



New genetic characteristics of latent autoimmune diabetes in adults (LADA)

Yan Chen¹, Gang Chen²

¹Department of Internal Medicine, South Branch of Fujian Provincial Hospital, Fuzhou 350000, China; ²Department of Endocrinology, Fujian Provincial Hospital, Fuzhou 350000, China

Correspondence to: Gang Chen. Department of Endocrinology, Fujian Provincial Hospital, Num 134 East Street, Fuzhou 350000, China.

Email: chengangfj@163.com.

Provenance: This is an invited article commissioned by the Section Editor Kaiping Zhang (AME College, AME Group, Hangzhou, China).

Comment on: Cousminer DL, Ahlqvist E, Mishra R, *et al.* First Genome-Wide Association Study of Latent Autoimmune Diabetes in Adults Reveals Novel Insights Linking Immune and Metabolic Diabetes. *Diabetes Care* 2018;41:2396-403.

Submitted Dec 18, 2018. Accepted for publication Dec 28, 2018.

doi: 10.21037/atm.2019.01.01

View this article at: <http://dx.doi.org/10.21037/atm.2019.01.01>

Latent autoimmune diabetes in adults (LADA) is assigned to a subtype of immune-mediated type 1 diabetes (T1DM) according to the typing method for diabetes of WHO in 1999 which shares clinical features of T1DM and type 2 diabetes (T2DM). The association of LADA with T1DM and T2DM still remains unclear and the precise definition of LADA has always been controversial (1,2). There have been some genetic studies on LADA that are directed at a limited number of candidate genes that support the role of risk loci in the pathogenesis of T1DM and T2DM (1,3-5). The study entitled “First Genome-Wide Association Study of Latent Autoimmune Diabetes in Adults Reveals Novel Insights Linking Immune and Metabolic Diabetes” published online in *Diabetes Care* of September 25, 2018 is the first genome-wide association study (GWAS) for LADA, making the genetic characteristics of LADA more clear (6). The study included multiple cohorts of European descent from Denmark, Sweden and so on. The inclusion and exclusion criteria for LADA, T1DM, T2DM and population control subjects varied by cohort. In general, LADA was defined by an age older than 20, 30, or 35 years, while some cohorts setting the upper age limit to 70 years; the existence of diabetes associated autoimmune auto antibodies, especially GAD autoantibody (GADA) positivity; and the lack of insulin requirement for half of a year or one year after diagnosis. In some cohorts, C-peptide level was also applied as a filter. A variety of efficient and reliable analysis methods were adopted in this research including meta-analysis, signal path enrichment

analysis, condition analysis, stratified analysis, regression analysis and HLA interpolation analysis. A meta-analysis was first performed in LADA patients versus healthy subjects (n=2,634 *vs.* 5,947) and it was found that four signals reached genome-wide significance ($P < 5 \times 10^{-8}$), all of which at the identified T1DM risk loci (HLA, PTPN22, INS and SH2B3). Signal pathway analysis supported the important role of immunity in the pathogenesis of LADA ($P < 10^{-5}$). Further gene enrichment analysis revealed that physiological abnormalities were associated with cytotoxic T cells ($P = 6.39 \times 10^{-7}$), mTOR regulatory network ($P = 6.03 \times 10^{-5}$), cell cycle ($P = 1.67 \times 10^{-5}$), natural killer cells and T lymphocytes ($P = 0.0079$ and 0.0082 , respectively).

The researchers found a new signal at the 10p15.1 locus between two identified T1DM risk alleles, IL2RA and PRKCQ with genome-wide significance (7). The investigators further tested SNPs associated with T1DM and noticed that rs1983890 was strongly associated with LADA. The DEPICT gene-first analysis confirmed that the PFKFB3 gene was closest to LADA and was most likely to be a functional gene candidate.

The researchers also extracted candidate genes by extracting T1DM and T2DM related loci, and found that the P values of T1DM and T2DM loci in LADA were lower than the predicted values. Approximately 90.6% of the T1DM sites ($P = 4.51 \times 10^{-12}$) and 72.3% of the T2DM sites ($P = 2.10 \times 10^{-4}$) were directly consistent with LADA. There were 81.4% of loci directional in LADA in combination with T1DM and T2DM sites ($P = 1.40 \times 10^{-13}$).

Therefore, it can be observed from the results of the study that the confirmed T1DM-related genes exhibited the same effect in LADA.

The investigators also performed GWAS analysis of LADA patients versus T1DM patients ($n=2,454$ vs. 968) while LADA patients versus T2DM patients ($n=2,779$ vs. 10,396). It was found that there were four risk loci in the whole genome between LADA and T2DM which included HLA, PTPN22, INS, and SH2B3. There was only a significant difference in HLA regions between LADA and T1DM. This indicates that the key signal in LADA is relatively depleted compared to T1DM. The entire genome-wide associated analysis showed that LADA was directly correlated with T1DM and T2DM.

GADA stratified analysis of LADA patients showed that OR of the key loci was the strongest in the LADA case with the highest GADA titer. For an instance, rs9273368 (HLA-DQB1) showed the strongest relationship with LADA including the highest tertile titer of GADA [OR (95% CI), 3.30 (2.81–3.88); $P=1.89 \times 10^{-47}$]. However, the association with the lowest GADA titer was the weakest [OR (95% CI), 2.42 (2.06–2.85); $P=2.13 \times 10^{-26}$]. In addition, only the HLA-DQB1 locus was significantly associated in the lowest GADA titer group while the PTPN22, INS and SH2B3 loci were only evident in the group with higher GADA titer. In addition, the OR of rs7903146 in the TCF7L2 locus was slightly higher in the case with the lowest GADA titer than in the highest GADA titer group (OR 1.09 and 1.05, respectively).

To make further efforts to distinguish HLA regions between LADA patients and T1DM patients, the investigators used the SNP2HLA partial cohort to extrapolate HLA regions and compared them with the frequency of key T1DM-associated HLA haplotypes. There were statistically significant differences in the frequency of 11 T1DM haplotypes between LADA and T1DM ($P<0.003$) after repeated detection and correction, and there were four T1DM susceptibility haplotypes whose frequency in LADA patients significantly reduced (HLADRB1*0301-DQA1*0501-DQB1*0201, HLA-DRB1*0401-DQA1*0301-DQB1*0302, HLA-DRB1*0404-DQA1*0301-DQB1*0302 and HLA-DRB1*0405-DQA1*0301-DQB1*0302).

In general, LADA is genetically related to both T1DM and T2DM, but the strongest genetic risk locus is shared with T1DM. Researchers have observed a new independent gene (*PFKFB3*) at the known T1DM locus which encodes glycolysis and insulin signaling in T2DM. *PFKFB3* is

associated with inflammation, autophagy in autoimmune diseases, and regulates haplotype frequency of the T1DM-related HLA. All of the above are the factors that distinguish childhood T1DM and LADA.

But there are still limits in this study. Firstly, some defects in the cases screened by the study, including differences in age, autoantibody detection, and the like, given that the exact standard of diagnosis used to diagnose LADA, adult-onset T1DM and T2DM remains controversial. The inclusion and exclusion criteria for this study vary by cohort. For example, the age of diagnosis is not uniform, usually over 20, 30 or 35 years, and even the cohort limits the upper age limit to over 70 years. Therefore, a more rigorous, deep phenotype of cohort is needed to truly confirm the location of LADA in the spectrum of diabetes.

Secondly, the GADA assay has a specificity of 95–98%. Therefore, the titer of GADA and even other islet autoantibodies may affect the estimation of the genetic correlation between LADA and T2DM. Therefore, further research is needed to determine the heterogeneity and misdiagnosis rate of LADA patients.

Despite the above limitations, it yet can learn from the study to verify the importance of further investigations in the genetic factors that distinguish forms of autoimmune diabetes as more accurate classification methods. This study is still the first GWAS for LADA opening the door to it. The sample size involved in the study can achieve sufficient test efficiency, and a variety of efficient and reliable data analysis methods and conditions for repeated test verification are also adopted. So, the results have certain reference given all the methods.

The strongest genetic risk locus of LADA is shared with T1DM. T1DM has multiple low-frequency risk variants with high OR, while T2DM has many common risk variants with less influential effects. These structural differences can explain the strong T1DM characteristics of LADA. In view of these structural differences, the characteristics of the genetic component of T1DM make it possible to detect the T1DM signal first, and the signal of T2DM can be detected as the statistical power is increased. This is of great significance for the genetic study of T2DM, as patients with T2DM also have cases of misdiagnosis as LADA. The LADA data set for this study should be used as a resource to help to identify the unexplained LADA in patients with T2DM.

Previous studies have found that the 10p15.1 locus is a complex region associated with LADA. However, some scientists have found that there is a potential correlation between the new signals *PFKFB3* and T1DM found in this

region ($P=1.3 \times 10^{-7}$) (7). Therefore, it cannot be used as a separate LADA correlation signal. Previous studies have found that the *PFKFB3* gene product acts as a regulator of glycolysis and insulin transmission, so *PFKFB3* can be used as a reasonable biological candidate for diabetes (8). It is necessary to further investigate the role of *PFKFB3* in LADA. It is important to carry out functional studies to explore the exact mechanism of the glycolytic regulator *PFKFB3* located at the intersection of autoimmunity and to identify whether this signal is really between adult and childhood autoimmune diabetes.

A comparative analysis of HLA haplotypes in this study showed a decrease in the frequency of T1DM-associated risk haplotypes in LADA. This may have a relationship to the age gradient determined in the HLA frequency of T1DM groups (9). However, the frequency of HLA risk genotypes in older LADA patients and T1DM patients over 35 years is also different (10). Therefore, future in-depth studies of HLA risk haplotype differences between T1DM and LADA subdivided into age and ethnicity are also necessary.

The study concluded that LADA is a mixture of T1DM and T2DM. LADA has T1DM-like autoimmune genetic components and T2DM-like metabolic genetic components. LADA is a delayed type of T1DM. Factors that may distinguish LADA from children's T1DM and T2DM were also identified: (I) new signals for *PFKFB3* sites; (II) reduction in T1DM-related HLA risk haplotypes. The findings also promote the hypothesis that polygenic components that cause T2DM susceptibility can act as a modifier to T1DM risk, maybe as a "second hit" of patients who have medium underlying autoimmune susceptibility which is lacking to attack childhood T1DM but sufficient than that of the common population and sufficient to lead to clinical diabetes in adulthood. Therefore, future research should focus on the role of BMI, which is lower in T1DM but higher in T2DM patients. At the same time, attention should be paid to further identifying factors that may distinguish adult autoimmune diabetes with T1DM and T2DM.

In summary, the study provides new genetic features for LADA, and there is a need for further research to distinguish LADA forms and more precise classification strategies.

Acknowledgements

None.

Footnote

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

References

1. Tuomi T, Santoro N, Caprio S, et al. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet* 2014;383:1084-94.
2. Thomas NJ, Jones SE, Weedon MN, et al. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol* 2018;6:122-9.
3. Desai M, Zeggini E, Horton VA, et al. An association analysis of the HLA gene region in latent autoimmune diabetes in adults. *Diabetologia* 2007;50:68-73.
4. Andersen MK, Sterner M, Forsen T, et al. Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes. *Diabetologia* 2014;57:1859-68.
5. Howson JM, Rosinger S, Smyth DJ, et al. Genetic analysis of adult-onset autoimmune diabetes. *Diabetes* 2011;60:2645-53.
6. Cousminer DL, Ahlqvist E, Mishra R, et al. First Genome-Wide Association Study of Latent Autoimmune Diabetes in Adults Reveals Novel Insights Linking Immune and Metabolic Diabetes. *Diabetes Care* 2018;41:2396-403.
7. Bradfield JP, Qu HQ, Wang K, et al. A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci. *PLoS Genet* 2011;7:e1002293.
8. Duran J, Obach M, Navarro-Sabate A, et al. *Pfkfb3* is transcriptionally upregulated in diabetic mouse liver through proliferative signals. *FEBS J* 2009;276:4555-68.
9. Graham J, Kockum I, Sanjeevi CB, et al. Negative association between type 1 diabetes and HLA DQB1*0602-DQA1*0102 is attenuated with age at onset. Swedish Childhood Diabetes Study Group. *Eur J Immunogenet* 1999;26:117-27.
10. Andersen MK, Lundgren V, Turunen JA, et al. Latent autoimmune diabetes in adults differs genetically from classical type 1 diabetes diagnosed after the age of 35 years. *Diabetes Care* 2010;33:2062-4.

Cite this article as: Chen Y, Chen G. New genetic characteristics of latent autoimmune diabetes in adults (LADA). *Ann Transl Med* 2019;7(5):81. doi: 10.21037/atm.2019.01.01