2D becoming increasingly hard to come by and more expensive to uncover after the initial rush of high-profile publications describing the “low-hanging fruit.” Therefore, more detailed genetic studies of LADA could also help further unravel the genetic etiology of its two larger cousins as well.

Acknowledgments

Address all correspondence and requests for reprints to: Stanley Schwartz, M.D., Penn Presbyterian Medical Center, Philadelphia Heart Institute, Suite 400, 38th and Market Streets, Philadelphia, Pennsylvania 19104. E-mail: stan.schwartz@uphs.upenn.edu; or Struan F. A. Grant, Ph.D., 1216F Children's Hospital of Philadelphia Research Institute, 3615 Civic Center Boulevard, Philadelphia, Pennsylvania 19104. E-mail: grants@chop.edu.

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