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GENETICS (AP MORRIS, SECTION EDITOR)

New Insights into the Genetics of Latent Autoimmune Diabetes in Adults

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Abstract

Purpose of Review Diabetes is a spectrum of clinical manifestations, including latent autoimmune diabetes in adults (LADA). However, it has been questioned whether LADA exists or simply is a group of misclassified type 1 diabetes (T1D) and type 2 diabetes (T2D) patients. This review will provide an updated overview of the genetics of LADA, highlight what genetics tell us about LADA as a diabetes subtype, and point to future directions in the study of LADA.

Recent Findings Recent studies have verified the genetic overlap between LADA and both T1D and T2D and have contributed identification of a novel LADA-specific locus, namely, *PFKFB3*, and subtype-specific signatures in the HLA region. Genetic risk scores comprising T1D-risk variants have been shown to be a promising tool for discriminating diabetes subtypes and identifying patients rapidly progressing to insulin dependence.

Summary Genetic data support the existence of LADA, but further studies are needed to fully determine the place of LADA in the diabetes spectrum.

Keywords LADA · Latent autoimmune diabetes in adults · HLA · *TCF7L2* · *PFKFB3* · Genetic risk score

Introduction

Diabetes is a major health challenge, causing an estimated 1.6 million deaths in 2016, and is a severe economic burden, with an estimated cost of US$1.3 trillion in 2015 [1–3]. Diabetes is a heterogeneous disease, where the diagnostic categories range from the primarily autoimmune-related insulin-deficient type 1 diabetes (T1D), to the metabolically related type 2 diabetes (T2D). Recently, the World Health Organization (WHO) has included latent autoimmune diabetes in adults (LADA) in their classification of diabetes. According to WHO, LADA is defined as slowly evolving immune-mediated diabetes of adults, in the category of hybrid forms of diabetes [4]. LADA is characterized by the presence of autoantibodies, adult age of diagnosis, and preserved beta-cell function at the time of diagnosis. However, no consensus about diagnostic criteria exists for LADA, and it has even been questioned if LADA is a true diabetes subtype, or merely a group of misclassified T1D and T2D patients.

Phenotypically, LADA seems to be intermediate between T1D and T2D (Table 1) [5–10]. Similar to T2D, the primary risk factors for development of LADA are age, adiposity, and family history of diabetes [11, 12]. On the other hand, LADA has, like T1D, been shown to be characterized by insulitis. However, in contrast to T1D, where all islets are infiltrated [13, 14], only two-thirds of islet cells were infiltrated at the time of disease manifestation, both in LADA patients and in a rat model of LADA [15]. These morphological differences were accompanied by a shift in the presentation of immune cells and proinflammatory cytokines [15], which might explain the slower progression of insulin deficiency in LADA compared to T1D. With regard to complications, LADA patients seem most similar to T1D and are less likely to develop cardiovascular complications and early microvascular events compared to patients with T2D [16–18], likely due to a healthier metabolic profile. However, compared to T2D, LADA patients more often have difficulties achieving glycemic control [17, 19], resulting in worse long-term microvascular outcomes [17, 18].

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Table 1 Presentation of LADA in relation to T1D and T2D

	T1D	LADA	T2D
Clinical characteristics			
Autoantibodies	+++	++	–
Metabolic syndrome	−/+	++	+++
Islet inflammation	++	+	−/+
Beta-cell function	–	−/+	++
Genetic characteristics			
HLA	++++++	+++++	–
PTPN22	++++	+++	–
INS	++(+)	++(+)	–
SH2B3	++	++	–
TCF7L2	–	+	++
PFKFB3	–	+	–
T1D GRS	+++	+	–
T2D GRS	–	−/+	++

In order to verify LADA as a diabetes subtype, and to improve the understanding of the pathophysiology of LADA, it is vital to identify markers that can assist in the diagnoses of LADA and separate LADA from other diabetes subtypes. Discrimination of diabetes subtypes and stratification with respect to disease progression is important, as these aspects have implications for choice of treatment and well-being of patients. Recent studies have indicated that markers of low-grade inflammation, including soluble tumor necrosis factor receptor type II (sTNFRII), could help differentiate between LADA, T1D, and T2D [20]. Also, the secretion pattern of proinsulin has been suggested to differ between diabetes subtypes [21]. However, these markers, as well as autoantibodies such as glutamic acid decarboxylase autoantibodies (GADA) [22], are dependent on timing in clinical sampling and disease progression. In contrast, genetic markers are stable over time and are not confounded by lifestyle, disease state, or medication and can easily be obtained from a blood sample. Hence, genetics have the potential to inform about pathogenic pathways characterizing LADA compared to T1D and T2D and maybe even to stratify LADA patients by identifying those with rapid decreasing beta-cell function who should be prioritized for early intervention.

This review provides an overview of the current knowledge of the genetics of LADA, discusses what genetics tells us about LADA as a diabetes subtype, and points to future directions in the genetic research of LADA.

Genetics of Latent Autoimmune Diabetes in Adults

Since the first reports of association between variants in the HLA region and T1D in the 1970s [23, 24], genetic predisposition to diabetes has been studied intensively. To date, more than 60 risk-associated loci have been identified for T1D [25–27], and for T2D more than 400 [28]. Increasing evidence is pointing towards a partial genetic overlap between T1D and T2D [29–33]. One of the most well-documented loci that are associated with both T1D and T2D is *GLIS3*, which encodes the GLIS family zinc finger 3. The functional link between genetic variation in *GLIS3* and diabetes has been suggested to be fragile beta-cells, with increased apoptosis and senescence [34, 35]. A recent study assessed linkage disequilibrium (LD)-score regression and found positive genetic correlation between T1D and T2D. To ensure that the correlation between T1D and T2D was not explained by misclassified patients, these findings were replicated in restricted case groups. T1D was restricted to individuals with onset below the age of 17, treated with insulin from diagnosis, and with a body mass index (BMI) ≤ 30, whilst T2D was restricted to patients negative for GADA and treated without insulin for at least 1 year after diagnosis [32•]. The study further highlighted that particular T2D-relevant processes and genetic risk factors contribute to risk of T1D, likely via beta-cell stress by affecting islet function and through affecting insulin resistance [32•]. Taken together, these genetic studies favor the presentation of diabetes as a spectrum of phenotypes with partly overlapping etiology and genetic predisposition and adds to the emerging clinical picture of T1D and T2D being heterogeneous phenotypes [19, 36].

The precise positioning of LADA within this spectrum is still unclear. Progress in understanding the genetic contribution to LADA is less advanced than for T1D and T2D. Until recently, genetic studies of LADA were candidate-gene studies assessing T1D or T2D-associated variants. Due to small sample sizes, these studies had limited statistical power, and the findings were likely contaminated with false-positives. Within the last 5 years, larger samples of LADA patients have been compiled by collaboration across research groups, and a genome-wide association study (GWAS) has been conducted as well as a few larger candidate-gene studies and a meta-analysis (Table 2). Hence, a clearer picture of the genetic predisposition to LADA is starting to emerge. The best-validated genetic loci associated with LADA are described below (Table 3).

The Human Leukocyte Antigen Complex

Variation within the human leukocyte antigen (HLA) region remains the strongest genetic risk factor for T1D, and this locus contributes at least 40% of the heritability of T1D, primarily through variation in the HLA-DR and HLA-DQ genes [25, 26, 37]. It has consistently been shown that the frequency of HLA-risk alleles correlates with age at diagnosis of T1D, whereas the opposite has been shown for protective HLA alleles [33, 38].

Table 2 Overview of genetic studies of LADA

Study	Ethnicity	Sample size LADA/controls	Reference
Candidate-gene studies			
Mishra et al. (2020)	European	1428/2850	[45]
Heneberg et al. (2018)	European	156/NA	[54]
Mishra et al. (2017)	European	978/1057	[42]
Luo et al. (2016)	Asian	562/1065	[41]
Andersen et al. (2014)	European	911/4002	[80]
Liu et al. (2012)	Asian	229/210	[55]
Pettersen et al. (2010)	European	113/1482	[44]
Zampetti et al. (2010)	European	250/545	[81]
Andersen et al. (2010)	European	213/–	[8]
Cervin et al. (2008)	European	361/1704	[40]
Petrone et al. (2008)	European	250/545	[53]
Desai et al. (2007)	European	385/327	[39]
Desai et al. (2006)	European	400/332	[64]
Meta analyses of candidate genes			
Ramu et al. (2019)	European/Asian	4299/12,022	[56]
Lukacs et al. (2012)	European	999/5358	[79]
Genome-wide association studies			
Cousminer et al. (2018)	European	2634/5947	[43]

The table includes genetic studies comprising > 100 LADA patients.

NA not available

The HLA region is also the strongest genetic predictor of LADA [5, 8, 39–41, 42•, 43••], with the strongest association shown in LADA patients with high GADA levels or LADA patients positive for two autoantibodies, GADA and insulinoma-associated antigen-2 autoantibodies (IA2A) [8, 42•, 43•, 44]. Compared to T1D, the effect sizes for T1D HLA-risk haplotypes in LADA are smaller, whilst the impact of T1D HLA-protective haplotypes is greater in LADA [8, 37, 39, 41•, 43•, 45••]. Interestingly, these differences are apparent, even when comparing LADA patients to T1D patients diagnosed in adulthood [8, 44]. Recent studies have indicated that the pattern of associated alleles in the HLA region might differ between T1D and LADA. In a stepwise conditional analysis, T1D was associated with independent signals for the *HLA-DQB1*0302* allele, and in the HLA class I genes *HLA-B*39*, *HLA-A*, and *HLA-G*. LADA on the other hand showed no HLA class I association that was independent of the *HLA-DQB1*0302* association [45••]. This observation is in line with reports of HLA class I markers, including (i) *HLA-B*39* is associated with younger age at onset in T1D [46, 47]; (ii) *HLA-B*3906* transgenic NOD mice show accelerated development of T1D; and (iii) *HLA-B*3906* has been shown to

Table 3 Best-validated LADA-associated variants

Locus	Lead SNP	Effect size (OR (95% CI))	*p* value	Reference
T1D associated loci				
HLA-DQB1	rs9273368	3.12 (2.86–3.40)	7.9×10^{-143}	[43]
PTPN22	rs2476601	1.62 (1.48–1.78)	< 0.0001	[56]
INS	rs689	1.39 (1.29–1.48)	< 0.0001	[56]
SH2B3	rs7310615	1.28 (1.19–1.38)	4.9×10^{-11}	[43]
T2D-associated loci				
TCF7L2	rs7903146	1.19 (1.00–1.40)	0.04	[56]
T1D and T2D independent loci				
PFKFB3	rs1983890	1.16 (1.14–1.32)	3.0×10^{-8}	[43]

The reported effect sizes per allele and *p* values are from the largest study reporting association. Variants are considered validated if replicated in at least two independent studies, or identified with a *p* value below the threshold for genome-wide significance ($p = 5 \times 10^{-8}$)

mediate the development of $CD8^+$ T cells, essential for T1D onset [48]. These HLA class I markers are thereby likely to contribute less to the genetic susceptibility to LADA.

The functional link between variation in the HLA region and autoimmune diabetes is through the role of the HLA proteins in the presentation of foreign- and self-derived antigens to immune cells, which activate the immune system and control T cell selection [49]. Genetic variation, particularly in *HLA-DQB1*, has been suggested to affect the affinity and stability of the antigen binding. Less efficient binding of pancreatic antigens might cause autoreactive T cells to escape negative selection in the thymus, which could induce an autoimmune reaction towards pancreatic beta-cells [50, 51].

Protein Tyrosine Phosphatase Non-Receptor Type 22

Protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) is also a validated T1D-associated locus [25, 26, 52]. The association between the minor T-allele of the *PTPN22* rs2476601 variant and LADA has been assessed in a number of smaller candidate-gene studies, and significant association was shown in the majority [8, 40, 42•, 53–55]. Recently, the association was replicated in a relatively large meta-analysis including 3187 patients with LADA [55] and a LADA GWAS comprising 2634 LADA patients [43••]. Compared to the reported effect size in T1D patients with an odds ratio (OR) of 1.95 (95% confidence interval (CI), 1.86–2.04) [52], the estimated effect in LADA patients is smaller, namely, an OR of 1.62 (95% CI, 1.48–1.78) [56]. Notably, the effect size has been suggested to be greater in LADA patients with high GADA levels [53] or positive for both GADA and IA2A [42•].

PTPN22 encodes a lymphoid tyrosine phosphatase, which is involved in negative selection of thymocytes and regulation of peripheral T cell activation [57–59]. The T1D-associated T-allele of the *PTPN22* rs2476601 variant has been shown to be associated with reduced elimination of naïve B cells expressing autoreactive antibodies in the bone marrow and reduced negative selection of regulatory T cells in the thymus [60, 61], which may induce autoimmunity and thereby predispose to T1D and LADA.

Insulin

Insulin (*INS*) is also an established T1D-associated locus, estimated to account for around 10% of T1D heritability [25, 26, 62]. The *INS* rs689 T1D-associated allele is in near-perfect LD with the short class I variable number of tandem repeats (VNTR) in the *INS* promoter [63]. Association of the variant was initially reported with LADA in candidate-gene studies [40, 42•, 64] and subsequently confirmed in a relatively large meta-analysis [56], and in the LADA GWAS [43••]. The LADA-*INS* association has been suggested to be stronger in LADA patients positive for both GADA and IA2A [42•]. For T1D, association has been reported for different *INS* variants, but for rs689 or rs3842753, which are in high LD with each other, the reported effect sizes in T1D patients are greater than the estimated effect reported for LADA patients of an OR (95% CI) of 1.39 (1.29–1.48) [27, 56, 65••]. Functionally, the *INS* promoter VNTR has been shown to affect *INS* expression; hence, the T1D-associated class I VNTR is associated with lower *INS* expression in thymus [66, 67]. The lower level of insulin in the thymus reduces the deletion of autoreactive T cells targeting insulin antigens and thereby increases the risk of autoimmune destruction of insulin-producing beta-cells [68, 69].

The SH2B Adaptor Protein 3

In a recent candidate-gene study, and later in a GWAS, variants in the SH2B adaptor protein 3 (*SH2B3*) locus were found to be associated with LADA with an OR (95% CI) of 1.28 (1.19–1.38), again with a suggested larger effect size in LADA patients positive for both GADA and IA2A [42•, 43••]. This locus has also consistently been associated with T1D, with an effect size similar to the one reported for LADA [25, 26, 62]. The T1D-associated T-allele of the *SH2B3* rs3184504 missense variant has been suggested to be the causal variant in the locus. This variant is in high LD with the lead SNPs identified in LADA-association studies (rs17696736 and rs7310615) [42•, 43••] and is predicted to disrupt the subcellular localization and function of the SH2B3 gene product [70]. However, it is a complex genomic region that is associated with a range of different diseases and conditions [71].

In humans, *SH2B3* encodes the lymphocyte adaptor protein LNK, which is widely expressed across different tissues [72] and is involved in transduction and regulation of growth factor and cytokine receptor-mediated signaling [73]. Lack of LNK function in humans is linked to a range of phenotypes including triggered autoimmune processes [74], and in mice, *Sh2b3* knock-out leads to adipose inflammation, as well as impaired glucose tolerance and insulin response [75]. These changes might predispose to T1D as well as LADA.

Transcription Factor 7-Like 2

Transcription factor 7-like 2 (*TCF7L2*) remains the strongest common genetic risk factor for T2D with an OR (95% CI) of 1.37 (1.35–1.39) [28, 76]. Based on functional studies and trans-ethnic association analyses, the intronic rs7903146 variant is thought to be the major causal variant in the *TCF7L2* locus [28, 77, 78].

In candidate-gene studies, the *TCF7L2* rs7903146 variant has shown association with LADA, despite some discrepancy between studies [41, 42•, 79, 80], and the association has been

suggested to depend on GADA level, being strongest in LADA patients with low GADA levels [80, 81]. Association was not replicated in the LADA GWAS [43••]; however, in a recent meta-analysis comprising an even larger sample of LADA patients, association was reported with an OR (95% CI) of 1.19 (1.00–1.40) [56]. This meta-analysis revealed high heterogeneity between samples, supporting the observations from the GWAS, where the LADA-*TCF7L2* association was shown to be highly dependent on selection of the control group. Hence, choosing a selected normal glucose-tolerant control population resulted in a stronger association signal than choosing a population-based control group. Moreover, the origin of the LADA patients might also affect the result, with strongest association signal observed among LADA patients from Northern Europe [43••].

Discrepant findings have also been reported with respect to the relationship between *TCF7L2* and T1D. Most studies show no association between variation in *TCF7L2* and T1D, neither in childhood nor in adult-onset T1D [30, 80, 82–85], and no association with age at onset of T1D [30, 82]. However, in a recent study assessing 8967 patients with T1D and 6076 control subjects, the *TCF7L2* rs7903146 variant was associated with T1D, notably with opposite direction of effect to that reported for T2D [32•]. Association between the *TCF7L2* variant and presence of autoantibodies has also been assessed. In children with T1D parents, the T2D-associated *TCF7L2* allele was not associated with development of islet autoantibodies [84]. However, in 810 newly diagnosed T1D patients, association was observed between the T2D-associated *TCF7L2* alleles and a milder autoimmune presentation at diagnosis in patients 12 years or older [86]. These T2D-associated *TCF7L2* alleles have also been associated with slower progression of T1D, indicated by higher C-peptide levels [33, 86] and lower glucose levels during an oral glucose tolerance test [86]. Hence, *TCF7L2* might affect the pathophysiological presentation of T1D and predispose to a milder autoimmune response as well as milder metabolic impact in T1D patients. Taken together, variation in *TCF7L2* seems to play a role in disease presentation across the spectrum of diabetes subtypes.

The *TCF7L2* gene product is a transcription factor and has been shown to regulate transcription of the proglucagon gene, which yields the product GLP-1 [87], to mediate GLP-1 induced beta-cell proliferation [88], and to affect insulin secretion [89–91]. In adipose tissue, rs7903146 has been shown to affect adipocyte development [92], as well as glucose and fatty acid metabolism [93]. Moreover, carriers of the rs7903146-risk genotype have been shown to have a reduced number of beta-cells [94]. Taken together, these alterations likely affect glucose homeostasis, adipose-tissue homeostasis, and risk of diabetes.

6-Phosphofructo-2-Kinase/Fructose-2, 6-Biphosphatase 3

In the LADA GWAS, a novel signal was identified in the 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (*PFKFB3*) locus on chromosome 10, where the rs1983890 C-allele was genome-wide significantly associated with LADA with an OR (95% CI) of 1.16 (1.14–1.32) [43•]. This genomic region is not associated with T2D [28] but harbors two well-established T1D-associated loci, namely, *IL2RA* and *PRKCQ* [25, 26]. However, the LADA signal is independent of these two T1D signals, as the LADA association remained significant when conditioning on the T1D-associated lead SNPs. DEPICT analysis indicated that *PFKFB3* was the most likely functional candidate explaining the association signal in LADA [43•]. *PFKFB3* encodes 6-phosphofructo-2-kinase/fructode-2,6-biphosphatase 3 and is a strong functional candidate to explain the signal. PFKFB3 is involved in regulation of glycolysis and insulin signaling [95] and is highly expressed in adipose tissue where it is a master regulator of adipocyte nutrient metabolism [96]. In mice, loss of PFKFB3 function in adipose tissue results in high-fat diet-induced systemic insulin resistance and inflammation of the adipose tissue [97], whereas PFKFB3 over-expression was protective for these conditions [98]. PFKFB3 is also involved in a highly conserved HIF1 α/PFKFB3-signaling pathway, which protects against cellular stress, including beta-cell stress [99, 100]. This pathway is activated in islets from adult T1D patients, with a fivefold increased *PFKFB3* expression, where it delays cytokine-induced beta-cell death [100]. The exact role of the *PFKFB3* locus in LADA pathogenesis remains to be determined. It could be hypothesized that LADA-associated variation in the *PFKFB3* locus increases the activity of PFKFB3 and thereby induce the HIF1 α/PFKFB3-signaling pathway to delay beta-cell death, causing later and milder onset compared to childhood onset T1D. However, in a study of T1D and LADA patients, the *PFKFB3* rs1983890 variant was neither associated with age at onset nor C-peptide level [33].

Genetic Risk Scores and Characterization of Diabetes Subtypes

Instead of assessing genetic variants separately, they can also be combined in genetic risk scores (GRS). The use of a GRS is likely to be a more promising way to translate genetic findings into prediction, identification of diabetes subtypes, and perhaps even into personalized treatment.

Genetic Risk Scores in Type 2 Diabetes

For T2D, GRS comprising different numbers of risk variants have been tested in their ability to predict the disease. However, the benefit from a GRS, compared to easily

available factors such as age, BMI, sex, and family history, is very limited for T2D [101]. Most recently, a polygenic risk score comprising 7 million variants has been shown to identify 3.5% of the population at > 3 threefold increased risk of T2D. However, the screening performance of this score is poor with an area under the curve (AUC) of just 0.73 [102] and an estimated detection rate of only 13%, with a false discovery rate of 5%. These statistics mean that the score would incorrectly identify 5% of unaffected individuals as having T2D, while only correctly identifying 13% of individuals truly having T2D [103, 104]. Moreover, a T2D GRS has very limited power to discriminate T2D from T1D [42•, 105].

Genetic Risk Scores in Type 1 Diabetes

In contrast, a T1D GRS is far more powerful for prediction and discrimination of diabetes subtypes, due to the larger effect estimates of T1D-associated variants compared to T2D-associated variants. Hence, a score comprising 67 T1D-associated variants and including HLA interaction terms has an AUC of 0.93 for discriminating T1D from controls [65••] and is in UK Biobank data able to correctly identify 83% of T1D patients, and at the same time correctly identifying 89% of the background population as unaffected. Similarly, when discriminating T1D from T2D, the GRS correctly identified 83% of patients with T1D and correctly identified 88% of the T2D patients [65••]. Moreover, a T1D GRS comprising 30 variants has been shown to predict insulin deficiency among T1D and T2D patients diagnosed at 20–40 years of age [105], and among GADA-positive T2D patients, to identify those rapidly progressing to insulin treatment [106••]. Hence, among GADA-positive T2D patients, those with a high T1D GRS had a probability of 48% to require insulin treatment within 5 years of diagnosis, whereas those with the lowest score had a probability of just 18%. Yet, it should be noted that a probability of 48% among GADA-positive T2D patients with a high GRS means that the majority of these patients will not require insulin after 5 years [106••], and hence, the GRS is not readily clinically relevant. Interestingly, the probability of insulin treatment for GADA-positive individuals with a low T1D GRS is higher than the probability for insulin treatment for GADA-negative T2D patients, who have 7% risk regardless of the T1D GRS [106••]. This supports the notion that even the least T1D-like LADA patients differ from T2D patients.

Genetic Risk Scores in Latent Autoimmune Diabetes in Adults

In LADA patients, combined analyses of T1D- and T2D-associated variants showed enrichment of association for both sets of loci [43•], supporting the results from single-variant analyses of a genetic overlap between LADA and T1D as well as between LADA and T2D. In addition, LD-score regression supports a direct genetic correlation between LADA and T1D, and the key role of autoimmunity in LADA is further supported by genetic correlation between LADA and additional autoimmune conditions. LD-score regression also supports the genetic overlap between LADA and T2D, by direct genetic correlation between LADA and T2D, but also indicated by correlation between LADA and other metabolic phenotypes, including BMI [43•].

GRS have also been assessed in LADA patients. With respect to a T1D GRS comprising 69 variants, the AUC for LADA compared to control subjects was 0.67, whereas the AUC for a T2D GRS comprising 67 variants was 0.57. Hence, both scores have low predictive value for LADA. However, it was shown that the mean value of both scores for LADA patients differed significantly from both T1D and T2D patients as well as control subjects [42•], again indicating that both T1D and T2D risk variants are enriched among LADA patients. Moreover, the scores also differed according to the number of autoantibodies among the LADA patients; LADA patient only positive for GADA had a lower T1D score, and a higher T2D score than LADA patients positive for both GADA and IA2A [42•]. Clinical application of the T1D GRS in its current form for distinguishing diabetic subtypes seems limited as the distribution of the T1D GRS within T1D, T2D, LADA, and controls overlapped between all groups [42•]. However, a more advanced version of the T1D GRS [65••] might perform better in this discrimination. Of note, the distribution of the T1D GRS within LADA patients did not support a bimodal distribution of the T1D GRS, which might be expected if the group of LADA patients consisted only of misdiagnosed T1D and T2D patients.

Taken together, studies of GRS support the notion that both T1D-associated and T2D-associated variants contribute to the genetic susceptibility to LADA. However, to firmly classify LADA, as either a diabetes subtype distinct from both T1D and T2D, or a group of misdiagnosed T1D and T2D patients, further research is required.

Conclusions

Genetic studies seem to support the notion that diabetes is more than two easily separated groups of patients with either T1D or T2D, in line with what has been shown based on clinical data [19, 36].

Based on current knowledge, LADA seems to share genetic predisposition with both T1D and T2D (Tables 1 and 3). For *HLA*, *PTPN22*, *INS*, *SH2B3*, and *TCF7L2*, the variants associated with LADA overlap with those associated with either T1D or T2D, although the effect sizes are in general smaller for LADA.

Pathway and tissue enrichment analyses [43••], as well as functional observations, indicate a key role of the immune system in the pathogenesis of LADA. T1D-associated variants are likely linked to the autoimmune process in LADA, and T2D-associated variants likely add to the genetic burden increasing the susceptibility to LADA, thereby contributing to the intermediate phenotype of LADA. Recent studies have contributed interesting insights into the genetics of LADA. These findings include (i) an independent LADA GWAS signal, namely, *PFKFB3* [43••], which might contribute to the slower disease progression in LADA compared to T1D, and (ii) HLA class I loci only showing independent association to T1D, and not LADA, when conditioning on the main HLA class II risk variants [45••]. These findings indicate that LADA differs genetically from T1D.

It has been heavily debated whether LADA truly is an independent subtype of diabetes, intermediate between T1D and T2D, a subtype of T1D, or whether it is a group of primarily T1D patients and some T2D patients with a false-positive autoantibody results. Genetic findings can be interpreted to support the existence of LADA. Hence, even among the most T1D-like LADA patients with high GADA levels or multiple autoantibodies, the HLA-risk alleles are not as common, and the T1D GRS is lower, when compared to T1D children [8, 42•], indicating that these patients are not simply misclassified T1D patients. Similarly, the most T2D-like LADA patients with low GADA levels, or only single autoantibody positivity, differ from T2D patients with a lower T2D-genetic load [42•], and a greater probability for insulin treatment [106••].

Interestingly, the hypothesis that LADA is simply a mixture of T1D patients and T2D patients with a false-positive autoantibody test was investigated in a study assessing similarities and differences in HLA association between T1D and LADA. A cohort of 714 T1D patients and 714 T2D patients were randomly sampled to generate a LADA sample, which was compared to 2219 control subjects. Analyses demonstrated that the generated LADA sample was much more T1D-like than the real LADA cohort with respect to HLA association [45••]. Additional studies assessing a simulated against a real cohort of LADA patients should test these aspects further. Moreover, to firmly establish the nature of LADA and to determine if it can be separated from T1D and T2D, large well-powered genetic-association studies assessing separate variants and GRS in LADA patients with a large spectrum of age at diagnosis, as well as numbers and levels of autoantibodies, are also warranted. Particularly, with optimization, GRS could become relevant both in terms of timely diagnosis, and for determination of disease management in LADA. In the future, partitioned GRS capturing specific intermediary disease-related phenotypes or pathways driving an individual's disease progression might also be generated. Genetic clustering has already been used to characterize clusters of different underlying etiologies within T2D [28, 107], and similar analyses in a suitably sized cohort of LADA patients would be of great interest.

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Compliance with Ethics Standards

Conflict of Interest Mette K. Andersen declares that she has no conflict of interest.

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