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# Impact of Genetic Polymorphisms on Insulin Resistance

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## 1. Introduction

The identification of DNA polymorphisms in human populations is an important step towards understanding the contribution of functional genetic variants to predisposition of diseases or clinical phenotypes. Approach to the determination of the predisposition uses polymorphisms as marker for a disease in an affected DNA population compared to a control DNA population. Subsequently, the polymorphisms statistically associated with the disease group may be directly informative or linked to the probable causative variant. There are currently over 10 million single nucleotide polymorphisms (SNPs) including insertion/deletion variants in public databases that potentially provide a marker set for disease-gene association studies. This large variant set might not represent the variants causative of disease because it was performed in genomes of only a limited number of individuals. For this reason, the discovery genetic variation in regions of functional DNA sequence in the genomes of individuals with disease is important for disease-gene association studies. However, this situation is not practicable for complex polygenic disease. Therefore, recently, genome-wide association (GWA) or candidate gene approaches are used in the understanding of the molecular genetic background of complex polygenic disease.

Insulin resistance has a complex and heterogeneous genetic background. Insulin resistance is caused by the reduced ability of peripheral target tissues to respond properly to insulin stimulation. Insulin resistance predates beta cell dysfunction and plays the crucial role in the pathogenesis of type 2 diabetes. In addition, insulin resistance is considered the core factor in the pathogenesis of atherosclerosis and the metabolic syndrome, and is often associated with obesity, hypertension and also a dyslipidemic profile characterized by high plasma triacylglycerol concentrations and low HDL-C (Reaven, 1988; Filippi et al., 2004). Until now, many hypotheses have been proposed to explain the molecular mechanisms of insulin resistance such as insulin signaling cascade, the role of free fatty acids, adipocytokines, and

inflammation (Perseghin et al., 2003; Bhattacharya et al. 2007; Choi & Kim, 2010; Erion & Shulman, 2010; Muoio & Newgard, 2008). Given the crucial roles of pathways in the pathogenesis of liver and muscle insulin resistance, understanding the molecular mechanism of insulin resistance is vital for the development of new and more effective therapies for metabolic disorders. The homeostasis model assessment (HOMA) index for insulin resistance was calculated as the product of fasting plasma insulin (in microunits per milliliter) and fasting plasma glucose (in millimoles per liter), divided by 22.5 (Matthews et al. 1985). Higher HOMA values indicate higher insulin resistance.

Genetic and epidemiological studies strongly suggest that insulin resistance is, at least in part, genetically determined. However, the involved genes and their effective variants are mostly unknown. The numerous genes have been suggested as a potential candidate gene for insulin resistance, but the findings of these studies were controversial. This chapter is to provide an overview of our recent understanding of genetic predisposition to insulin resistance. It is aimed to summarize the results of the recent studies about the genetics of insulin resistance.

## **2. Genes related to the lipid homeostasis**

### **2.1. The polymorphisms of the FABP genes**

Fatty acid-binding proteins (FABPs) are members of a superfamily of lipid-binding proteins. These tissue specific proteins (FABP1-4) play the physiological role in the uptake, intracellular metabolism and excretion of long-chain fatty acids (LCFA) (Zimmerman & Veerkamp, 2002). The polymorphisms of these genes have been studied in several metabolic phenotypes such as obesity, metabolic syndrome, hypertriglyceridemia and insulin sensitivity (Mansego et al. 2012).

The liver FABP (FABP1) is an abundant cytosolic lipid-binding protein that regulates lipid transport and metabolism. The c.334-135G>A polymorphism (rs2197076) located in the 3 prime untranslated region (UTR) of the FABP1 gene was associated with the risk of type 2 diabetes and HOMA index in the Spanish population. In this study, it has been shown that carriers of the allele A of this polymorphism had HOMA index values higher than homozygotes GG. However, none of the other analyzed variants in FABP2, FABP3 and FABP4 genes were associated with type 2 diabetes and insulin resistance in this study (Mansego et al. 2012).

The intestinal FABP (FABP2) plays a key role in the absorption and intracellular transport of dietary LCFA (Weiss, 2002). Therefore, the FABP2 gene has been suggested as a possible candidate gene for type 2 diabetes and insulin resistance. In vitro experiments have shown that Ala54Thr polymorphism increases the affinity of FABP2 for LCFA and is associated with increased triglyceride transport in human intestinal cells (Baier et al., 1996; Prochazka et al., 1993). Previous studies have reported significant associations between the FABP2 gene and increased prevalence of insulin resistance (Baier et al., 1995; Mitchell et al., 1995; Yamada et al. 1997; Chiu et al., 2001; Kim et al., 2001) as well as no association was found in

Finnish individuals (Sipiläinen et al., 1997) and Spanish population (Mansego et al. 2012). Baier et al. reported the significant associations between the common FABP2 Ala54Thr polymorphism (rs1799883) and increased fasting insulin concentration, fasting fatty acid oxidation, and decreased insulin sensitivity in Pima Indians, a population with a high prevalence of obesity and type 2 diabetes (Baier et al., 1995). Furthermore, the linkage analysis of the FABP2 locus with insulin resistance was also found in a study in Mexican Americans who were of a mixed American-Indian and -European ancestry (Mitchell et al., 1995). However, sib-pair analysis failed to detect any linkage of the FABP2 locus or the Ala54Thr polymorphism with diabetes-related phenotypes in other ethnic groups. The homozygous Thr54/Thr54 genotype has found the associations with higher fasting insulin levels and also TNF- $\alpha$  levels in 33 adult obese women (Albala et al., 2004). However, the findings of this study would need to be confirmed in studies involving a larger number of subjects. A number of conflicting and inconclusive studies have investigated the possible association of the FABP2 Ala54Thr polymorphism with insulin resistance. A meta-analysis of these published studies has suggested that the Thr54 allele of the FABP2 Ala54Thr is weakly associated with a higher degree of insulin resistance, higher fasting insulin and blood glucose level. As gender and ethnicity probably were important variables in determining associative risk with insulin resistance and type 2 diabetes, Zhao et al. have performed subgroup analyses of gender and ethnicity. These weak effects of Ala54Thr polymorphism on insulin resistance and fasting insulin have been particularly established in East Asians (Zhao et al., 2010).

## 2.2. The polymorphisms of the ELOVL6 gene

Elongase of long chain fatty acids family 6 (ELOVL6) is expressed in lipogenic tissues. This enzyme specifically catalyze the elongation of saturated and monounsaturated fatty acids with 12, 14 and 16 carbons. A population-based study has suggested that the genetic variations in the ELOVL6 gene are related with insulin resistance. In this study, five SNPs of the ELOVL6 gene and their haplotypes were analyzed. In this population from southern Spain, carriers of the minor alleles of the rs9997926 and rs6824447 polymorphisms had a lower risk of having high HOMA index, whereas carriers of the minor allele rs17041272 had a higher risk of being insulin resistant. Finally, Morcillo et al. has suggested that the ELOVL6 gene could be a future therapeutic target in the treatment of diabetes and related disorders (Morcillo et al., 2011). However, the validation of associations between this novel candidate gene and insulin resistance should be performed in different and large populations.

## 2.3. The polymorphisms of the APOE gene

Apolipoprotein E (ApoE) is primarily involved in plasma lipid homeostasis. However, a number of studies with experimental mouse models have shown that apoE also has an important role in the development of obesity and insulin resistance (Kypreos et al., 2009; Gao et al., 2007). ApoE is involved in excess fat accumulation and energy metabolism, including the regulation of food intake and energy expenditure. Therefore, excess fat

accumulation via an apoE-dependent pathway might play a role in the development of insulin resistance (Kypreos et al., 2006). Some studies have suggested that the APOE  $\epsilon 2/\epsilon 3/\epsilon 4$  polymorphism may modify the effect of insulin on CHD or some CHD risk factors, including obesity and lipid profile levels (Després et al., 1993; Valdez et al., 1995; Elosua et al., 2003), whereas the Framingham Offspring Study and Turkish Adult Risk Factor (TARF) Study found that this polymorphism was not associated with insulin resistance (Meigs et al., 2000; Komurcu-Bayrak et al., 2011). Two other of the functional SNPs, i.e., -219G>T (rs405509) and +113G>C (rs440446) in APOE gene had shown association with plasma apoE concentrations (Lambert et al., 2000; Moreno et al., 2003), insulin resistance (Viitanen et al., 2001), insulin sensitivity in response to a diet rich in saturated fats (Moreno et al., 2005). In a cross-sectional study, the impacts of these polymorphisms have been analyzed on lipid, apolipoprotein, glucose, and serum insulin concentrations in the TARF cohort, a representative of Turkish adults. In this study, the -219G>T and +113G>C genotypes and diplotypes of haplotype 2 (TC $\epsilon 3$ ) showed negative correlation to serum fasting insulin and the HOMA index, but not to serum lipids. The significant associations between these functional polymorphisms and fasting insulin levels and the HOMA index were found only in the apoE3 group ( $\epsilon 3/\epsilon 3$  genotypes of the APOE  $\epsilon 2/\epsilon 3/\epsilon 4$  polymorphism) without type 2 diabetes (Komurcu-Bayrak et al., 2011). On the other hand, a large population-based family study related with type 2 diabetes found a relationship for the polymorphisms of the APOE gene and the nearby muscle glycogen synthase (GYS1) gene on chromosome 19 with cardiovascular mortality, independently of each other (Fredriksson et al., 2007). Other functional polymorphisms in the GYS1 gene may relate to developing insulin resistance.

### 3. Genes related to the energy metabolism

#### 3.1. The polymorphisms of the UCP genes

Uncoupling protein 2 and 3 (UCP2 and UCP3) play an important role in human energy homeostasis (Brand et al., 2004) and have been considered candidate genes for obesity, type 2 diabetes and insulin resistance. Thus, UCP2 and UCP3 are involved in regulating ATP synthesis, generation of reactive oxygen species and glucose-stimulated insulin secretion by pancreatic  $\beta$  cells. The -866G>A (rs659366) polymorphism of UCP2 gene was located in a region with putative binding sites for two  $\beta$ -cell transcription factors (Dalgaard et al., 2003). A number of studies have been performed seeking for an association between genetic variants in this gene cluster with type 2 diabetes and/or insulin resistance. These studies have demonstrated association of the -866A-allele with increased (D'Adamo et al., 2004; Krempler et al., 2002; Gable et al., 2006) and decreased (Wang et al., 2004; Bulotta et al., 2005; Lyssenko et al., 2005; Rai et al., 2007) risk of type 2 diabetes as well as no association at all (Kovacs et al., 2005; Reis et al., 2004; Zee et al., 2011). Finally, the two recent meta-analysis on the association of type 2 diabetes with -866G>A polymorphism concluded that this variant does not confer increased risk of type 2 diabetes (Xu et al., 2011; 40, Andersen et al., 2012). However, Andersen et al has found an association between this variant and obesity in

Danish individuals and established case-control studies. This study has shown that the -866G-allele was associated with elevated fasting serum insulin levels and insulin resistance (HOMA index) and decreased insulin sensitivity in Danish subjects (Andersen et al., 2012). Furthermore, in a study performed with a Spanish group of 193 obese children and adolescents and 170 controls, Ochoa et al. reported that the -55C>T (rs1800849) polymorphism of the UCP3 gene directly associated with higher fasting insulin levels and insulin resistance in heterozygous subjects from the control group. In addition, they found that the individual polymorphisms were not associated with obesity, but the (-866G) - (Del; 45 bp) - (-55T) haplotype was significantly associated with obesity and its presence in the control group increased about nine times the insulin resistance risk (Ochoa et al., 2007). Recently, a study has demonstrated that morbidly obese patients with -55CT genotype (n=15) had higher weight, fat mass, and insulin resistance (HOMA index) than the individuals with -55CC genotype (n=32) (de Luis Roman et al., 2010).

### **3.2. The polymorphisms of the ADRB genes**

$\beta$ -adrenoceptors (ADRB1, ADRB2, ADRB3) in the sympathetic nervous system play a role in regulating energy expenditure and lipolysis. ADRBs gene variation is an intense area of investigation because  $\beta$ -adrenoceptors are well described in organ system distribution, catecholamine-mediated physiological processes, disease states and treatment targets (Eisenach & Wittwer, 2010). One of the most studied polymorphism (rs1801253) in the ADRB1 gene encode for arginine or glycine in amino acid 389 (Arg389Gly). In 238 healthy young Caucasians and African-Americans, Gly389 carriers had a higher level of insulin and insulin resistance than non-carriers, and this allele was more prevalent in the subjects with higher body mass index (BMI; Lima et al. 2007). In previous studies, it has been found that this polymorphism was associated with serum insulin levels and insulin resistance (HOMA index) but, no association with obesity among Swedish women (Mottagui-Tabar et al., 2008). However, there are limited number of studies evaluating the association between these genes and insulin resistance. In larger scale studies with different populations should be performed for these genes to support the association between genotype and phenotype.

## **4. Genes encoding hormones and hormone receptors**

### **4.1. The polymorphisms of the APM1, ADIPOR1, and ADIPOR2 genes**

Adiponectin is an adipokine secreted by adipocytes. The polymorphisms in adiponectin (APM1,ADIPOQ, ACRP30) gene, and its receptors (ADIPOR1 and ADIPOR2) are strongly associated with metabolic syndrome, obesity, type 2 diabetes and, insulin resistance. High adiponectin predicts increased insulin sensitivity (Tschritter et al. 2003). There is evidence indicating that insulin directly affects plasma adiponectin (Möhlig et al., 2002; Hung et al., 2008; Brame et al., 2005). In recent studies, plasma adiponectin concentrations were reduced in type 2 diabetes and obesity (Arita et al., 1999; Lindsay et al. 2002; Spranger et al., 2003). Furthermore, administration of thiazolidinediones (TZD), an insulin-sensitising class of drugs, to insulin-resistant subjects significantly increased the plasma adiponectin

levels, and this effect was correlated with the amelioration of insulin resistance in these subjects (Maeda et al., 2001). Many studies have, in fact, reported the association between polymorphisms of the APM1, ADIPOR1, and ADIPOR2 and adiponectin concentrations, insulin resistance, type 2 diabetes and metabolic syndrome phenotypes (Kondo et al., 2002; Hara et al., 2002; Menzaghi et al., 2002; Stumvoll et al., 2002; Hivert et al., 2008; Menzaghi et al., 2007; Sheng et al., 2008; Ferguson et al., 2010). While, in the study from Stumvoll et al, the +45T>G (rs2241766) polymorphism was associated with obesity and derangement of insulin sensitivity (Stumvoll et al., 2002), in the study from Melistas et al, this polymorphism was associated with lower insulin levels in Greek women without diabetes (Melistas et al., 2009). In a study from Menzaghi et al, a haplotype of the adiponectin gene was associated with several features of insulin resistance in nondiabetic individuals, including low serum adiponectin levels (Menzaghi et al., 2002). In addition, the +276G>T (rs1501299) polymorphism in the adiponectin gene was associated with higher insulin levels and insulin resistance (HOMA index) in Italian population from the Lazio region (diabetes and/or the metabolic syndrome was excluded) (Filippi et al., 2004) and in Greek female population without diabetes (Melistas et al., 2009). The association of the -11391G>A (rs17300539) polymorphism with plasma insulin and HOMA index was independent of plasma adiponectin in another study, which implies a direct effect of this polymorphism on plasma insulin and insulin sensitivity (Henneman et al., 2010). Recently, Vasseur et al have reported on the association of a haplotype G-G (including -11391G>A and -11377C>G polymorphisms located in the APM1 proximal promoter) with plasma adiponectin levels and type 2 diabetes, although no association with HOMA index was observed (Vasseur et al., 2002). The reasons for partially discrepant results between polymorphisms in these genes and metabolic measures could be due to the different genetic background of the studied populations or environmental interactions, particularly dietary factors. Gene-nutrient interactions can modulate in the development of metabolic phenotypes. Although, so far, there has been little focus on gene-nutrient interactions with adiponectin and its receptors, two studies found that there was an interaction between the rs266729 polymorphism of APM1 and the percentage of dietary-derived energy from fat with the development of obesity in women (Santos et al., 2006) and an association between this polymorphism and also the rs10920533 polymorphism of ADIPOR1 and plasma saturated fatty acids with the insulin resistance (Ferguson et al., 2010).

#### **4.2. The polymorphisms of the D2 and TSHR genes**

Thyroid hormones are known to upregulate the expression of glucose transporter type 4 (GLUT4) in skeletal muscle, and consequently increase glucose uptake (Weinstein et al., 1994). Thyroxine (T4), a major secretory product of the thyroid gland, needs to be converted to triiodothyronine (T3) to exert its biological activity. Type 2 deiodinase (D2) catalyzes T4 to T3 conversion, and plays a critical role in maintaining intracellular T3 levels in specialized tissues, such as the anterior pituitary and brown adipose tissue (Bianco et al., 2005). Thr92Ala polymorphism of D2 gene showed an association with lower glucose disposal rate in nondiabetic subjects and also a higher prevalence of insulin

resistance in Pima Indians and Mexican–Americans (Mentuccia et al., 2002). Furthermore, D2 Ala/Ala genotype was also associated in previous studies with increased insulin levels and increased insulin resistance (increased HOMA index) and also worse glycemic control (increased HbA1c levels) in a cohort of patients with type 2 diabetes (Grozovsky et al., 2009; Dora et al., 2010). In addition, this polymorphism was associated with greater insulin resistance in type 2 diabetes patients and with lower enzyme activity in thyroid tissue samples (Canani et al., 2005). However, some population-based studies failed to demonstrate an association between the D2 Thr92Ala polymorphism and increased risk for type 2 diabetes (Mentuccia et al., 2005; Maia et al., 2007; Grarup et al. 2007). Thyroid hormone interacts with the TSH receptor (TSHR) in the thyroid gland. A previous study has investigated the association between serum thyroid parameters and the TSHR Asp727Glu polymorphism in nondiabetic elderly men. Peeters et al. reported that this polymorphism was associated with relative insulin resistance. Carriers of the Glu727 allele had also a significantly higher glucose, insulin, HOMA index and leptin levels, but no association with serum TSH levels (Peeters et al., 2007). Peeters et al. have suggested that this association was studied in one cohort only, and as the mechanism remains to be elucidated, replication of results in an independent cohort (of healthy elderly subjects) was essential.

#### **4.3. The polymorphisms of the SHBG gene**

Some studies have suggested that the polymorphisms in genes encoding sex hormones may be effective on the development of insulin resistance. Previous studies have shown that androgen supplementation in the presence of central obesity and low testosterone levels increases insulin sensitivity in men (Mårin et al., 1992; Simon et al., 2001; Boyanov et al., 2003). Moreover, polycystic ovarian syndrome was associated with higher risk of type 2 diabetes and insulin resistance in women (Dunaif, 1995). Recent studies have demonstrated that higher levels of circulating sex hormone binding protein (SHBG) were associated with reduce risk of type 2 diabetes (Ding et al., 2009; Perry et al., 2010). In addition, rs6259, rs6257 and rs1799941 polymorphisms in the SHBG gene were strongly associated with SHBG levels and type 2 diabetes (Zeggini et al., 2008; Perry et al., 2010). However, there was no evidence that this variant is associated with diabetes-related intermediate traits, including several measures of insulin secretion and resistance (Perry et al., 2010).

#### **4.4. The polymorphisms of the LEP and LEPR genes**

Leptin (LEP), a hormone secreted by adipocytes, and its receptor (LEPR) are other candidate genes for insulin resistance. Common variants in the LEPR gene have been associated with hyperinsulinemia (Lakka et al., 2000; Wauters et al., 2002), type 2 diabetes (Lakka et al., 2000), obesity, and leptin levels (Chagnon et al., 1999; Chagnon et al., 2000; Chagnon et al., 2001; de Luis Roman et al., 2006). However, the roles of leptin and its receptor in the development of metabolic traits in the general population are less clear. A few studies have, in fact, reported the association between polymorphisms of the LEP and LEPR genes and



insulin resistance (Wauters et al., 2001; de Luis et al., 2008; Gu et al., 2012; Takahashi-Yasuno et al., 2004; Ren et al., 2004). While, in the study from Wauters et al, Lys109Arg, Gln223Arg, and Lys656Asn polymorphisms in LEPR gene were associated with insulin and glucose metabolism in postmenopausal obese women with impaired glucose homeostasis (Wauters et al., 2001), in the study from de Luis et al, Lys656Asn polymorphism was associated with higher levels of insulin, HOMA, and leptin in men without diabetes (de Luis et al., 2008) , in the study from Gu et al, Lys109Arg was associated with waist-to-hip ratio, oral glucose tolerance test (OGTT)-2h glucose, and HOMA index in Chinese subjects with essential hypertension, but no correlation between Lys109Arg polymorphism and hypertension were found (Gu et al., 2012). Also' -2549C>A polymorphism in the promoter region of the LEP gene is related to fasting plasma leptin level (Mammès et al., 1998; Le Stunff et al., 2000; Gu et al., 2012), obesity phenotypes (Mammès et al., 1998; Mammès et al., 2000; Le Stunff et al., 2000), and also fasting serum insulin level and HOMA index in Chinese patient with type 2 diabetes (Ren et al., 2004). However, the findings of the study from Ren et al. should be confirmed with studies involving larger number of subjects and different populations.

#### 4.5. The polymorphisms of the RBP4 gene

Retinol-binding protein 4 (RBP4) is an adipokine with potential contribution to systemic insulin resistance (Yang et al., 2005). The -803G>A promoter polymorphism (rs3758539) of RBP4 gene is associated with increased risk for obesity and type 2 diabetes in adults (Munkhtulga et al., 2010 ; Munkhtulga et al., 2007; van Hoek et al., 2008). Munkhtulga et al. have reported in 2010 that the -803A allele of this polymorphism was associated with higher BMI in Japanese men and women and in Mongolian women (Munkhtulga et al., 2010) and also in 2007 they found that the rare alleles of four SNPs (-803G>A, +5169C>T, +6969G>C, +7542T>del) were associated with increased risk of diabetes in Mongolian case-control study (Munkhtulga et al., 2007). van Hoek et al. have shown that homozygosity for the -803A allele was associated with increased risk of type 2 diabetes in the Rotterdam population (van Hoek et al., 2008). More recent studies failed to confirm an association of this variant with circulating RBP4 levels, type 2 diabetes susceptibility, adiposity or metabolic parameters (Friebe et al., 2011; Kovacs et al., 2007; Shea et al., 2010; Wu et al., 2009; Craig et al., 2007). Shea et al. have analyzed five SNPs including -803G>A polymorphism within RBP4 gene and they have found a significant association between the minor allele of rs10882280 (C>A intron) and rs11187545 (A>G intron) polymorphisms and higher serum HDL-C levels in Newfoundland population, but not between insulin resistance and any polymorphism (Shea et al., 2010). Craig et al. have found that only a haplotype (-804G, 390G, 406T, 759G, 6969G, 9476T, 10670G, and 11881C) in RBP4 gene showed an association with type 2 diabetes in African Americans and Caucasians. Furthermore, -803G>A and +9476T>G (rs34571439) polymorphisms were associated with reduced insulin secretion, and +390C>G (novel) with reduced insulin sensitivity in Caucasians (Craig et al., 2007). The discrepancy among previous publications about insulin resistance may be resolved by analyzing a larger number of samples.

#### 4.6. The polymorphisms of the RETN gene

Resistin (RETN), a hormone secreted by adipocytes, has been examined as candidate gene for obesity and type 2 diabetes and insulin resistance. However, there are many conflicting findings about these metabolic phenotypes. Osawa et al. have reported that the GG genotype of RETN -420C>G promoter polymorphism (rs1862513), increased type 2 diabetes susceptibility (Osawa et al., 2004) and fasting plasma resistin (Osawa et al., 2007; Azuma et al., 2004) in the Japanese population. Silha et al. and Osawa et al. have found correlation between resistin levels and insulin resistance (Silha et al., 2003; Osawa et al., 2007), but not Lee et al. (Lee et al., 2003). Some genetic association studies have found an association between certain resistin gene variants and insulin resistance in Finnish nondiabetic individuals (Conneely et al., 2004), in nondiabetic Caucasians from Sicily and Gargano areas of Italy (Pizzuti et al., 2002), and in 20 nondiabetic Caucasians (Wang et al., 2002), while others report no such association in 60 Japanese obese nondiabetic individuals (Azuma et al., 2004) and in 258 families with 323 affected with polycystic ovary syndrome offspring (Urbanek et al., 2003). These conflicting findings have made it difficult to determine a role for resistin in insulin resistance. The reasons for discrepant results are not known, and may reside in the different genetic background of the studied populations or the different-designed studies.

### 5. Genes related to the renin-angiotensin system

The renin-angiotensin system (RAS) plays a central role in the regulation of insulin sensitivity (Reaven, 1995; Higashiura et al., 2000; Ura et al., 1999). Many studies have examined the genetic effect of homozygous deletion polymorphism (DD) in exon 16 of the angiotensin-converting enzyme gene (ACE) in insulin resistance, but their results have been controversial (Katsuya et al., 1995; Perticone et al., 2001; Yamamoto et al., 1999). Hypertension is related to insulin resistance and a number of studies have reported an association between RAS gene polymorphisms and hypertension (Sugimoto et al. 2004; Jin et al., 2003; Kikuya et al., 2003; Ono et al., 2003). Akasaka et al., 2006; The insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme gene (ACE), the Met235Thr polymorphism of the angiotensinogen gene (AGT), and the 1166A>C polymorphism of the angiotensin II type 1 receptor gene (AGTR1) were not associated with HOMA index, whereas borderline association was found between the 1166A>C polymorphism and dichotomous categorization of insulin resistance (defined as HOMA index  $\geq 1.73$ ). However, further studies are required to confirm the impact of these candidate gene polymorphisms in the larger and different populations.

### 6. Genes related to the inflammation

#### 6.1. The polymorphisms of the TNF- $\alpha$ gene

Tumor necrosis factor alpha (TNF- $\alpha$ ) is a multifunctional proinflammatory cytokine and also an adipokine produced in adipocytes. Increased levels of the TNF- $\alpha$  have been shown

to elevate the risk of insulin resistance by impairing  $\beta$  cell function and glucose homeostasis (Hotamisligil et al., 1993; Hotamisligil et al., 1994; Katsuki et al., 1998). In addition, the TNF- $\alpha$  affects lipid metabolism and may lead to hypertriglyceridemia by decreasing hepatic lipoprotein lipase activity and by increasing hepatic de novo fatty acid synthesis (Zinman et al., 1999). Circulating levels of TNF- $\alpha$  have also been reported to correlate with insulin resistance and type 2 diabetes (Hotamisligil & Spiegelman, 1994; Hu et al., 2004). Previous studies have shown that TNF- $\alpha$  -308G>A polymorphism is associated with insulin resistance (Fernandez-Real et al., 1997), obesity (Hoffstedt et al., 2000), type 2 diabetes (Vendrell et al., 2003; Kubaszek et al., 2003) and metabolic syndrome (Gupta et al., 2012). However, many other studies have reported conflicting results, with no association between this variant and insulin resistance (Gupta et al., 2012; Ranjith et al., 2008). A meta-analysis of many published studies including different populations has suggested that -308A TNF- $\alpha$  gene variant is associated with increased risk of developing obesity compared with controls and significantly higher systolic arterial blood pressure and plasma insulin levels (Sookoian et al., 2005). On the other hand, another recent meta-analysis has reported that TNF- $\alpha$  -238G>A and -308G>A polymorphisms were not associated with type 2 diabetes mellitus; however, -308G>A polymorphism was positively associated with type 1 diabetes (Feng et al., 2009a; Feng et al., 2009b; Feng et al., 2011). TNF- $\alpha$  -857C>T polymorphism is also associated with obese type 2 diabetes (Kamizono et al. 2000) and insulin resistance in Japanese diabetic subjects with adiponectin +276GG genotype (Ohara et al., 2012). The study of Ohara et al has shown interaction of TNF- $\alpha$  and adiponectin genes with insulin resistance and fatty liver (Ohara et al., 2012).

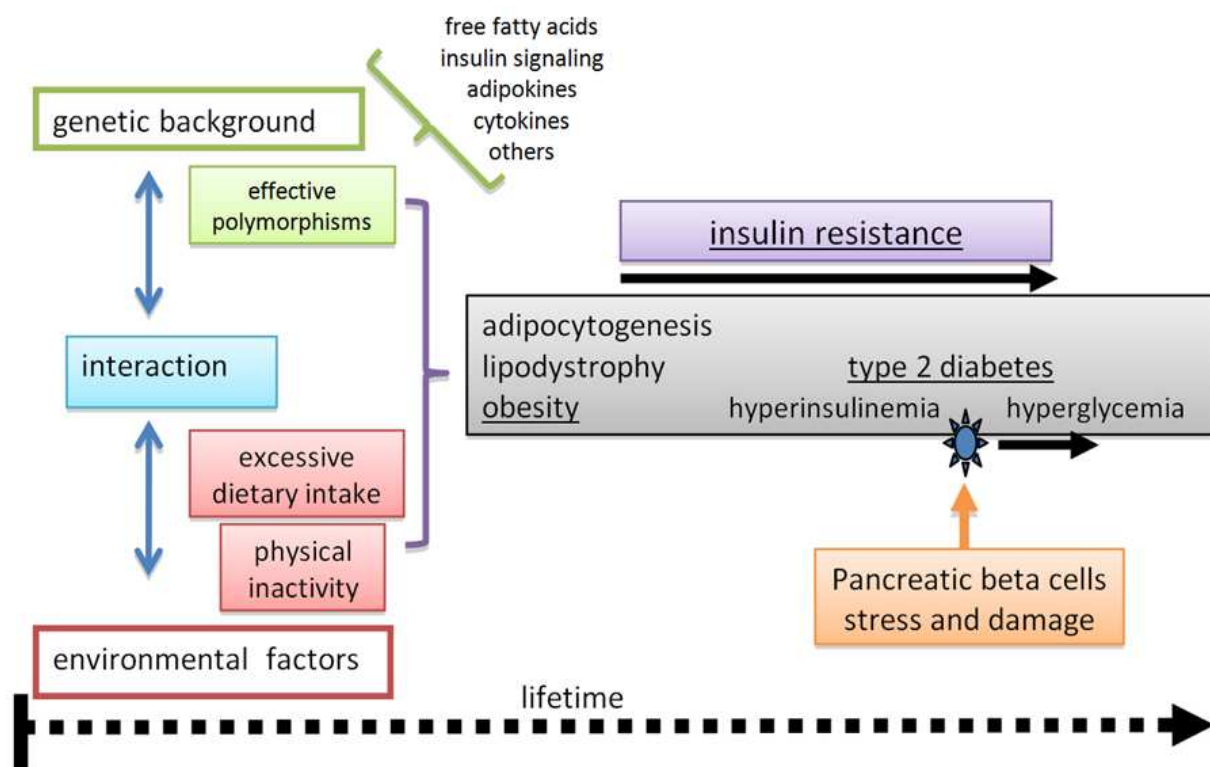
## 6.2. The polymorphisms of the IL-6 gene

Interleukin-6 (IL-6) is a proinflammatory cytokine that is associated with type 2 diabetes and insulin resistance (Di Renzo et al., 2008; Wannamethee et al., 2007; Hu et al., 2004). Recent studies have demonstrated that the association between -174G>C polymorphism (rs1800795) in the promoter region of the IL-6 gene and insulin resistance is modified by body mass index (BMI), with the -174C allele associated with higher insulin resistance and type 2 diabetes in individuals with obesity (Herbert et al., 2006; Mohlig et al., 2004; Goyenechea et al., 2007; Di Renzo et al., 2008; Underwood et al., 2012). However, in meta-analysis including 5383 diabetes cases and 12 069 controls, it has been found that -174G>C polymorphism was not associated with the risk of type 2 diabetes (Qi et al., 2006). The reasons underlying the discrepancy among studies are unclear. Other genetic or environmental factors may play important roles in modulating the relationships.

## 7. Conclusion

The insulin resistance is highly heritable and originates from the interactions of multiple genes and environmental factors. Figure 1 shows the main factors contributing to the development of insulin resistance and type 2 diabetes. However, the molecular mechanism of insulin resistance is not clear yet. Until now, goal of many studies was to use a candidate

gene approach to identify genes associated with insulin resistance and several genes have been investigated in many association-based studies. However, most of the time, results of these studies reveal conflicting findings. These discrepant results might be due to differences in the study populations and design of these studies. In addition, the candidate gene polymorphisms have been searched in a number of small-scale studies with variable results. Limited number meta-analyses have been done to demonstrate the effect of several candidate gene polymorphisms on insulin resistance. But, the larger, well-characterized and independent association studies will be needed. On the other hand, the use of genome-wide association (GWA) studies will identify novel polymorphisms related to insulin resistance. This knowledge will allow the determination of the genetic predisposition to the insulin resistance and new approaches to treatment and prevention of the clinical phenotypes such as type 2 diabetes, obesity, hypertension and metabolic syndrome.



**Figure 1.** General overview of genetic and environmental factors contributing to the development of insulin resistance and type 2 diabetes. The combination of genetic predisposition (genetic polymorphisms effecting free fatty acid metabolism, insulin signalling, adipokines and cytokines) and some environmental factors such as excessive dietary intake and physical inactivity results with the occurrence of adipocytogenesis, lipodystrophy and obesity which increase the development risk of insulin resistance. Insulin resistance predates pancreatic beta cell dysfunction and plays the crucial role in the pathogenesis of type 2 diabetes.

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