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Insulin receptor and β-adrenergic receptor gene polymorphism in Turkish population

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Genetic and enviromental factors are involved in Diabetes Mellitus's etiology. Previous studies showed that IRS-I and BAR polymorphisms have been associated with type 2 Diabetes Mellitus. In this study, we investigated IR NsiI and β3-AR Trp64Arg polymorphisms in 55 patients with Type I DM, 92 patients with Type II DM and 102 healthy controls. We observed, IR G allel in Type I Diabetic patients is higher than controls. Also β3-AR 64Arg allel is observed to be lower than control group.

Key words: Diabetes Mellitus, insuline receptor, gene polymorphism

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Introduction

Diabetes mellitus is a group of metabolic diseases characterised by hyperglisemia as a result of defects in insulin secretion, insulin effect or both. Diabetes mellitus (DM) can be divided into two groups; Type I DM and Type II DM. Genetic and enviromental factors are involved in its etiology.

Among the different genes proposed as diabetogenes, the insulin gene (INS), insulin receptor gene (INSR) and insulin receptor substrate 1 gene (IRS1) are particularly important because their encoded proteins form the insulin–insulin receptor–insulin receptor substrate 1 functional complex.[1] Figure 1 shows that schematic structure of insuline receptor. Several polymorphisms have been described in these genes, some of which have been associated with type 2 diabetes mellitus. Polymorphisms of interest in the INS gene are the MaeIII RFLP at position 216 of the first intron, and the PstI RFLP at position 1367 of the 3-untranslated region.[2,3] In the INSR gene, the MspI, FokI and RsaI polymorphisms (3313C allele, 3317T and 3443T, respectively), have a particular importance since they are located within exon 3, close to exon 2, which is the region that codes for the insulin binding site on the receptor.[4] Another polymorphism, the NsiI RFLP at exon 8, has been associated with arterial hypertension.[5] Finally, the IRS1 gene contains polymorphisms located at codon 513 (DraIII)[6] and codon 972 (BstNI),[7] which have been associated with type 2 diabetes mellitus and insulin resistance.[7,8]

The 3-BAR is a G-protein-coupled transmembrane receptor located in brown and white adipose tissue and playing a role in the regulation of thermogenesis and lipolysis in rodents;[9] stimulation of

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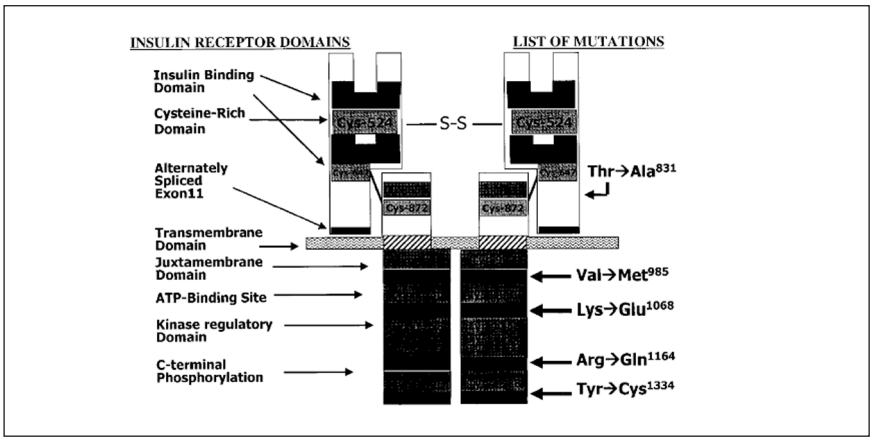

Figure 1

Schematic illustration of the human insulin receptor with map of structural domains and mutations in the insulin receptor gene (Sesti G, et al). Molecular mechanism of insulin resistance in type 2 diabetes mellitus: role of the insulin receptor variant forms. Diabetes Metab Res Rev 2001; 17: 363-73)

the 3-BAR is discussed to have an antidiabetic effect.[10] The detected mutation results in a tryptophan/arginine exchange at position 64 (Trp64Arg polymorphism) of the amino acid chain. Figure 2 shows that β3-adrenergic receptor. structure of insuline receptor. In the initial and in following studies, an earlier onset of type 2 diabetes mellitus, a higher capacity to gain weight,[11,12] a high body mass index (BMI),[13] and elevated fasting insulin levels[14] were found in homozygous carriers of the Arg64 allele in different ethnic groups. These findings prompted us to examine the prevalence of the Arg64 gene allele in a large population-based cohort in Germany and to look for possible associations with metabolic disorders such as diabetes mellitus, obesity, hypertension, and dyslipidemia.

The Arg64/Arg64 genotype of the Trp64Arg polymorphism of the 3-BAR gene has been related to obesity, insulin resistance, and/or hyperlipidemia in selected Pima Indian, Caucasian, and Japanese

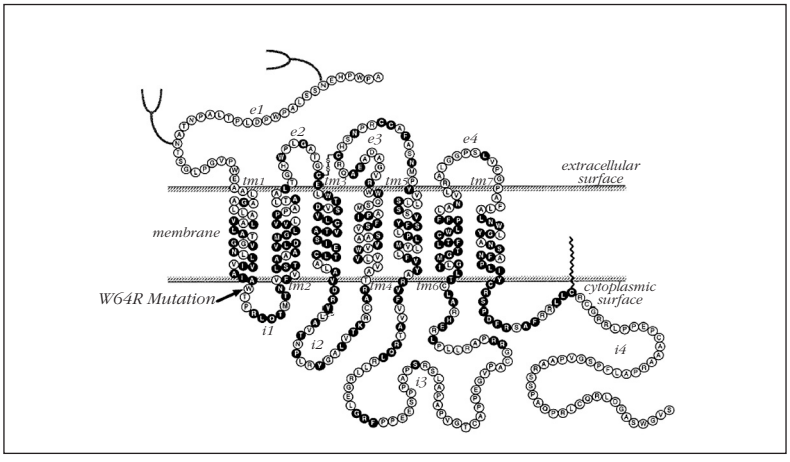

Figure 2

Structure of β3 adrenergic receptor (Strosberg AD. Structure and function of the β3-adrenergic receptor. Annu Rev Pharmacol Toxicol 1997; 37: 421–50)

Table 1
β3-AR and IR genotype distribution

GROUP	CONTROL	TYPE I DM	TYPE II DM
IR GENOTYPE			
AA	67 (%68,4)	14 (%34,1)	51(%56,0)
GG	9 (%9.2)	9 (%22,0)	9(%9,9)
AG	22 (%22,4)	18 (%43,9)	31(%34,1)
ALLELE			
A	156 (79,59%)	46(%56,09)	133 (% 73,07)
G	40 (%20,40)	36 (%43,90)	49 (% 26,92)
BAR GENOTYPE			
AA	20 (%19,8)	7 (%12,7)	7(%7,6)
TT	51 (%50,5)	29 (%52,7)	56(%60,9)
AT	30 (%29,7)	19 (%34,5)	29(%31,5)
ALLELE			
A	70 (%34,65)	33(%30,00)	43 (% 23,36)
T	132 (%65,34)	77 (%70,00)	141 (% 76,63)

populations,[9,12-15] suggesting that it might play a role in the pathogenesis of metabolic disorders by impaired lipolysis, thermogenesis, and insulin sensitivity.

Materials and Methods

We study the distribution of insulin receptor (IR) NsiI and (β3-AR) Trp64Arg polymorhisms and their effect on the development of both types of diabetes mellitus in 55 patients with Type I DM, 92 patients with Type II DM and 102 healthy controls.

Results and Discussion

Mutant allel (G) of IR Nsi I polymorhism in Type I DM patients is higher than the control group and it is statistically significant. It is suggested that it may be involved in pathogenesis of Type I DM. However in Type II DM patient group G allel is observed to be higher than the control group, but it is not statistically significant.

As IR mutant allel is observed to be related to high diastolic blood pressure in Type I and Type II DM patient groups, IR NsiI polymorhism can be proposed as a predictive factor for high diastolic blood pressure.

No difference has been observed in β3-AR 64Arg allel distribution between Type I DM and control groups. However in Type II DM patient group mutant allel is observed to be statistically significantly lower than the control group. Therefore it is thought that β3-AR 64Arg mutation may be related to low risk group for Type II DM in our population.

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