Latent Autoimmune Diabetes in Adults Differs Genetically From Classical Type 1 Diabetes Diagnosed After the Age of 35 Years

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OBJECTIVE — We studied differences between patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes, and classical type 1 diabetes diagnosed after age 35 years.

RESEARCH DESIGN AND METHODS — Polymorphisms in HLA-DQB1, INS, PTPN22, and CTLA4 were genotyped in patients with LADA (n = 213), type 1 diabetes diagnosed at >35 years of age (T1D_{>35y}, n = 257) or ≤20 years of age (T1D_{≤20y}, n = 158), and type 2 diabetes.

RESULTS — Although patients with LADA had an increased frequency of HLA-DQB1 and PTPN22 risk genotypes and alleles compared with type 2 diabetic subjects, the frequency was significantly lower compared with T1D_{>35y} patients. Genotype frequencies, measures of insulin secretion, and metabolic traits within LADA differed according to GAD antibody (GADA) quartiles, but even the highest quartile differed from type 1 diabetes. Having two or more risk genotypes was associated with lower C-peptide concentrations in LADA.

CONCLUSIONS — LADA patients differed genetically and phenotypically from both T1D_{>35y} and type 2 diabetic patients in a manner dependent on GADA levels.

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All risk genotypes and alleles were most prevalent in patients in the highest GADA quartile (LADA_{high}, GADA > 278 IU/ml) compared with the two middle (LADA_{mid}, 44–278 IU/ml) or the lowest quartiles (LADA_{low}, 33–43.9 IU/ml; Fig. 1), but the difference was significant only for HLA-DQB1 (P = 0.009). However, even LADA_{high} subjects differed from T1D_{>35y} subjects (P = 0.001), and LADA_{low} subjects had nonsignificantly more HLA-DQB1 risk genotypes than type 2 diabetic subjects (19.6 vs. 14.0%). LADA_{high} subjects also differed from the type 2 diabetic subjects with respect to the allele frequency of PTPN22 (P = 0.02) and CTLA4 (P = 0.03).

In a joint analysis of the four genes, two or more risk genotypes were most common in T1D_{<20y} patients (82.1%), followed by T1D_{>35y} patients (74.4%), LADA (54.1%), and type 2 diabetic (38.7%) patients (P < 0.00001). The frequency differed across the GADA quartiles (P = 0.004), and it was similar in LADA_{high} and T1D_{>35y} patients (72.5 vs. 74.4%), as well as in LADA_{low} and type 2 diabetic patients (46.0 vs. 38.7%) (online appendix Table A3, available at http://care.diabetesjournals.org/cgi/content/full/dc09-2188/DC1). LADA patients with an increasing number of risk genotypes had decreasing fasting serum (fS)–C-peptide concentrations (P = 0.015).

The LADA patients had higher BMI and lipid concentrations than the T1D_{>35y} patients (online appendix Table A1). Compared with type 2 diabetic patients, LADA patients had lower insulin secretion and BMI, as well as a better lipid profile. Going from LADA_{low} to LADA_{high}, there was a significant trend toward lower insulin secretion, lipid levels, and BMI (online appendix Table A2). However, the fS–C-peptide concentration was higher in LADA_{low} patients compared with T1D_{>35y} patients and was somewhat lower in LADA_{low} compared with type 2 diabetic patients. Despite the marked age difference, the T1D_{>35y} and T1D_{<20y} patients were metabolically similar.

**CONCLUSIONS** — We have shown a significant genetic difference between LADA and type 1 diabetes diagnosed after age 35 years. Although HLA-DQB1 and PTPN22 risk genotypes were increased in LADA, they were much less common than in type 1 diabetes. INS and CTLA4 were only associated with type 1 diabetes.

As suggested previously (3, 5, 10), genetic differences and clinical phenotype were associated with GADA levels, explaining some of the observed heterogeneity within LADA. Of note, the LADA_{high} group (GADA > 278 IU/ml) roughly corresponds to the high GADA group (>300 IU/ml) in the Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study, in which association with PTPN22 was also found only in patients with high GADA (10).

Our study is the largest to date in adult-onset type 1 diabetic patients. In agreement with a smaller study (11), we clearly showed a lower frequency of DQB1 risk genotypes in T1D_{>35y} compared with T1D_{<20y} patients. However, protective HLA-DQB1 genotypes were as
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The prevalence of INS, PTPN22, and CTLA4 risk genotypes was similar in the two groups. As expected (2, 4, 10, 12–14), LADA had an increased frequency of HLA-DQB1 and PTPN22 risk genotypes as well as a decreased frequency of HLA-DQB1 protective genotypes compared with type 2 diabetic subjects. Contrary to previous reports (4, 14, 15), the INS variant was not associated with LADA in the Finnish subjects.

In conclusion, we have shown that patients with LADA differ genetically and phenotypically from type 1 diabetic patients diagnosed after age 35 years. The LADA group was heterogeneous, and both the genotype distribution and phenotypic characteristics were associated with GADA level. A significant trend was observed toward lower insulin secretion and metabolic trait values going from the lowest GADA quartile to the highest. Thus, LADA patients with high GADA concentrations were more similar, but not identical, to type 1 diabetic patients, and those with low GADA concentrations were more similar to type 2 diabetic patients.

References

1. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R. UKPDS 25. Autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet 1997;350:1288–1293

2. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehrnstrom BO, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999;48:150–157

3. Buzzetti R, Di Pietro S, Giaccari A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigaluppi E, Dotta F, Bosi E, Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. Diabetes Care 2007;30:932–938

4. Cervin C, Lyssenko V, Bakhtadze E, Lindholm E, Nilsson P, Tuomi T, Cilio CM, Groop L. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes 2008;57:1433–1437

5. Pettersen E, Skorpen F, Kvaløy K, Forsblom C, Saloranta C, Taskinen MR, Groop LC. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999;48:150–157

6. Buzzetti R, Di Pietro S, Giaccari A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigaluppi E, Dotta F, Bosi E, Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. Diabetes Care 2007;30:932–938

7. Gale EA. Latent autoimmune diabetes in adults: a guide for the perplexed. Diabetologia 2005;48:2195–2199

8. Lundgren VM, Isomaa B, Lyssenko V, Laurila E, Korhonen P, Groop LC, Tuomi T, Botnia Study Group. GAD antibody positivity predicts type 2 diabetes in an adult population. Diabetes 2010;59:416–422

9. Sjöroos M, Ittia A, Ilonen J, Reijonen H, Lövgren T. Triple-label hybridization assay for type-1 diabetes-related HLA alleles. BioTechniques 1995;18:870–877

10. Petrone A, Suraci C, Capizzi M, Giaccari A, Bosi E, Tiberti C, Costes E, Pozzilli P, Falorni A, Buzzetti R, NIRAD Study Group. The protein tyrosine phosphatase nonreceptor 22 (PTPN22) is associated with high GAD antibody titer in latent autoimmune diabetes in adults: Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study. Diabetes Care 2008;31:534–538

11. Caillat-Zucman S, Garchon HJ, Timsit J, Assran A, Boutilier D, Djilali-Salah I, Bougherères P, Bach JF. Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. J Clin Invest 1992;90:2242–2250

12. Hossztulasi N, Vatay A, Rajczy K, Prohásza Z, Pozsonyi E, Horváth A, Grosz A, Gerő L, Madácsy L, Romics L, Karádi I, Füst G, Pánczel P. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. Diabetes Care 2003;26:452–457

13. Desai M, Zeggini E, Horton VA, Owen KR, Hattersley AT, Levy JC, Walker M, Gillespie KM, Bingley PJ, Hitman GA, Holman RR, McCarthy MI, Clark A. An association analysis of the HLA gene region in latent autoimmune diabetes in adults. Diabetologia 2007;50:68–73

14. Haller K, Kisand K, Pisarev H, Salur L, Laisk T, Nemvalts V, Uibo R. Insulin gene VNTR, CTLA-4 +49A/G and HLA-DQB1 alleles distinguish latent autoimmune diabetes in adults from type 1 diabetes and from type 2 diabetes group. Tissue Antigens 2007;69:121–127

15. Desai M, Zeggini E, Horton VA, Owen KR, Hattersley AT, Levy JC, Hitman GA, Walker M, Holman RR, McCarthy MI, Clark A. The variable number of tandem repeats upstream of the insulin gene is a susceptibility locus for latent autoimmune diabetes in adults. Diabetes 2006;55:1890–1894

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