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Original Research Paper

Olfactory Receptor Gene is a Possible MHC-linked Gene

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ABSTRACT

Background: Type 1 diabetes is one of the fastest growing non-communicable diseases worldwide. A single nucleotide polymorphism in the Olfactory Receptor family 14, subfamily J, and member 1 gene in the neighborhood of human leukocyte antigen-F has been shown to be significantly associated with type 1 diabetes. Methods: In order to confirm the latter finding, we studied the olfactory receptor gene in a case-control study comprising of 984 cases and 576 controls of European Caucasoid origin. Case and control subjects were genotyped for OR14 gene adjacent to HLA-F region, major histocompatibility complex-X, gene using Taqman SNP genotyping, Applied Biosystems. Results: The current results showed that the OR14-CC genotype is most significantly associated with the disease, p=0.001, and Odds Ratio=0.43. Furthermore, the -AC genotype showed a higher difference among cases than controls, p=0.02, and Odds Ratio=1.28. The OR14 gene did not show any substantial gender specificity association. Conclusion: These findings confirm our previous study, which showed a significant correlation between the OR14 gene and type 1 diabetes. The extension of such studies in this particular region is highly recommended. Different factors, including pathologic variables and co-morbidities, can help to recognize the pathophysiology of olfactory dysfunction with regard to OR14 gene variation in diabetic patients.

Keywords: Autoimmune diseases, Olfactory Receptor Gene, Type 1 diabetes, MHC-X gene, T1D

INTRODUCTION

The prevalence of type 1 diabetes (T1D) is increasing at an alarmingly high rate, and its burden is among the fastest growing diseases worldwide [1,2]. The International Diabetes Federation estimated that more than 415 million people worldwide had diabetes in 2015, and this number is likely to reach 642 million by 2040, which indicates that the incidence of T1D might have reached 41.8 million by 2015 and will reach 64.2 million by 2040, the incidence of T1D accounts for 10% of total diabetes [3,4].

T1D, which develops as a result of autoimmune destruction of insulin-producing β cells, has a strong genetic component, this is evidenced by the fact that monozygotic twins have a strong disease concordance [5,6], with the human leukocyte antigen (HLA) loci having the greatest impact [7,8]. In addition, genes outside the major histocompatibility complex (MHC) region have been associated with the onset of T1D [6-11].

Early studies have reported the presence of 'smell' dysfunction in patients with diabetes mellitus, which was also associated with degenerative complications [12]. Since then, a relationship between olfactory impairment and a variety of diseases have emerged; these include pulmonary, heart, and autoimmune diseases, as well as those associated with the central nervous system [13-15]. In addition, more recent data from animal models have shown that the presence of 'smell' impairment and autoimmune deregulations (via specific autoantibodies) are intimately associated with neuropsychiatric manifestations [16]. In this regard, the olfactory receptor (OR) gene has been confirmed to be associated with the aforementioned diseases which suggest an important role for OR (in addition to smell) in the central nervous system [17]. Furthermore, previous studies have indicated the presence of a significant association among single

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nucleotide polymorphism (SNP) in the OR genes which link autoimmunity, psychiatric disorders, and smell impairment [18-20].

OR14 has been found on chromosome 6 in proximity to the HLA-F gene, which is highly polymorphic [21,22]. This proximity of the OR14 gene to the polymorphic region of HLA gives it a unique nature among all other ORs around the body [6,21], particularly in the context of T1D. In support of this notion, an interesting haplotype-specific association between T1D and OR14 gene polymorphism has been reported [6]. Furthermore, the OR14 gene has been clinically associated with diabetic nephropathy [23], which may suggest an epigenetic phenomenon of the gene. The current case-control study aims to confirm our current understanding of the significance of the OR14 gene in T1D using European Caucasoid large case-control subjects.

MATERIALS AND METHODS

This study comprised of 984 cases of Europid Caucasian with T1D defined by the UK National Diabetes Data Group [24] and 576 healthy controls from the same ethnicity, Table 1. In order to investigate association, rather than the well-known DR/DQ susceptibility to diabetes, all subjects were stratified conditionally for the above haplotype as previously described [6]. The cases and controls were genotyped for rs9257691 using Taqman™ SNP typing technology, Applied Biosystems.

Table 1: Characteristics of subjects

Subject	Gender	Number
Case	Male	432
Case	Female	552
Control	Male	275
Control	Female	301

Distribution and frequency of male vs female case and control as well as their age category

High molecular weight DNA was prepared from 5 to 10mLof EDTA-peripheral blood by using a Nucleon kit, Scot lab, Paisley. In order to amplify the OR14 gene polymorphism of the OR14, the Taqman™ SNP Genotyping Assay Protocol (C-2519386-10), Applied Biosystems, was used. Each reaction tube contained 1.0 µL of genomic DNA (50–150 ng), 10 µL of the assay mix, and 0.4 µL of Taq (HT Biotechnology). Tubes were mixed thoroughly and cycled in a real-time thermocycler, Bio-Rad™.

The case and control subjects were genotyped for the OR14 gene polymorphism using Taqman SNP genotyping, Applied Biosystems as discussed previously [6]. To determine whether there is a gender specificity of cases versus controls, the susceptibility of the gene in male versus female cases were examined.

Results:

All genotypic and allelic frequencies met the Hardy–Weinberg equilibrium. The association analysis of the OR SNP were performed by comparing genotype and allele frequencies in the case versus control subjects. There was a critical and significant association among the OR14-CA and -CC genotypes in cases with T1D, p=0.02, Odd Ratio=1.28 and p= 0.001, Odd Ratio =0.43 respectively, compared to normal healthy controls (Table 2).

Table 2: Frequencies of cases and controls genotype

Genotype	Cases #	Controls #	P value	Odd Ratio
CC	189	141	0.001	0.43
CA	467	269	0.02	1.28
AA	318	169	ns	-

The frequency of genotype of cases and controls is tabulated. The CC is more recurrent in cases than controls, p=0.001, Odd Ratio= 0.43. The AC also showed statistical significance, p=0.02, Odd Ratio=1.28.

There was no association between the allelic frequency of the OR14 gene in case vs control subjects. We did not observe gender specificity differences between case and control subjects.

CONCLUSION

There is accumulating evidence that confirms an important role for olfactory abnormalities in many autoimmune conditions. The highly polymorphic OR14 gene is mapped in the vicinity to HLA-F in the MHC extended region on chromosome 6 and is clustered with the HLA genes in haplotypes [6]. Interestingly, the findings of our large scale case control study suggest that the OR14-CA and -CC genotypes in the telomeric region of the HLA-F, which has been reported to be associated with T1D by our previous familial study [6], is substantially associated with T1D.

Regarding the pathophysiology of OD in diabetic patients, previous studies manifested contradictory results. Naka and co-workers concluded that there is no correlation between micro- or macroangiopathic complications of diabetes and OD. They have studied only the diabetic patients with other co-morbidities (hypo- or hyperthyroidism, chronic intake of antidepressant, antiepileptic or antirheumatic drugs, disease of the liver, kidney or central nervous system) had diminished olfactory function [25].

Obstinately, Le Floch et al associated OD with microalbuminuria ($P<0.05$) and peripheral neuropathy ($P<0.01$) and suggested a degenerative mechanism related to diabetes [12]. Besides, Weinstock et al somewhat correlated macrovascular disease with olfactory impairment [25]. Seraj et al have clearly revealed a significant difference between the olfactory threshold of diabetic and nondiabetic [27].

Our case control genetic data justifies the existence of a significant association between OR14 and T1D. We are not intending to correlate OD to T1D, however, this strong association of OR14 gene being in the vicinity of HLA-F on chromosome 6 might be a good indication and support our hypothesis and OR14 might have another effect other than smell. Perhaps, larger case and control groups considering more features including pathologic variables and co-morbidities can help to recognize the

pathophysiology of OD with regard to OR14 gene variation in diabetic patients.

Competing Interest & Data sharing

The author declare that he has no competing interests. The author is a supporter of data sharing and release from this particular research.

Written informed consent

Written informed consent was given by participants (or next of kin/caregiver in the case of children) for their clinical records to be used in this study. Patient's records/information was anonymized and de-identified prior to analysis.

ETHICAL APPROVAL

Ethical approval was obtained from Salmaniya Medical Complex Research and Ethical Committee, SMC/REC/402/23.

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The author also declare that no funding bodies had any role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

LIST OF ABBREVIATIONS

T1D- Type 1 diabetes
HLA-Human leucocyte antigen
MHC- Major Histocompatibility complex
OR- Olfactory Receptor
SNP-single nucleotide polymorphism

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