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Genetics of type 1 diabetes in Asian and Caucasian populations

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Abstract

Among candidate genes for type 1 diabetes, *HLA*, *INS*, *CTLA4*, *PTPN22* and *SUMO4* have been shown to be associated with the disease in Caucasian populations. To clarify the similarities and differences in the contribution of these genes to type 1 diabetes between Asian and Caucasian populations, association of these genes with type 1 diabetes was studied in a large number of samples in Japanese and Korean populations. Class II HLA was strongly associated with type 1 diabetes in both Asian and Caucasian populations, but haplotypes associated with type 1 diabetes were markedly different due to difference in the presence and absence of haplotypes in each population. *INS* was consistently associated with type 1 diabetes in both Japanese and Caucasian populations, but frequency of disease-associated haplotype was markedly high in Japanese general population. *CTLA4* was associated with type 1 diabetes only in a subset of patients with type 1 diabetes complicated with AITD in Japanese. A variant (R620W) of *PTPN22* was associated with type 1 diabetes and other autoimmune diseases in Caucasians, but the variant was absent in Asians. *SUMO4* was associated with type 1 diabetes in Asians, but not in Caucasian, suggesting a genetic heterogeneity among diverse ethnic groups. Trans-racial study with a large number of samples in both Asian and Caucasian populations will contribute to genetic dissection of type 1 diabetes and identification of causative variants.

Keywords: Type 1 diabetes; Genetics; Autoimmune disease; HLA; *INS*; *CTLA4*; *PTPN22*; *SUMO4*

1. Introduction

Type 1 diabetes is divided into two subtypes, autoimmune and idiopathic. Etiology and pathogenesis of idiopathic type 1 diabetes is yet to be identified, but recent studies suggested that a rare subtype of type 1 diabetes, termed fulminant type 1 diabetes, appears to belong to this subtype. Most type 1 diabetes is thought to be autoimmune in etiology, caused by autoimmune destruction of insulin-producing beta cells of the pancreas in genetically susceptible individuals. Autoimmune type 1 diabetes is a multifactorial disease caused by complex interaction of genetic and environmental factors, with the former consisting of multiple susceptibility genes. Among multiple susceptibility genes, at least four genes, i.e. *HLA*, *INS*, *CTLA4* and *PTPN22*, have been repeatedly shown to be associated with type 1 diabetes in Caucasian populations [1–5]. In addition, recent studies suggested that *SUMO4* is responsible for *IDDM5* mapped on chromosome 6q25 [6]. In Asian population, however, contribution of these genes to type 1 diabetes is yet to be clarified. To clarify the similarities and differences in the contribution of

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these genes to type 1 diabetes susceptibility between Asian and Caucasian populations, we studied the association of these genes with type 1 diabetes in Japanese and Korean populations in comparison with Caucasian populations.

2. Type 1 diabetes cluster in families in Japanese as well as in Caucasian populations

In Caucasian populations, life-time risk in siblings of type 1 diabetic probands is much higher than that in general populations (6% versus 0.4%, λs 15) [7], indicating that type 1 diabetes clusters in families. It is difficult to study familiar clustering of type 1 diabetes in Asian populations because of a limited number of multiplex families with type 1 diabetes due to low incidence of type 1 diabetes [8]. We therefore performed a nation-wide survey on multiplex families with type 1 diabetes, and found a high frequency of type 1 diabetes in siblings of diabetic probands (3.8%) (Table 1) [9], which is similar to that in Caucasian populations. Studies from different data sources confirmed much higher frequencies of type 1 diabetes in siblings of diabetic probands than in general populations in Japan (1.3–3.8% versus 0.01–0.02%, λs >65) (Table 1), indicating that type 1 diabetes clusters in families in Japan.

3. Establishment of Japanese Study Group on Type 1 diabetes genetics, a multi-center collaborative study group

Large-scale studies with sufficient statistical power are necessary in identifying disease-causing variants with a modest effect, as is evidenced by recent progress in identification of susceptibility genes for type 1 diabetes by large-scale studies in Caucasian populations [4]. In Asian populations, however, no such study has been performed because of the very low incidence (less than 1/10 of that in Caucasians) of type 1 diabetes in Asian countries [8]. To overcome this, we assembled a multi-center study group ''the Japanese Study Group on Type 1 Diabetes Genetics'', in which each member had experience in genetic association studies on type 1 diabetes and had previously collected moderate number of samples (200–300) from cases and controls [10]. To date, a total of >1500 samples from type 1 diabetic patients and control subjects were accumulated for the collaborative effort, and large-scale case-control association studies on several candidate genes have been completed ([10–12], A. Shimada et al., submitted).

4. Candidate genes for type 1 diabetes in Asian populations

4.1. HLA (IDDM1)

Despite the well established contribution of HLA locus to type 1 diabetes susceptibility across different ethnic groups, alleles and haplotypes conferring susceptibility to type 1 diabetes are markedly different among different ethnic groups. In contrast to the strong positive association of DR3 (*DRB1*0301-DQB1*0201*) and DR4 (*DRB1*0401-DQB1*0302*) haplotypes with type 1 diabetes in Caucasian populations [1,9], DR4 (*DRB1*0405-DQB1*0401*) and DR9 (*DRB1*0901-DQB1*0303*) haplotypes are associated with the disease in Japanese [2,13]. The differences in haplotypes associated with type 1 diabetes in Japanese and Caucasian populations can be explained by the difference in the presence or absence of haplotypes in each population. Disease-associated DR3 and DR4 haplotypes in Caucasians are almost absent in Japanese, whereas Asian-specific DR4 and DR9 haplotypes are very rare in Caucasian populations (Table 2). The haplotypes absent in each population cannot contribute to the disease susceptibility simply because the absence of subjects possessing the haplotypes. Only haplotypes present with substantial frequencies can contribute to the disease susceptibility in each population. In fact, a DR2 haplotype (*DRB1*1501-DQB1*0602*), which is present in both populations with substantial frequencies, shows consistently negative association with type 1 diabetes in both populations (Table 2). Thus, differential association of HLA haplotypes with type 1 diabetes among different ethnic groups can be explained by the difference in the presence or absence of haplotypes in each population.

In Caucasian populations, combination of DR3 and DR4 haplotypes in heterozygous form (DR3/4) has been shown to confer particularly strong susceptibility to type 1 diabetes. To determine genotypes conferring strong susceptibility to type 1 diabetes in Japanese, we studied the impact of genotypic combination of HLA haplotypes in Japanese [13]. DR4 (*DRB1*0405-DQB1*0401*) haplotype conferred susceptibility to type 1 diabetes in either homozygous (DR4/4) or heterozygous (DR4/X) states [13]. In contrast, DR9 (*DRB1*0901-DQB1*0303*) haplotype conferred very strong susceptibility to type 1 diabetes when present in the homozygous state (DR9/9, odds ratio 23.1), but not in the heterozygous state (DR9/Y, odds ratio 1.0) [13]. Strong susceptibility conferred by DR9 homozygote was confirmed in Korean population (odds ratio 13.3)