Vitamin D receptor initiation codon polymorphism influences genetic susceptibility to type 1 diabetes mellitus in the Japanese population

ABSTRACT

Our findings suggest that the vitamin D receptor initiation codon polymorphism influences genetic susceptibility to T1DM among the Japanese. This polymorphism is also associated with GAD65-Ab-positive T1DM, although the absence of a significant difference between GAD65-Ab-negative patients and controls might be simply due to the small sample size of patients tested for GAD65 antibodies.

INTRODUCTION

Background Type 1 diabetes mellitus (T1DM) is a multifactorial disease with a strong genetic component. The main genetic contribution to T1DM susceptibility lies in the major histocompatibility complex (MHC) on the short arm of chromosome 6; several non-MHC chromosomal regions are also involved. Several approaches have been used to identify T1DM susceptibility regions, including case-control studies of candidate genes [human leukocyte antigen (HLA), insulin gene regulatory region, interleukin-1 receptor type 1 (ILIR1)], combined linkage and association-based studies of candidate genes [cytotoxic T lymphocyte associated-4 (CTLA-4)], and systematic total genome searches in addition to analyses of individual chromosomal regions. There are clear differences in immunogenetic predisposition to T1DM between countries, and disease incidence seems to vary along with these differences in predisposition. The incidence of T1DM in Southern India (10.4/100000 cases per year) is similar to that in Asian children in the UK and Caucasian children of European extraction. While an MHC component is apparent in T1DM susceptibility in Southern India, no association with either the insulin gene or ILIR1 has been found there in case-control studies. This suggests possible differences in the non-MHC T1DM component between Southern Indians and Caucasians of European extraction. In the latter population, an association with the insulin gene has been universally reported, and an IL1R1 association with T1DM has been reported in some Northern Europeans. VDR gene polymorphisms influence susceptibility to osteoporosis, primary hyperparathyroidism, and autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, and multiple sclerosis. Allelic variation in VDR also influences susceptibility to T1DM in Indian Asians, Germans, and Taiwanese. There are six known polymorphisms in the VDR locus: an exon 2 initiation codon polymorphism, which is detected with FokI restriction enzyme, the BsmI, Tru9I, and ApaI restriction fragment length polymorphisms (RFLPs) located between exons 8 and 9, the TaqI RFLP located in exon 9, and a poly A polymorphism downstream of the 3' untranslated region. There is apparently no significant linkage disequilibrium between the FokI polymorphism and the BsmI, ApaI, and TaqI polymorphisms. In this study, we analyzed the exon 2 initiation codon (VDR-FokI) gene polymorphism in Japanese patients with T1DM. We also investigated associations between this VDR polymorphism and GAD65 antibody (Ab) status, an immune marker.

CONCLUSION

Conclusions In conclusion, our data indicates an association between the VDR gene and T1DM among the Japanese. We suggest that the FF genotype may predispose Japanese individuals to T1DM and that this genotype appears to be a marker for T1DM. The role of the VDR gene

polymorphism should be studied further in other populations, and other polymorphisms, such as the BsmI, ApaI, Tru9I and TaqI polymorphisms, should be analyzed for association with T1DM susceptibility. In addition, the VDR-FokI polymorphism showed a possible association with GAD65-Ab-positive T1DM. The VDR plays a role in lymphocyte response to microorganisms (tuberculin reactive status in pulmonary tuberculosis, leprosy etc.). Thus, it is conceivable that it may also be involved in immune response to self antigens e.g. GAD65 antibodies.