Editorial

Results of the First Genome-Wide Association Study of Latent Autoimmune Diabetes in Adults further highlight the need for a novel diabetes classification system

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Latent autoimmune diabetes of the adults (LADA) is a type of autoimmune diabetes characterized by adult-onset, presence of autoantibodies and no need for insulin treatment for a period following diagnosis. Epidemiological data suggest that LADA is the most common cluster of adult-onset autoimmune diabetes, but also the predominant form of autoimmune etiology diabetes, in general (1). 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 to medical literature as type 1.5 diabetes.

The Immunology of Diabetes Society has proposed the following criteria for diagnosing LADA, which are widely used for both clinical and research purposes; (I) age of onset >30 years; (II) presence of any islet cell autoantibody and (III) absence of insulin dependency for at least six months after diagnosis (2). However, the aforementioned criteria have been repeatedly criticized (3), since they seem inadequate to detect the full spectrum of the significantly heterogenous LADA population. Moreover, the existence of LADA as a distinct clinical entity has been debated by numerous researchers and clinicians, who consider LADA and T1D as two opposing ends of the continuum of autoimmune diabetes (3).

Candidate gene studies that aimed, so far, to determine the genetic background of LADA have indicated a role for loci involved in the pathogenesis of both T1D and T2D (4). Previous research has pointed towards increased frequency of T2D associated CT/TT genotypes rs7903146 in the transcription factor 7 like 2 (*TCF7L2*) gene among LADA and T2D subjects as compared with healthy controls (5). Genetic similarities with T1D have been demonstrated with regard to human leukocyte antigen (*HLA*), insulin gene promoter (*INS VNTR*), and protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) genes (6). Nevertheless, it was only recently that the results of the first systematic genome-wide appraisal of LADA were brought into light.

In the genome-wide association study (GWAS) performed by Cousminer *et al.* and published in *Diabetes Care* (7), genetic data from 2,634, 2,454 and 2,779 people with LADA, T1D and T2D respectively, were included. In brief, the results of this trial reconfirm the hypothesis that the strongest genetic risk loci for LADA are common with T1D, however, alleles with an established role in T2D susceptibility also contribute—to a less extend—to LADA genetic risk.

One gene in particular, encoding 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and being the nearest gene to the LADA signal, was of great significance given that it was identified as the most likely functional candidate (7). *PFKFB3* plays key roles in regulating glycolysis and insulin signaling in

human homeostasis (8). Previous animal studies have demonstrated that *PFKFB3* knockout is related to diet-induced adiposity and systemic insulin resistance, through a variety of mechanisms including augmented lipolysis, defective adipokine expression and decreased insulin signaling, in addition to increased levels of proinflammatory cytokines (9). It is also involved in inflammation and autophagy in autoimmune disease; *PFKFB3* loss in T cells from patients with rheumatoid arthritis has been shown to result in attenuated immune response and increased cellular apoptosis (10). Further research is necessary to clarify whether this signal can be considered as a major distinguishing feature between adult and childhood-onset autoimmune diabetes.

Undeniably, GWASes have been a remarkable contribution to our understanding of complex diseases, not only by successfully identifying a number of disease risk genes, but mainly by deconvoluting the underlying pathophysiological pathways. Still, it is strongly believed that phenotypic misclassification reduces the power of genetic studies to detect potential gene-disease relationships (11). In addition, complex traits are heterogeneous in terms of individual genetic susceptibility and disease pathophysiology and this diversity has a negative impact on the credibility of reported genetic associations (12).

For example, in the GWAS by Cousminer *et al.* (7), the established criteria for LADA diagnosis were used, including glutamic acid decarboxylase autoantibody (GADA) positivity. As shown by previous works, diabetic patients with various levels of GADA titers present remarkable diversity regarding pathophysiological and clinical characteristics. In a large cross-sectional study from China (13), Zhou *et al.* demonstrated that patients with LADA and low GAD65 titers did not differ from "typical" T2D individuals in respect to sex, diagnosis age, glycated hemoglobin levels, beta-cell function reserve and metabolic syndrome components. In contrast, patients with high GADA levels, often reported as LADA 1 group, present more common phenotypic and laboratory features with T1D subjects, including lower C-peptide levels, lower body mass index and greater risk for ketosis (14).

As suggested by van Deutekom *et al.* (15), low anti-GADA titers may reflect a slowly progressive autoimmune beta-cell damage, not sufficient to severely disrupt insulin secretion and action, resulting in the formation of a T2D-like metabolic phenotype. Alternatively, low anti-GADA levels may be the result of beta-cell destruction mediated by non-autoimmune mechanisms, as for example amyloid formation in the pancreatic islets (16). The possibility of "false positive" results, related to random assay variation should be also considered. Finally, autoimmunity is an element of T2D pathogenesis too, and a small proportion of patients with "classical" T2D can be found positive for autoantibodies (14). Therefore, it becomes increasingly evident that single autoantibody positivity, particularly at low titers, may not be enough evidence for the role that autoimmunity plays in this type of diabetes development, and thus, not a fair criterion for classifying diabetes as autoimmune. Additionally, the current LADA definition seems to completely ignore insulin resistance as a pathophysiological component of the disorder, which may not significantly contribute to most cases of T1D, however, plays an important pathogenic role in slow-onset autoimmune diabetes (17).

Considering the aforementioned apprehensions, it is clear that the existing diabetes classification scheme lacks the ability to incorporate recent advances in the understanding of the pathophysiology of the disease. It also imposes unneeded barriers in the implementation of a modern, personalized and patient-centered therapeutic approach. For example, the current LADA definition preconceives insulin treatment even for individuals with retained endogenous insulin production; however, it has been shown that alternative therapies, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, and thiazolidinediones may effectively control hyperglycemia and preserve long-term beta-cell viability in individuals diagnosed with LADA (18-21).

In this context, novel diabetes classification schemes have recently emerged. Schwartz *et al.* (22) have suggested the beta-cell-centric classification system, in which an abnormal beta-cell is acknowledged as the primary diabetes defect; still it also recognizes the interaction between genetic factors, insulin resistance, inflammation and autoimmunity with impaired beta-cell mass and functionality. According to the authors, it is hoped to direct research towards the genes involved in beta-cell damage and dysfunction, thus, facilitating the effective translation of the results of genetic studies into daily clinical practice. Alternative classification systems have identified distinct diabetes clusters that are principally characterized, in terms of pathophysiology, by autoimmunity, insulin deficiency, insulin resistance or a combination of the above (23), and each of these clusters seems to be significantly correlated to specific types of diabetic micro- and macrovascular complications.

In conclusion, we consider the results of the first GWAS

in LADA as an important step forward, regarding the comprehension of diabetes' complex pathophysiology. On the other hand, the heterogeneity of included population, deriving from the current LADA definition itself, renders the interpretation of the results puzzling. The challenge for future research in the field is to develop novel markers that can effectively identify distinct diabetes clusters, providing rational choices for individualized treatments that target the unique mediating pathways of metabolic disarrangement in each patient (22,24). According to MJ Redondo: "*It is time for a new definition of LADA*" (17). Probably, it is time for a new diabetes classification system too.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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