
Type 1 and Type 2 Diabetes

What Do They Have in Common?

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Type 1 and type 2 diabetes frequently co-occur in the same families, suggesting common genetic susceptibility. Such mixed family history is associated with an intermediate phenotype of diabetes: insulin resistance and cardiovascular complications in type 1 diabetic patients and lower BMI and less cardiovascular complications as well as lower C-peptide concentrations in type 2 diabetic patients. GAD antibody positivity is more common in type 2 diabetic patients from mixed families than from common type 2 diabetes families. The mixed family history is associated with more type 1-like genetic (HLA and insulin gene) and phenotypic characteristics in type 2 diabetic patients, especially in the GAD antibody-positive subgroup. Leaving out the extreme ends of diabetes phenotypes, young children progressing rapidly to total insulin deficiency and strongly insulin-resistant subjects mostly with non-European ethnic origin, a large proportion of diabetic patients may have both type 1 and type 2 processes contributing to their diabetic phenotype. *Diabetes* 54 (Suppl. 2):S40–S45, 2005

Diabetes in most cases is caused by a loss of the physical or functional β -cell mass, mostly due to an autoimmune process (type 1 etiological process) and/or increased need for insulin due to insulin resistance (type 2 process) (1). Both of these major diabetes types are believed to include different stages of disease, ranging from non-insulin-requiring to insulin-requiring for control or survival. According to this classification adopted by the World Health Organization, it is quite possible that both processes would operate in a single patient and contribute to the phenotype of the patient. Also, factors other than autoimmunity can lead to a defective insulin response to glucose. Both major diabetes types are considered multifactorial diseases with several predisposing genetic and environmental factors, some of which could be common to both types. In populations with a high prevalence of type 1 diabetes, like in Finland, a large proportion of patients with type 2 diabetes should have inherited susceptibility genes for both types of dia-

betes. Also, the lifestyle changes leading to the type 2 diabetes epidemic around the world (2) may have an impact on the clinical picture of type 1 diabetes in the subjects at risk for type 2 diabetes as well. Indeed, obesity has been shown to be a risk factor for childhood type 1 diabetes (3–6). According to the “accelerator hypothesis,” there are two accelerators precipitating disease in all types of diabetes: the intrinsically high rate of β -cell apoptosis and insulin resistance resulting from weight gain and physical inactivity. In addition, a third accelerator, β -cell autoimmunity, would enhance the diabetic process in a subset (7). The aim of this article is to review the data on genetic interaction between type 1 and type 2 diabetes and its clinical consequences for especially type 2 diabetes.

FAMILIAL CLUSTERING OF TYPE 1 AND TYPE 2 DIABETES

Several studies have reported an increased frequency of type 2 diabetes in families with type 1 diabetes (8–13). In Sweden, 32% of patients with type 1 diabetes reported a family history of type 2 diabetes compared with 12.5% in a nondiabetic reference group (8). The true prevalence is difficult to ascertain, because most patients are diagnosed with type 1 diabetes at an age when their parents, or grandparents, might still be too young to have developed type 2 diabetes. Also, reliable age-adjusted prevalence data for type 2 diabetes in the general population is rarely available. Of note, a parental history of type 2 diabetes was associated with an increased risk of type 1 diabetes in sibs of type 1 diabetic patients (14,15).

In accordance with the above, frequent occurrence of type 1 diabetes in relatives of patients with type 2 diabetes has also been observed (16–19). A total of 14% of Finnish families with more than one type 2 diabetic patient also included type 1 diabetic patients, and 5% of the type 2 diabetic probands had a first-degree relative with type 1 diabetes (19). This is clearly increased compared with the overall 0.5 to 1% prevalence of type 1 diabetes in Finland.

PHENOTYPIC CONSEQUENCES OF THE FAMILIAL CLUSTERING

The consequence of such genetic admixture for type 1 or type 2 diabetes is not known, but the existing data suggest that patients with double genetic predisposition have an intermediate phenotype. Family history for type 2 diabetes is associated with insulin resistance and cardiovascular complications in type 1 diabetic patients. In the Epidemiology of Diabetes Complications Study, the best predictors of insulin resistance in type 1 diabetes were an elevated waist-to-hip ratio, the presence of hypertension, HbA_{1c} level, and family history of type 2 diabetes (20). Family history of type 2 diabetes was a significant risk factor for coronary artery disease (13), and parental type 2 diabetes

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GADA, autoantibody to GAD; LADA, latent autoimmune diabetes in adults; VNTR, variable number of tandem repeats.

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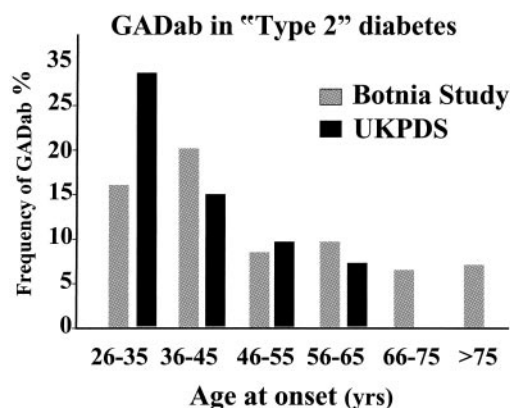


FIG. 1. Positivity (%) for GAD antibodies (GADab) according to age at diagnosis of type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS) (28) and the Botnia studies (27).

conferred a threefold risk for nephropathy after adjustment for sex, glycemic control, and family history of hypertension (21). Furthermore, family history of type 2 diabetes and/or hypertension predicted progression of carotid intima-media thickness in a 10-year follow-up study of type 1 diabetic patients, who at baseline were ~21 years old with diabetes duration of 12 years (22). Preliminary data from the FinnDiane Study showed that according to the National Cholesterol Education Program criteria for metabolic syndrome, one-third of normoalbuminuric type 1 diabetic patients had metabolic syndrome, and 14% fulfilled more than four diagnostic criteria (23).

Mixed family history has the opposite effect with respect to the phenotype of type 2 diabetes. Family history of type 1 diabetes was negatively associated with coronary artery disease in relatively young (<60 years of age) type 2 diabetic patients, and patients with such family history were leaner than those with family history for type 2 diabetes only (24). Also, type 2 diabetic patients with the type 1-associated HLA-DR4 allele had a lower cardiovascular mortality rate than DR4⁻ patients (25). Overall, the patients with mixed family history also had lower serum C-peptide concentrations, but this largely depended on the high frequency of circulating autoantibodies to GAD (GADAs) in this group, whereas the BMI and coronary artery disease association was present also in GADA⁻ patients (24). The frequency of GADA positivity was 18% among type 2 diabetic patients with mixed family history compared with 8% among patients with only type 2 diabetes family history (19). Thus, family history of type 1 diabetes could contribute to the heterogeneity observed in GADA⁺ patients (26).

LATENT AUTOIMMUNE DIABETES IN ADULTS

In two population-based studies, our Botnia study (27) and the much larger U.K. Prospective Diabetes Study (28), GADAs were present in 15–35% of patients diagnosed with type 2 diabetes at an age younger than 45 years, and in ~7–9% of older patients (Fig. 1). We called this subgroup latent autoimmune diabetes in adults (LADA) (29) and suggested a definition based on circulating GADAs, age at diagnosis of diabetes ≥ 35 years, and no treatment with insulin during the first year after diagnosis (27). According to this definition, excluding studies selecting for lean, young-onset, or insulin-treated patients as well as hospital-based studies, the prevalence of LADA is ~4.2–13.2% among Caucasians of mainly Anglo-Celtic or Scandinavian

ancestry (28–31) and 10.2% in African-Americans (31), but lower in Japanese (1.1% [32]) and possibly in Italians (2% [33]) and Australians with Southern European ancestry (1.7% [30]).

Clinically, LADA is a heterogeneous group and the mean concentration of GADAs is lower than in individuals diagnosed with type 1 diabetes (34). When subjects commencing permanent insulin treatment during the first year after diagnosis are excluded, ~50–60% of LADA patients compared with 2% of antibody-negative patients develop marked insulin deficiency during the 6–10 years from diagnosis (28,35). The progression of insulin deficiency seems to be associated with younger age at onset, high levels of GADAs, and positivity for multiple autoantibodies; this group may also have other endocrine autoantibodies (27,28,36,37). On the other hand, half of the patients with LADA will never need treatment with insulin and only have a mild deterioration of their maximal insulin secretory capacity compared with GADA⁻ patients (38). However, compared with GADA⁻ patients, they have less evidence of the metabolic syndrome (slightly lower BMI, better blood pressure levels, less dyslipidemia) (27,39). It could be speculated that because of the subclinical deterioration in β -cell function, a lower degree of insulin resistance precipitates diabetes in LADA compared with common type 2 diabetes (26).

IS THERE A COMMON GENETIC PREDISPOSITION?

HLA class II genes. The *IDDM1* locus in the HLA class II region on chromosome 6p21 is strongly linked to type 1 diabetes (logarithm of odds score 65.8 [40,41]). It is considered to explain 42% of the familial risk for type 1 diabetes (40). The risk associated with an HLA genotype is defined by the combination of susceptibility and protective alleles of especially DQB1, DQA1, and DRB1 genes (rev. in 42). The susceptibility DQB1 alleles 02 and 0302 were found in 49.6 and 71.1%, respectively, of Finnish type 1 diabetic patients ($n = 560$) compared with 25.5 and 20.6% of control subjects ($n = 10,541$). The protective alleles 0301 and 0602 (3) were found in 7.7 and 6.6% of patients compared with 21 and 42.2% of control subjects (42). Thus, at least one-third of the population in Finland carries at least one susceptibility allele.

Excess transmission of DR4-linked haplotypes from parents with type 2 diabetes to offspring with type 1 diabetes has been reported (43). Also, some studies have reported an increased frequency of HLA-DR4 or HLA-DR3/DR4 in patients with type 2 diabetes (44–47). However, this increase seems to be mainly restricted to patients with relative insulin deficiency or islet cell antibodies (ICAs) and/or GADAs (27,44,47). Patients with LADA have an increased frequency of the type 1-associated susceptibility HLA alleles DQB1*0302 and 02 (27,47), but the family history of type 1 diabetes could be a confounding factor. As mentioned earlier, patients with LADA have family history of type 1 diabetes more often than other phenotypically type 2 diabetic patients. Figure 2 shows the DQB1 genotype data in the Botnia study in patients diagnosed with classic type 1 diabetes and in subgroups of patients diagnosed with type 2 diabetes according to the presence of GADAs and mixed family history. Only data for adult-onset type 1 diabetes is included, because of previously published genotype differences between young-onset and adult-onset type 1 diabetes (rev. in 26). The type 2 diabetic patients from the mixed families shared an increase in the

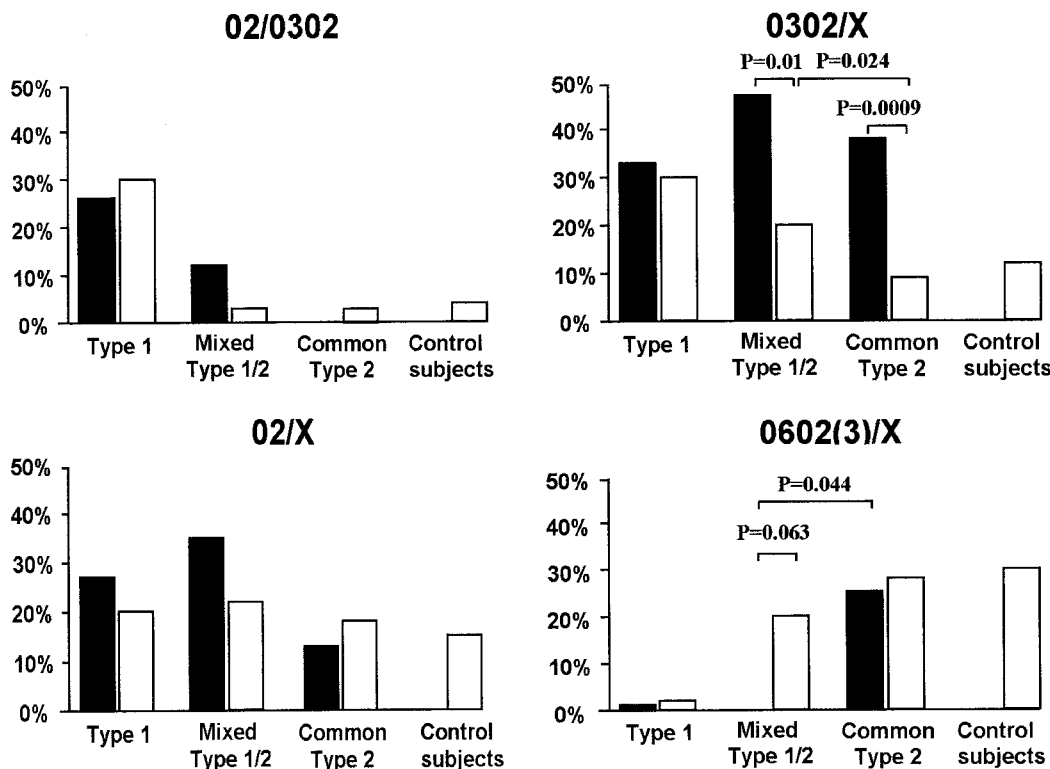


FIG. 2. The HLA-DQB1 genotype frequency in the Botnia study in patients diagnosed with type 1 diabetes in adult age, in subgroups of patients diagnosed with type 2 diabetes according to family history for both type 1 and type 2 diabetes (mixed type 1/2) or for type 2 only (common type 2), and in control subjects without family history for diabetes. ■, GAD antibody-positive patients; □, GAD antibody-negative patients. Adapted from Li et al. (19). © 2001, The Endocrine Society.

moderate-risk HLA-DQB1*0302/X genotype with the adult-onset type 1 diabetic patients (Fig. 2 [19]). Because they were relatives of type 1 diabetic patients, this was not unexpected. However, similar sharing of the genotype conferring the highest risk (02/0302) or absence of the genotype conferring protection [0602(3)/X] was not observed except for the GADA⁺ subgroup of patients from the mixed families. Thus, among the LADA patients, only those from type 1 diabetic families share the 02/0302 and 0602(3) association with type 1 diabetic patients, whereas all LADA patients share the 0302/X association. This finding suggests that part of the observed heterogeneity among the LADA patients could be ascribed to type 1 diabetes family history.

However, the effect of type 1 diabetes family history on the diabetic phenotype is not restricted to the GADA⁺ group, as mentioned earlier. Sharing type 1 diabetes-associated risk HLA haplotype with a type 1 diabetic relative was associated with impaired insulin secretion in response to oral glucose in type 2 diabetic patients. However, no such effect was seen in type 2 diabetic patients who had similar risk haplotypes without type 1 diabetic relatives, suggesting that other genes on the short arm of chromosome 6 need to be shared (19). All in all, these data point at a genetic interaction between type 1 and type 2 diabetes that could be mediated by the HLA locus or a nearby gene.

Insulin gene. A variable number of tandem repeats (VNTR) polymorphism in the insulin gene promoter affects the transcription level of insulin and insulin-like growth factor II genes (48–50). The VNTR is highly variable with respect to both number and sequence of the repeats. In Caucasians, the length distribution is bimodal with 75% of short (class I) and 25% of long alleles (class III) (51). Intriguingly, the VNTR has been associated with both type 1 and type 2 diabetes. Linkage to this region on chromosome 11p15 (40,41) and an increased frequency of either

two class I alleles (Caucasians [48]) or two short class I alleles (Japanese [52]) has been shown in type 1 diabetes in several populations. The effect of the insulin gene on type 1 diabetes risk seems to be strongest in the subjects carrying moderate- or low-risk HLA genotypes, although it is detectable in all HLA risk categories (53,54).

On the other hand, class III alleles might be associated with hyperinsulinemia, high body mass, and type 2 diabetes, but the data are controversial. A meta-analysis of small case-control studies suggested an increased frequency of class III homozygosity among the type 2 diabetic patients compared with control subjects (relative risk 1.4, $P < 0.037$) (55,56). In a population-based follow-up study from the U.K., class III homozygosity increased the risk for type 2 diabetes in women (hazard ratio 4.25; 95% CI 1.76–10.3), but not in men (57). An increased transmission of paternal class III alleles to affected offspring was seen in British patients with type 2 diabetes (58) or polycystic ovary syndrome (59), but not in Scandinavian type 2 diabetic patients (60). Moreover, class III alleles have been associated with high insulin concentrations and/or increased body mass in morbidly obese women (61) and patients with polycystic ovary syndrome (62), as well as with high birth weight and high rate of weight gain after birth (63). However, childhood obesity was associated with class I alleles and their paternal transmission (64,65). In pigs, the syntenic region was linked to paternally inherited quantitative trait loci affecting muscle and fat mass (66,67).

Except for the study of Huxtable et al. (58), in which GADA⁺ subjects were excluded, the effect of admixture of late-onset type 1 diabetes or family history of type 1 diabetes has not been studied. We examined the association between the insulin VNTR and type 2 diabetes and its sub-phenotypes, taking into account the potential of a simultaneous family history of type 1 diabetes, in 679 unrelated patients with type 2 diabetes, 148 patients with young-onset (<20 years), and 131 patients with adult-

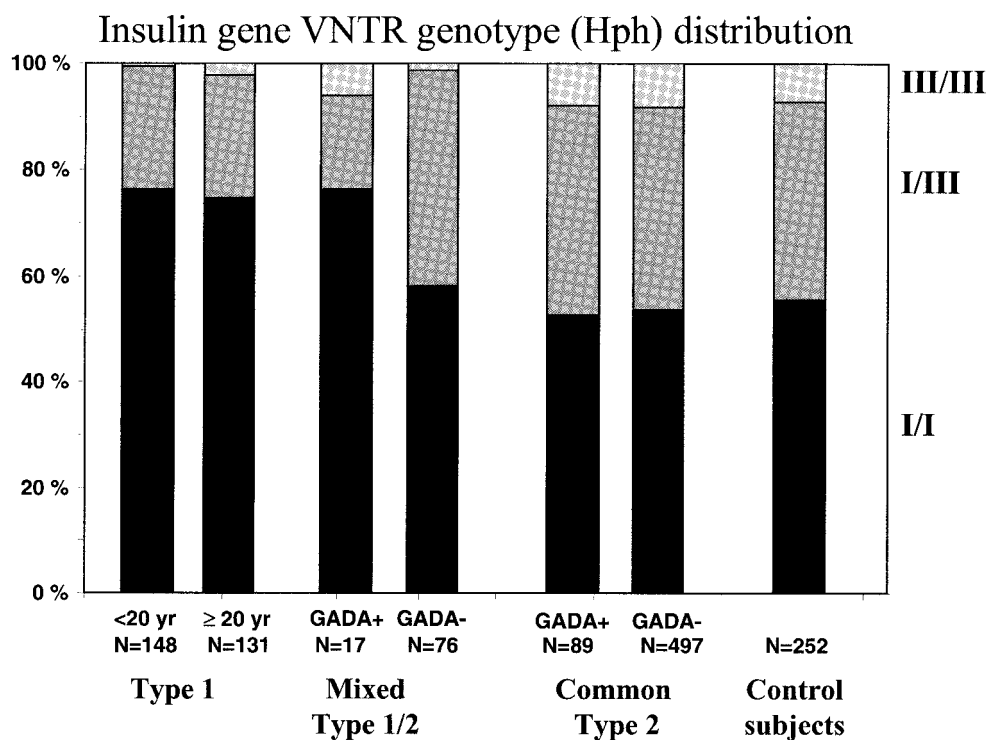


FIG. 3. The insulin gene *HphI* polymorphism genotype frequency in patients diagnosed with type 1 diabetes before or after the age of 20 years, in subgroups of patients diagnosed with type 2 diabetes according to family history for both type 1 and type 2 diabetes (mixed type 1/2) or for type 2 only (common type 2), and in control subjects without family history for diabetes.

onset (≥ 20 years) type 1 diabetes and 252 nondiabetic control subjects from the Botnia study. The type 2 diabetic patients included 93 patients who had type 1 diabetic relatives (mixed type 1/2 diabetes) (24) as well as 89 GADA⁺ (27) and 497 GADA⁻ patients (60,27) without family history for type 1 diabetes (common type 2 diabetes). As shown in Fig. 3, the type 1 diabetic patients were more often homozygous for the VNTR class I-associated *HphI* allele (76%) than the control (56%) or common type 2 diabetic subjects, irrespective of GADA positivity (53%, $P = 0.0001$). The type 2 diabetic patients with mixed family history had an intermediate frequency (61.3%). An increased frequency of the class I-associated allele was found in the U.K. Prospective Diabetes Study (47), but not in our Finnish LADA patients (27). However, the GADA⁺ mixed patients had a comparable I/I genotype frequency (76%) than the adult type 1 diabetic patients (75%), whereas the GADA⁻ mixed patients (58%) differed less from the GADA⁻ common type 2 diabetic patients (54%). Obviously, larger numbers of mixed patients are needed to statistically test this difference. It is possible that some of the discrepancies in the literature concerning the association between LADA and insulin VNTR reflect the degree of type 1 diabetes family history in the series.

The *HphI* genotype was not associated with any clinical parameters in the control, type 1 diabetic, or mixed type 2 diabetic subjects, but the small number of class III/III homozygous patients precluded their separate analysis. Although we did not find an excess of class III/III in type 2 diabetes, our data supported an association between class III alleles and body mass and insulin concentration in males but not in females. The class III allele was significantly associated with high BMI [I/I vs. I/III vs. III/III: 27.5 (5.3) vs. 28.6 (4.9) vs. 31.6 (6.6) kg/m², $P = 0.002$] and fat-mass [24.5 (7.1) vs. 27.2 (7.6) vs. 27.4 (8.9)%, $P = 0.001$]. Men with class III alleles had higher fasting insulin concentrations than those with only class I alleles [11.1 (8.9) vs. 8.7 (8.3) mU/l, $P = 0.009$] and they were also more

insulin resistant [homeostasis model assessment for insulin resistance: 4.71 (4.64) vs. 3.12 (4.22), $P = 0.012$].

Together with previous data in nondiabetic subjects (61–67), these results support a role for the insulin gene VNTR in affecting body mass and insulin sensitivity. However, although our study and some other studies have advocated class III alleles to be associated with high in vivo insulin concentrations (61–63), others have shown this association for class I alleles (64,65). Moreover, in vitro, class I leads to higher expression of insulin than class III does. More studies in much larger carefully phenotyped groups and functional data are needed to solve these discrepancies.

WHERE TO GO NEXT

Except for the HLA locus, major genes contributing to diabetes have not been revealed. The common variant-common disease hypothesis assumes that common single nucleotide polymorphisms (frequency >10% in the population) increase susceptibility to a polygenic disease like type 2 diabetes, but that these variants act in concert with environmental factors. During recent years, several variants have been identified in genes that increase the risk of type 2 diabetes, e.g., in the *PPAR γ* , *calpain 10*, and *Kir 6.2* genes (60,68–70). Considering the data that are emerging on familial clustering of type 1 and type 2 diabetes, many of the minor genes are expected to contribute to features common to both types of diabetes. To solve this puzzle, it will be imperative to collect careful phenotypic data on all types of patients to allow stratification for various subphenotypes in the analyses.

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