Chapter 3

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 polymophism 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-α 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 ε2/ε3/ε4 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 satured 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 (TCε3) 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 (ε3ε3 genotypes of the APOE ε2/ε3/ε4 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., 200 4) 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 β cells. The -866G>A (rs659366) polymorphism of UCP2 gene was located in a region with putative binding sites for two β-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

β-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 β-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

Adiponection 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 ≥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-α gene

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

to elevate the risk of insulin resistance by impairing β cell function and glucose homeostasis (Hotamisligil et al., 1993; Hotamisligil et al., 1994; Katsuki et al., 1998). In addition, the TNF-α 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-α 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-α -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-α 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-analyses has reported that TNF-α -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-α -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-α 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 has 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.

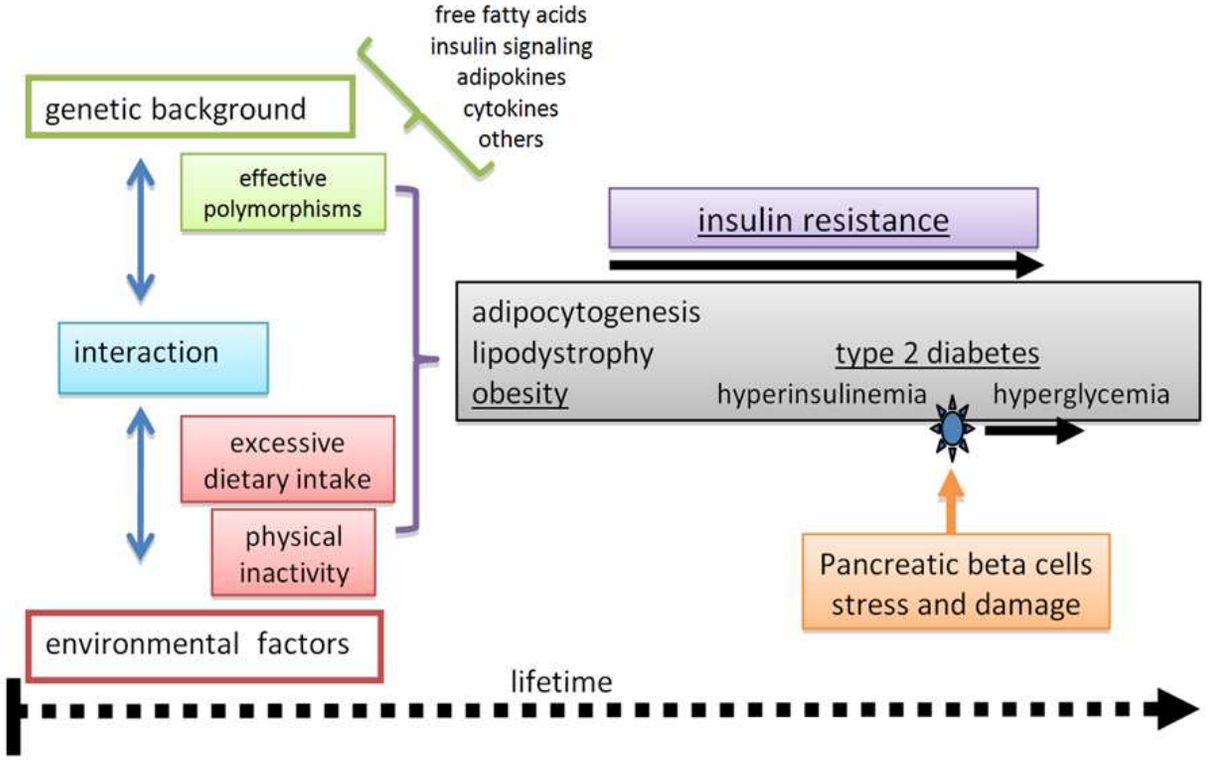

Figure 1. General overview of genetic and environmental factors contributing to the development of insulin resistance and type 2 diabetes. The combination of genetic predisposition (genetic polymorphisms effecting free fatty acid metabolism, insulin signalling, adipokines and cytokines) and some environmental 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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8. References

Akasaka H, Katsuya T, Saitoh S, Sugimoto K, Fu Y, Takagi S, Ohnishi H, Rakugi H, Ura N, Shimamoto K & Ogihara T. (2006). Effects of angiotensin II type 1 receptor gene polymorphisms on insulin resistance in a Japanese general population: the Tanno-Sobetsu study. *Hypertens Res.* 29(12), pp. 961-7.

Albala C, Santos JL, Cifuentes M, Villarroel AC, Lera L, Liberman C, Angel B & Pérez-Bravo F. (2004). Intestinal FABP2 A54T polymorphism: association with insulin resistance and obesity in women. *Obes Res.* 12(2), pp. 340-5.

Andersen G, Dalgaard LT, Justesen JM, Anthonsen S, Nielsen T, Thørner LW, Witte D, Jørgensen T, Clausen JO, Lauritzen T, Holmkvist J, Hansen T & Pedersen O. (2012). The frequent UCP2 -866G>A polymorphism protects against insulin resistance and is associated with obesity: a study of obesity and related metabolic traits among 17636 Danes. *Int J Obes* (Lond). doi: 10.1038/ijo.2012.22.

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T & Matsuzawa Y. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun.* 257(1), pp. 79-83.

Azuma K, Oguchi S, Matsubara Y, Mamizuka T, Murata M, Kikuchi H, Watanabe K, Katsukawa F, Yamazaki H, Shimada A & Saruta T. (2004). Novel resistin promoter polymorphisms: association with serum resistin level in Japanese obese individuals. *Horm Metab Res.* 36(8), pp. 564-70.

Baier LJ, Sacchettini JC, Knowler WC, Eads J, Paolisso G, Tataranni PA, Mochizuki H, Bennett PH, Bogardus C & Prochazka M. (1995). An amino acid substitution in the human intestinal fatty acid binding protein is associated with increased fatty acid binding, increased fat oxidation, and insulin resistance. *J Clin Invest.* 95(3), pp. 1281-7.

Baier LJ, Bogardus C & Sacchettini JC. (1996). A polymorphism in the human intestinal fatty acid binding proteins alters fatty acid transport across Caco-2 cells. *J Biol Chem.* 271, pp. 10892–6.

Bhattacharya S, Dey D & Roy SS. (2007). Molecular mechanism of insulin resistance. *J Biosci.* 32(2):405-13.

Bianco AC, Maia AL, da Silva WS, Christoffolete MA. (2005). Adaptive activation of thyroid hormone and energy expenditure. *Biosci Rep.* 25(3-4), pp. 191-208.

Boyanov MA, Boneva Z & Christov VG. (2003). Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male.* 6(1), pp. 1-7.

Brame LA, Considine RV, Yamauchi M, Baron AD & Mather KJ. (2005). Insulin and endothelin in the acute regulation of adiponectin in vivo in humans. *Obes Res* 13, pp. 582–588

Brand MD, Affourtit C, Esteves TC, Green K, Lambert AJ, Miwa S, Pakay JL & Parker N. (2004). Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. *Free Radic Biol Med*. 37(6), pp. 755-67.

Bulotta A, Ludovico O, Coco A, Di Paola R, Quattrone A, Carella M, Pellegrini F, Prudente S & Trischitta V. (2005). The common -866G/A polymorphism in the promoter region of

the UCP-2 gene is associated with reduced risk of type 2 diabetes in Caucasians from Italy. *J Clin Endocrinol Metab.* 90(2), pp. 1176-80.

Canani LH, Capp C, Dora JM, Meyer EL, Wagner MS, Harney JW, Larsen PR, Gross JL, Bianco AC & Maia AL. (2005). The type 2 deiodinase A/G (Thr92Ala) polymorphism is associated with decreased enzyme velocity and increased insulin resistance in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 90(6), pp. 3472-8.

Chagnon YC, Chung WK, Pérusse L, Chagnon M, Leibel RL & Bouchard C. (1999). Linkages and associations between the leptin receptor (LEPR) gene and human body composition in the Québec Family Study. *Int J Obes Relat Metab Disord.* 23(3), pp. 278-86.

Chagnon YC, Wilmore JH, Borecki IB, Gagnon J, Pérusse L, Chagnon M, Collier GR, Leon AS, Skinner JS, Rao DC & Bouchard C. (2000). Associations between the leptin receptor gene and adiposity in middle-aged Caucasian males from the HERITAGE family study. *J Clin Endocrinol Metab.* 85(1), pp. 29-34.

Chiu KC, Chuang LM &Yoon C. (2001). The A54T polymorphism at the intestinal fatty acid binding protein 2 is associated with insulin resistance in glucose tolerant Caucasians. *BMC Genet.* 2, pp. 7–13.

Choi K & Kim YB. (2010). Molecular mechanism of insulin resistance in obesity and type 2 diabetes. *Korean J Intern Med.* 25(2), pp. 119-29.

Conneely KN, Silander K, Scott LJ, Mohlke KL, Lazaridis KN, Valle TT, Tuomilehto J, Bergman RN, Watanabe RM, Buchanan TA, Collins FS & Boehnke M. (2004). Variation in the resistin gene is associated with obesity and insulin-related phenotypes in Finnish subjects. *Diabetologia.* 47(10), pp. 1782-8.

Craig RL, Chu WS & Elbein SC. (2007). Retinol binding protein 4 as a candidate gene for type 2 diabetes and prediabetic intermediate traits. *Mol Genet Metab.* 90(3), pp. 338-44.

D'Adamo M, Perego L, Cardellini M, Marini MA, Frontoni S, Andreozzi F, Sciacqua A, Lauro D, Sbraccia P, Federici M, Paganelli M, Pontiroli AE, Lauro R, Perticone F, Folli F & Sesti G. (2004). The -866A/A genotype in the promoter of the human uncoupling protein 2 gene is associated with insulin resistance and increased risk of type 2 diabetes. *Diabetes.* 53(7), pp. 1905-10.

Dalgaard LT, Andersen G, Larsen LH, Sørensen TI, Andersen T, Drivsholm T, Borch-Johnsen K, Fleckner J, Hansen T, Din N & Pedersen O. (2003). Mutational analysis of the UCP2 core promoter and relationships of variants with obesity. *Obes Res.* 11(11), pp. 1420-7.

de Luis DA, Gonzalez Sagrado M, Aller R, Izaola O & Conde R.(2008). Influence of Lys656Asn polymorphism of the leptin receptor gene on insulin resistance in nondiabetic obese patients. *J Diabetes Complications.* 22(3), pp. 199-204.

de Luis Roman D, de la Fuente RA, Sagrado MG, Izaola O & Vicente RC. (2006). Leptin receptor Lys656Asn polymorphism is associated with decreased leptin response and weight loss secondary to a lifestyle modification in obese patients. *Arch Med Res.* 37(7), pp. 854-9.

de Luis Roman DA, Aller R, Izaola Jauregui O, Gonzalez Sagrado M, Conde Vicente R, de la Fuente Salvador B & Romero Bobillo E. (2010). Relation of -55CT polymorphism of uncoupling protein 3 gene with fat mass and insulin resistance in morbidly obese patients. *Metabolism.* 59(4), pp. 608-12.

Després JP, Verdon MF, Moorjani S, Pouliot MC, Nadeau A, Bouchard C, Tremblay A & Lupien PJ. (1993). Apolipoprotein E polymorphism modifies relation of hyperinsulinemia to hypertriglyceridemia. *Diabetes.* 42, pp. 1474-81.

Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM & Liu S. (2009). Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med.* 361(12), pp. 1152-63.

Di Renzo L, Bertoli A, Bigioni M, Del Gobbo V, Premrov MG, Calabrese V, Di Daniele N & De Lorenzo A. (2008). Body composition and -174G/C interleukin-6 promoter gene polymorphism: association with progression of insulin resistance in normal weight obese syndrome. *Curr Pharm Des.* 14(26), pp. 2699-706.

Dora JM, Machado WE, Rheinheimer J, Crispim D & Maia AL. (2010). Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. *Eur J Endocrinol.* 163(3), pp. 427-34.

Dunaif A. (1995). Hyperandrogenic anovulation (PCOS): a unique disorder of insulin action associated with an increased risk of non-insulin-dependent diabetes mellitus. *Am J Med.* 98(1A), pp. 33S-39S.

Eisenach JH & Wittwer ED. (2010). {beta}-Adrenoceptor gene variation and intermediate physiological traits: prediction of distant phenotype. *Exp Physiol.* 95(7), pp. 757-64.

Elosua R, Demissie S, Cupples LA, Meigs JB, Wilson PW, Schaefer EJ, Corella D & Ordovas JM. (2003). Obesity modulates the association among APOE genotype, insulin, and glucose in men. *Obes Res.* 11:1502-8.

Erion DM & Shulman GI. (2010). Diacylglycerol-mediated insulin resistance. *Nat Med.* 16(4), pp. 400-2.

Feng RN, Li Y & Sun CH (2009a) TNF 308 G/A polymorphism and type 1 diabetes: a meta-analysis. *Diab Res Clin Pract* 85, pp. e4–e7.

Feng R, Li Y, Zhao D, Wang C, Niu Y & Sun C. (2009b). Lack of association between TNF 238 G/A polymorphism and type 2 diabetes: a meta-analysis. *Acta Diabetol* 46, pp. 339–343.

Feng RN, Zhao C, Sun CH & Li Y. (2011). Meta-Analysis of TNF 308 G/A Polymorphism and Type 2 Diabetes Mellitus. *PLoS One* 6, pp. e18480.

Ferguson JF, Phillips CM, Tierney AC, Pérez-Martínez P, Defoort C, Helal O, Lairon D, Planells R, Shaw DI, Lovegrove JA, Gjelstad IM, Drevon CA, Blaak EE, Saris WH, Leszczynska-Golabek I, Kiec-Wilk B, Risérus U, Karlström B, Miranda JL & Roche HM. (2010). Gene-nutrient interactions in the metabolic syndrome: single nucleotide polymorphisms in ADIPOQ and ADIPOR1 interact with plasma saturated fatty acids to modulate insulin resistance. *Am J Clin Nutr.* 91(3), pp. 794-801.

Fernández-Real JM, Gutierrez C, Ricart W, Casamitjana R, Fernández-Castañer M, Vendrell J, Richart C & Soler J. (1997). The TNF-alpha gene Nco I polymorphism influences the relationship among insulin resistance, percent body fat, and increased serum leptin levels. *Diabetes*. 46(9), pp. 1468-72.

Filippi E, Sentinelli F, Trischitta V, Romeo S, Arca M, Leonetti F, Di Mario U & Baroni MG. (2004). Association of the human adiponectin gene and insulin resistance. *Eur J Hum Genet.* 12(3), pp. 199-205.

Fredriksson J, Anevski D, Almgren P, Sjögren M, Lyssenko V, Carlson J, Isomaa B, Taskinen MR, Groop L, Orho-Melander M & Botnia Study Group. (2007). Variation in GYS1 interacts with exercise and gender to predict cardiovascular mortality. *PLoS One.* 2, pp. e285.

Friebe D, Kovacs P, Neef M, Blüher S, Schleinitz D, Kiess W & Körner A. (2011). The promoter variant -803G>A in the RBP4 gene is not associated with BMI, metabolic parameters or blood pressure in Caucasian children. *Exp Clin Endocrinol Diabetes.* 119(10), pp. 628-32.

Gable DR, Stephens JW, Cooper JA, Miller GJ & Humphries SE. (2006). Variation in the UCP2-UCP3 gene cluster predicts the development of type 2 diabetes in healthy middle-aged men. *Diabetes* 55, pp. 1504- 1511.

Gao J, Katagiri H, Ishigaki Y, Yamada T, Ogihara T, Imai J, Uno K, Hasegawa Y, Kanzaki M, Yamamoto TT, Ishibashi S & Oka Y. (2007). Involvement of apolipoprotein E in excess fat accumulation and insulin resistance. *Diabetes.* 56, pp. 24-33.

Goyenechea E, Parra D & Martínez JA. (2007). Impact of interleukin 6 -174G>C polymorphism on obesity-related metabolic disorders in people with excess in body weight. *Metabolism.* 56(12), pp. 1643-8.

Grarup N, Andersen MK, Andreasen CH, Albrechtsen A, Borch-Johnsen K, Jørgensen T, Auwerx J, Schmitz O, Hansen T & Pedersen O. (2007). Studies of the common DIO2 Thr92Ala polymorphism and metabolic phenotypes in 7342 Danish white subjects. *J Clin Endocrinol Metab.* 92(1), pp. 363-6.

Grozovsky R, Ribich S, Rosene ML, Mulcahey MA, Huang SA, Patti ME, Bianco AC & Kim BW. (2009). Type 2 deiodinase expression is induced by peroxisomal proliferator-activated receptor-gamma agonists in skeletal myocytes. *Endocrinology.* 150(4), pp. 1976-83.

Gu P, Jiang W, Chen M, Lu B, Shao J, Du H & Jiang S. (2012). Association of leptin receptor gene polymorphisms and essential hypertension in a Chinese population. *J Endocrinol Invest.*

Gupta V, Gupta A, Jafar T, Gupta V, Agrawal S, Srivastava N, Kumar S, Singh AK, Natu SM, Agarwal CG & Agarwal GG. (2012). Association of TNF-α promoter gene G-308A polymorphism with metabolic syndrome, insulin resistance, serum TNF-α and leptin levels in Indian adult women. *Cytokine.* 57(1), pp. 32-6.

Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, Kadowaki H, Hagura R, Akanuma Y, Yazaki Y, Nagai R, Taniyama M, Matsubara K, Yoda M, Nakano Y, Tomita M, Kimura S, Ito C, Froguel P & Kadowaki T. (2002). Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes.* 51(2), pp. 536-40.

Henneman P, Aulchenko YS, Frants RR, Zorkoltseva IV, Zillikens MC, Frolich M, Oostra BA, van Dijk KW & van Duijn CM. (2010). Genetic architecture of plasma adiponectin overlaps with the genetics of metabolic syndrome-related traits. *Diabetes Care.* 33(4), pp. 908-13.

Herbert A, Liu C, Karamohamed S, Liu J, Manning A, Fox CS, Meigs JB & Cupples LA. (2006). BMI modifies associations of IL-6 genotypes with insulin resistance: the Framingham Study. *Obesity* (Silver Spring). 14(8), pp. 1454-61.

Higashiura K, Ura N, Takada T, Li Y, Torii T, Togashi N, Takada M, Takizawa H & Shimamoto K. (2000). The effects of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor antagonist on insulin resistance in fructose-fed rats. *Am J Hypertens.* 13(3), pp. 290-7.

Hivert MF, Manning AK, McAteer JB, Florez JC, Dupuis J, Fox CS, O'Donnell CJ, Cupples LA & Meigs JB. (2008). Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: the Framingham Offspring Study. *Diabetes* 57, pp. 3353–3359.

Hoffstedt J, Eriksson P, Hellström L, Rössner S, Rydén M & Arner P. (2000). Excessive fat accumulation is associated with the TNF alpha-308 G/A promoter polymorphism in women but not in men. *Diabetologia.* 43(1), pp. 117-20.

Hotamisligil GS, Shargill NS & Spiegelman BM. (1993). Adipose expression of tumour necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science.* 259, pp. 87–91.

Hotamisligil GS & Spiegelman BM. (1994). Tumour necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes.* 43, pp. 1271–8.

Hotamisligil GS, Murray DL, Choy LN & Spiegelman BM. (1994). Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proc Natl Acad Sci U S A.* 91, pp. 4854–8.

Hu FB, Meigs JB, Li TY, Rifai N & Manson JE. (2004). Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes.* 53, pp. 693–700.

Hung J, McQuillan BM, Thompson PL & Beilby JP. (2008). Circulating adiponectin levels associate with inflammatory markers, insulin resistance and metabolic syndrome independent of obesity. *Int J Obes* (Lond) 32, pp. 772–779

Jin JJ, Nakura J, Wu Z, Yamamoto M, Abe M, Chen Y, Tabara Y, Yamamoto Y, Igase M, Bo X, Kohara K & Miki T. (2003). Association of angiotensin II type 2 receptor gene variant with hypertension. *Hypertens Res.* 26(7), pp. 547-52.

Kamizono S, Yamada K, Seki N, Higuchi T, Kimura A, Nonaka K & Itoh K. (2000). Susceptible locus for obese type 2 diabetes mellitus in the 5'-flanking region of the tumor necrosis factor-alpha gene. *Tissue Antigens.* 55(5), pp. 449-52.

Katsuki A, Sumida Y, Murashima S, Murata K, Takarada Y, Ito K, Fujii M, Tsuchihashi K, Goto H, Nakatani K & Yano Y. (1998). Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab.* 83(3), pp. 859-62.

Katsuya T, Horiuchi M, Chen YD, Koike G, Pratt RE, Dzau VJ & Reaven GM. (1995). Relations between deletion polymorphism of the angiotensin-converting enzyme gene and insulin resistance, glucose intolerance, hyperinsulinemia, and dyslipidemia. *Arterioscler Thromb Vasc Biol*. 15(6), pp. 779-82.

Kikuya M, Sugimoto K, Katsuya T, Suzuki M, Sato T, Funahashi J, Katoh R, Kazama I, Michimata M, Araki T, Hozawa A, Tsuji I, Ogihara T, Yanagisawa T, Imai Y & Matsubara M. (2003). A/C1166 gene polymorphism of the angiotensin II type 1 receptor (AT1) and ambulatory blood pressure: the Ohasama Study. *Hypertens Res.* 26(2), pp. 141-5.

Kim CH, Yun SK, Byun DW, Yoo MH, Lee KU & Suh KI. (2001). Codon 54 polymorphism of the fatty acid binding protein 2 gene is associated with increased fat oxidation and hyperinsulinemia, but not with intestinal fatty acid absorption in Korean men. *Metabolism.* 50(4), pp. 473-6.

Komurcu-Bayrak E, Onat A, Yuzbasiogullari B, Mononen N, Laaksonen R, Kähönen M, Hergenc G, Lehtimäki T & Erginel-Unaltuna N. (2011). The APOE -219G/T and +113G/C polymorphisms affect insulin resistance among Turks. *Metabolism.* 60(5), pp. 655-63.

Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M, Ouchi N, Kihara S, Kawamoto T, Sumitsuji S, Funahashi T & Matsuzawa Y. (2002). Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. *Diabetes.* 51(7), pp. 2325-8.

Kovacs P, Ma L, Hanson RL, Franks P, Stumvoll M, Bogardus C & Baier LJ. (2005). Genetic variation in UCP2 (uncoupling protein-2) is associated with energy metabolism in Pima Indians. *Diabetologia.* 48(11), pp. 2292-5.

Kovacs P, Geyer M, Berndt J, Klöting N, Graham TE, Böttcher Y, Enigk B, Tönjes A, Schleinitz D, Schön MR, Kahn BB, Blüher M & Stumvoll M. (2007). Effects of genetic variation in the human retinol binding protein-4 gene (RBP4) on insulin resistance and fat depot-specific mRNA expression. *Diabetes.* 56(12), pp. 3095-100.

Krempler F, Esterbauer H, Weitgasser R, Ebenbichler C, Patsch JR, Miller K, Xie M, Linnemayr V, Oberkofler H & Patsch W. (2002). A functional polymorphism in the promoter of UCP2 enhances obesity risk but reduces type 2 diabetes risk in obese middle-aged humans. *Diabetes.* 51(11), pp. 3331-5.

Kubaszek A, Pihlajamäki J, Komarovski V, Lindi V, Lindström J, Eriksson J, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Tuomilehto J, Uusitupa M, Laakso M & Finnish Diabetes Prevention Study. (2003). Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes.* 52(7), pp. 1872-6.

Kypreos KE, Karagiannides I, Fotiadou EH, Karavia EA, Brinkmeier MS, Giakoumi SM & Tsompanidi EM. (2009). Mechanisms of obesity and related pathologies: role of apolipoprotein E in the development of obesity. *FEBS J.* 276, pp. 5720-8.

Lakka HM, Oksanen L, Tuomainen TP, Kontula K & Salonen JT. (2000). The common pent-nucleotide polymorphism of the 3- untranslated region of the leptin receptor gene is associated with serum insulin levels and the risk of type 2 diabetes in non-diabetic men: a prospective case-control study. *J Intern Med* 248, pp. 77-83.

Lambert JC, Brousseau T, Defosse V, Evans A, Arveiler D, Ruidavets JB, Haas B, Cambou JP, Luc G, Ducimetière P, Cambien F, Chartier-Harlin MC & Amouyel P. (2000). Independent association of an APOE gene promoter polymorphism with increased risk of myocardial infarction and decreased APOE plasma concentrations-the ECTIM study. *Hum Mol Genet.* 9, pp. 57-61.

Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, Orlova C & Mantzoros CS. (2003). Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-

sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab.* 88(10), pp. 4848-56.

Le Stunff C, Le Bihan C, Schork NJ & Bougnères P. (2000). A common promoter variant of the leptin gene is associated with changes in the relationship between serum leptin and fat mass in obese girls. *Diabetes*. 49(12), pp. 2196-200.

Lima JJ, Feng H, Duckworth L, Wang J, Sylvester JE, Kissoon N & Garg H. (2007). Association analyses of adrenergic receptor polymorphisms with obesity and metabolic alterations. *Metabolism.* 56(6), pp. 757-65.

Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J. (2002). Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet.* 6;360(9326):57-8.

Lyssenko V, Almgren P, Anevski D, Orho-Melander M, Sjögren M, Saloranta C, Tuomi T, Groop L & Botnia Study Group. (2005). Genetic prediction of future type 2 diabetes. *PLoS Med.* 2(12), pp. e345.

Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I & Matsuzawa Y. (2001). PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes.* 50(9), pp. 2094-9.

Maia AL, Dupuis J, Manning A, Liu C, Meigs JB, Cupples LA, Larsen PR & Fox CS. (2007). The type 2 deiodinase (DIO2) A/G polymorphism is not associated with glycemic traits: the Framingham Heart Study. *Thyroid.* 17(3), pp. 199-202.

Mammès O, Betoulle D, Aubert R, Giraud V, Tuzet S, Petiet A, Colas-Linhart N & Fumeron F. (1998). Novel polymorphisms in the 5' region of the LEP gene: association with leptin levels and response to low-calorie diet in human obesity. *Diabetes*. 47(3) pp. 487-9.

Mammès O, Betoulle D, Aubert R, Herbeth B, Siest G & Fumeron F. (2000). Association of the G-2548A polymorphism in the 5' region of the LEP gene with overweight. *Ann Hum Genet*. 64(Pt 5), pp.391-4.

Mansego ML, Martínez F, Martínez-Larrad MT, Zabena C, Rojo G, Morcillo S, Soriguer F, Martín-Escudero JC, Serrano-Ríos M, Redon J & Chaves FJ. (2012). Common variants of the liver Fatty Acid binding protein gene influence the risk of type 2 diabetes and insulin resistance in spanish population. *PLoS One.* 7(3), pp. e31853.

Mårin P, Holmäng S, Jönsson L, Sjöström L, Kvist H, Holm G, Lindstedt G & Björntorp P. (1992). The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord.* 16(12), pp. 991-7.

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28, pp. 412– 9.

Meigs JB, Ordovas JM, Cupples LA, Singer DE, Nathan DM, Schaefer EJ & Wilson PW. (2000). Apolipoprotein E isoform polymorphisms are not associated with insulin resistance: the Framingham Offspring Study. *Diabetes Care.* 23, pp. 669-74.

Melistas L, Mantzoros CS, Kontogianni M, Antonopoulou S, Ordovas JM & Yiannakouris N. (2009). Association of the +45T>G and +276G>T polymorphisms in the adiponectin gene with insulin resistance in nondiabetic Greek women. *Eur J Endocrinol.* 161(6), pp. 845-52.

Mentuccia D, Proietti-Pannunzi L, Tanner K, Bacci V, Pollin TI, Poehlman ET, Shuldiner AR & Celi FS. (2002). Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes.* 51(3), pp. 880-3.

Mentuccia D, Thomas MJ, Coppotelli G, Reinhart LJ, Mitchell BD, Shuldiner AR & Celi FS. (2005). The Thr92Ala deiodinase type 2 (DIO2) variant is not associated with type 2 diabetes or indices of insulin resistance in the old order of Amish. *Thyroid.* 15(11), pp. 1223-7.

Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, Trischitta V & Doria A. (2002). A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. *Diabetes.* 51(7), pp. 2306-12.

Menzaghi C, Trischitta V & Doria A.(2007). Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes* 56, pp. 1198–209.

Mitchell BD, Kammerer CM, O'Connell P, Harrison CR, Manire M, Shipman P, Moyer MP, Stern MP & Frazier ML. (1995). Evidence for linkage of postchallenge insulin levels with intestinal fatty acid-binding protein (FABP2) in Mexican-Americans. *Diabetes*. 44(9), pp. 1046-53.

Möhlig M, Wegewitz U, Osterhoff M, Isken F, Ristow M, Pfeiffer AF & Spranger J. (2002). Insulin decreases human adiponectin plasma levels. *Horm Metab Res* 34, pp. 655–658.

Möhlig M, Boeing H, Spranger J, Osterhoff M, Kroke A, Fisher E, Bergmann MM, Ristow M, Hoffmann K & Pfeiffer AF. (2004). Body mass index and C-174G interleukin-6 promoter polymorphism interact in predicting type 2 diabetes. *J Clin Endocrinol Metab.* 89(4), pp. 1885-90.

Morcillo S, Martín-Núñez GM, Rojo-Martínez G, Almaraz MC, García-Escobar E, Mansego ML, de Marco G, Chaves FJ & Soriguer F. (2011). ELOVL6 genetic variation is related to insulin sensitivity: a new candidate gene in energy metabolism. *PLoS One.* 6(6), pp. e21198.

Moreno JA, López-Miranda J, Marín C, Gómez P, Pérez-Martínez P, Fuentes F, Fernández de la Puebla RA, Paniagua JA, Ordovas JM & Pérez-Jiménez F.(2003). The influence of the apolipoprotein E gene promoter (-219G/ T) polymorphism on postprandial lipoprotein metabolism in young normolipemic males. *J Lipid Res.* 44, pp. 2059-64.

Moreno JA, Pérez-Jiménez F, Marín C, Pérez-Martínez P, Moreno R, Gómez P, Jiménez-Gómez Y, Paniagua JA, Lairon D & López-Miranda J. (2005). The apolipoprotein E gene promoter (-219G/T) polymorphism determines insulin sensitivity in response to dietary fat in healthy young adults. *J Nutr.* 135, pp. 2535-40.

Mottagui-Tabar S, Hoffstedt J, Brookes AJ, Jiao H, Arner P & Dahlman I. (2008). Association of ADRB1 and UCP3 gene polymorphisms with insulin sensitivity but not obesity. *Horm Res.* 69(1), pp. 31-6.

Munkhtulga L, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Erdenebulgan B, Zolzaya K, Lkhagvasuren T & Iwamoto S. (2007). Identification of a regulatory SNP in the retinol binding protein 4 gene associated with type 2 diabetes in Mongolia. *Hum Genet*. 120(6), pp. 879-88.

Munkhtulga L, Nagashima S, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Zolzaya K, Lkhagvasuren T, Kagawa Y, Fujiwara H, Hosoya Y, Hyodo M,

Horie H, Kojima M, Ishibashi S & Iwamoto S. (2010). Regulatory SNP in the RBP4 gene modified the expression in adipocytes and associated with BMI. *Obesity* (Silver Spring). 18(5), pp. 1006-14.

Muoio DM & Newgard CB. (2008). Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. *Nat Rev Mol Cell Biol.* 9(3), pp. 193-205.

Ochoa MC, Santos JL, Azcona C, Moreno-Aliaga MJ, Martínez-González MA, Martínez JA, Marti A & GENOI Members. (2007). Association between obesity and insulin resistance with UCP2-UCP3 gene variants in Spanish children and adolescents. *Mol Genet Metab.* 92(4), pp. 351-8.

Ohara M, Maesawa C, Takebe N, Takahashi T, Yamashina M, Ono M, Matsui M, Sasai T, Honma H, Nagasawa K, Fujiwara F, Kajiwara T, Taneichi H, Takahashi K & Satoh J. (2012). Different susceptibility to insulin resistance and fatty liver depending on the combination of TNF-α C-857T and adiponectin G+276T gene polymorphisms in Japanese subjects with type 2 diabetes. *Tohoku J Exp Med.* 226(2), pp. 161-9.

Ono K, Mannami T, Baba S, Yasui N, Ogihara T & Iwai N. (2003). Lack of association between angiotensin II type 1 receptor gene polymorphism and hypertension in Japanese. *Hypertens Res* 26, pp. 131–134.

Osawa H, Yamada K, Onuma H, Murakami A, Ochi M, Kawata H, Nishimiya T, Niiya T, Shimizu I, Nishida W, Hashiramoto M, Kanatsuka A, Fujii Y, Ohashi J & Makino H. (2004). The G/G genotype of a resistin single-nucleotide polymorphism at -420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. *Am J Hum Genet.* 75(4), pp. 678-86.

Osawa H, Tabara Y, Kawamoto R, Ohashi J, Ochi M, Onuma H, Nishida W, Yamada K, Nakura J, Kohara K, Miki T & Makino H. (2007). Plasma resistin, associated with single nucleotide polymorphism -420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese general, pp.population. *Diabetes Care.* 30(6):1501-6.

Peeters RP, van der Deure WM, van den Beld AW, van Toor H, Lamberts SW, Janssen JA, Uitterlinden AG &Visser TJ. (2007). The Asp727Glu polymorphism in the TSH receptor is associated with insulin resistance in healthy elderly men. *Clin Endocrinol* (Oxf). 66(6), pp. 808-15.

Perry JR, Weedon MN, Langenberg C, Jackson AU, Lyssenko V, Sparsø T, Thorleifsson G, Grallert H, Ferrucci L, Maggio M, Paolisso G, Walker M, Palmer CN, Payne F, Young E, Herder C, Narisu N, Morken MA, Bonnycastle LL, Owen KR, Shields B, Knight B, Bennett A, Groves CJ, Ruokonen A, Jarvelin MR, Pearson E, Pascoe L, Ferrannini E, Bornstein SR, Stringham HM, Scott LJ, Kuusisto J, Nilsson P, Neptin M, Gjesing AP, Pisinger C, Lauritzen T, Sandbaek A, Sampson M; MAGIC, Zeggini E, Lindgren CM, Steinthorsdottir V, Thorsteinsdottir U, Hansen T, Schwarz P, Illig T, Laakso M, Stefansson K, Morris AD, Groop L, Pedersen O, Boehnke M, Barroso I, Wareham NJ, Hattersley AT, McCarthy MI & Frayling TM. (2010). Genetic evidence that raised sex hormone binding globulin (SHBG) levels reduce the risk of type 2 diabetes. *Hum Mol Genet.* 19(3), pp. 535-44.

Perseghin G, Petersen K & Shulman GI. (2003). Cellular mechanism of insulin resistance: potential links with inflammation. *Int J Obes Relat Metab Disord.* 27 Suppl 3, pp. S6-11.

Perticone F, Ceravolo R, Iacopino S, Cloro C, Ventura G, Maio R, Gulletta E, Perrotti N & Mattioli PL. (2001). Relationship between angiotensin-converting enzyme gene polymorphism and insulin resistance in never-treated hypertensive patients. *J Clin Endocrinol Metab.* 86(1), pp. 172-8.

Pizzuti A, Argiolas A, Di Paola R, Baratta R, Rauseo A, Bozzali M, Vigneri R, Dallapiccola B, Trischitta V & Frittitta L. (2002). An ATG repeat in the 3'-untranslated region of the human resistin gene is associated with a decreased risk of insulin resistance. *J Clin Endocrinol Metab.* 87(9), pp. 4403-6.

Prochazka M, Lillioja S, Tait JF, Knowler WC, Mott DM, Spraul M, Bennett PH & Bogardus C. (1993). Linkage of chromosomal markers on 4q with a putative gene determining maximal insulin action in Pima Indians. *Diabetes.* 42(4), pp. 514-9.

Qi L, van Dam RM, Meigs JB, Manson JE, Hunter D & Hu FB. (2006). Genetic variation in IL6 gene and type 2 diabetes: tagging-SNP haplotype analysis in large-scale case-control study and meta-analysis. *Hum Mol Genet.* 15(11), pp. 1914-20.

Quinton ND, Lee AJ, Ross RJ, Eastell R & Blakemore AI. (2001). A single nucleotide polymorphism (SNP) in the leptin receptor is associated with BMI, fat mass and leptin levels in postmenopausal Caucasian women. *Hum Genet* 108, pp. 233-6.

Rai E, Sharma S, Koul A, Bhat AK, Bhanwer AJ & Bamezai RN. (2007). Interaction between the UCP2-866G/A, mtDNA 10398G/A and PGC1alpha p.Thr394Thr and p.Gly482- Ser polymorphisms in type 2 diabetes susceptibility in North Indian population. *Hum Genet* 122, pp. 535-40.

Ranjith N, Pegoraro RJ, Naidoo DP, Shanmugam R & Rom L. (2008). Genetic variants associated with insulin resistance and metabolic syndrome in young Asian Indians with myocardial infarction. *Metab Syndr Relat Disord* 6(3), pp. 209–14.

Reaven GM. (1988). Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* 37, pp. 1595-607.

Reaven GM. (1995). Pathophysiology of insulin resistance in human disease. *Physiol Rev* 75, pp. 473–86.

Reis AF, Dubois-Laforgue D, Bellanne-Chantelot C, Timsit J & Velho G. (2004). A polymorphism in the promoter of UCP2 gene modulates lipid levels in patients with type 2 diabetes. *Mol Genet Metab* 82: 339- 344.

Ren W, Zhang SH, Wu J & Ni YX. (2004). Polymorphism of the leptin gene promoter in pedigrees of type 2 diabetes mellitus in Chongqing, China. *Chin Med J* (Engl). 117(4), pp. 558-61

Santos JL, Boutin P, Verdich C, Holst C, Larsen LH, Toubro S, Dina C, Saris WH, Blaak EE, Hoffstedt J, Taylor MA, Polak J, Clement K, Langin D, Astrup A, Froguel P, Pedersen O, Sorensen TI, Martinez JA & NUGENOB* consortium.(2006). Genotype-by-nutrient interactions assessed in European obese women. A case-only study. *Eur J Nutr.* 45(8), pp. 454-62.

Shea JL, Loredo-Osti JC & Sun G. (2010). Association of RBP4 gene variants and serum HDL cholesterol levels in the Newfoundland population. *Obesity* (Silver Spring). 18(7), pp. 1393-7.

Sheng T & Yang K. (2008). Adiponectin and its association with insulin resistance and type 2 diabetes. J Genet *Genomics* 35, pp. 321–6.

Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL & Murphy LJ. (2003). Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *Eur J Endocrinol.* 149(4), pp. 331-5.

Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, Gouault-Heilmann M, Lemort N, Thibult N, Joubert E, Balkau B & Eschwege E. (2001). Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care.* 24(12), pp. 2149-51.

Sipiläinen R, Uusitupa M, Heikkinen S, Rissanen A & Laakso M. (1997). Variants in the human intestinal fatty acid binding protein 2 gene in obese subjects. *J Clin Endocrinol Metab.* 82(8), pp. 2629-32.

Sookoian SC, González C & Pirola CJ. (2005). Meta-analysis on the G-308A tumor necrosis factor alpha gene variant and phenotypes associated with the metabolic syndrome. *Obes Res.* 13(12), pp. 2122-31

Spranger J, Kroke A, Möhlig M, Bergmann MM, Ristow M, Boeing H & Pfeiffer AF. (2003). Adiponectin and protection against type 2 diabetes mellitus. *Lancet.* 361(9353), pp. 226-8.

Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, Machicao F & Häring H. (2002). Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. *Diabetes.* 51(1), pp. 37-41.

Sugimoto K, Katsuya T, Ohkubo T, Hozawa A, Yamamoto K, Matsuo A, Rakugi H, Tsuji I, Imai Y & Ogihara T. (2004). Association between angiotensin II type 1 receptor gene polymorphism and essential hypertension: the Ohasama Study. *Hypertens Res.* 27(8), pp. 551-6.

Takahashi-Yasuno A, Masuzaki H, Miyawaki T, Matsuoka N, Ogawa Y, Hayashi T, Hosoda K, Yoshimasa Y, Inoue G & Nakao K. (2004). Association of Ob-R gene polymorphism and insulin resistance in Japanese men. *Metabolism.* 53(5), pp. 650-4.

Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, Staiger H, Maerker E, Häring H & Stumvoll M. (2003). Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes.* 52(2), pp. 239-43.

Underwood PC, Chamarthi B, Williams JS, Sun B, Vaidya A, Raby BA, Lasky-Su J, Hopkins PN, Adler GK & Williams GH. (2012). Replication and meta-analysis of the gene-environment interaction between body mass index and the interleukin-6 promoter polymorphism with higher insulin resistance. *Metabolism.* 61, pp. 667-671.

Ura N, Higashiura K & Shimamoto K. (1999). The mechanisms of insulin sensitivity improving effects of angiotensin converting enzyme inhibitor. *Immunopharmacology* 44, pp. 153–159.

Urbanek M, Du Y, Silander K, Collins FS, Steppan CM, Strauss JF 3rd, Dunaif A, Spielman RS & Legro RS. (2003). Variation in resistin gene promoter not associated with polycystic ovary syndrome. *Diabetes.* 52(1), pp. 214-7

Valdez R, Howard BV, Stern MP & Haffner SM. (1995). Apolipoprotein E polymorphism and insulin levels in a biethnic population. *Diabetes Care.* 18, pp. 992-1000.

van Hoek M, Dehghan A, Zillikens MC, Hofman A, Witteman JC & Sijbrands EJ. (2008). An RBP4 promoter polymorphism increases risk of type 2 diabetes. *Diabetologia.* 51(8), pp. 1423-8.

Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, Hara K, Clément K, Bihain B, Kadowaki T & Froguel P. (2002). Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet.* 11(21), pp. 2607-14.

Vendrell J, Fernandez-Real JM, Gutierrez C, Zamora A, Simon I, Bardaji A, Ricart W & Richart C. (2003). A polymorphism in the promoter of the tumor necrosis factor-alpha gene (-308) is associated with coronary heart disease in type 2 diabetic patients. *Atherosclerosis*. 167(2), pp. 257-64.

Viitanen L, Pihlajamäki J, Miettinen R, Kärkkäinen P, Vauhkonen I, Halonen P, Kareinen A, Lehto S & Laakso M. (2001). Apolipoprotein E gene promoter (-219G/T) polymorphism is associated with premature coronary heart disease. *J Mol Med.* 79, pp. 732-7.

Wang H, Chu WS, Hemphill C & Elbein SC. (2002). Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. *J Clin Endocrinol Metab.* 87(6), pp. 2520-4.

Wang H, Chu WS, Lu T, Hasstedt SJ, Kern PA &Elbein SC. (2004). Uncoupling protein-2 polymorphisms in type 2 diabetes, obesity, and insulin secretion. *Am J Physiol Endocrinol Metab* 286, pp. E1-E7.

Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH & Sattar N. (2007). Adipokines and risk of type 2 diabetes in older men. *Diabetes Care.* 30, pp. 1200–1205.

Wauters M, Mertens I, Rankinen T, Chagnon M, Bouchard C & Van Gaal L. (2001). Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. *J Clin Endocrinol Metab.* 86(7), pp. 3227-32.

Wauters M, Considine RV, Chagnon M, Mertens I, Rankinen T, Bouchard C & Van Gaal LF.(2002). Leptin levels, leptin receptor gene polymorphisms, and energy metabolism in women. *Obes Res.* 10(5), pp. 394-400.

Weinstein SP, O'Boyle E & Haber RS. (1994). Thyroid hormone increases basal and insulin-stimulated glucose transport in skeletal muscle. The role of GLUT4 glucose transporter expression. *Diabetes.* 43(10), pp. 1185-9.

Weiss EP, Brown MD, Shuldiner AR & Hagberg JM. (2002). Fatty acid binding protein 2 gene variants and insulin resistance: gene and gene-environmental interaction effects. *Physiol Genomics.* 10, pp. 145–57.

Xu K, Zhang M, Cui D, Fu Y, Qian L, Gu R, Wang M, Shen C, Yu R & Yang T. (2011). UCP2 -866G/A and Ala55Val, and UCP3 -55C/T polymorphisms in association with type 2 diabetes susceptibility: a meta-analysis study. *Diabetologia.* 54(9), pp. 2315-24.

Yamada K, Yuan X, Ishiyama S, Koyama K, Ichikawa F, Koyanagi A, Koyama W& Nonaka K. (1997). Association between Ala54Thr substitution of the fatty acid-binding protein 2

gene with insulin resistance and intra-abdominal fat thickness in Japanese men. *Diabetologia.* 40(6), pp. 706-10.

Yamamoto J, Kageyama S, Sakurai T, Ishibashi K, Mimura A, Yokota K, Aihara K, Taniguchi I, Yoshida H & Tajima N. (1999). Insulin resistance and angiotensin converting enzyme polymorphism in Japanese hypertensive subjects. *Hypertens Res.* 22(2), pp. 81-4.

Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L & Kahn BB. (2005). Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature.* 436(7049), pp. 356-62.

Zee RY, Ridker PM & Chasman DI. (2011). Mitochondrial uncoupling protein gene cluster variation (UCP2-UCP3) and the risk of incident type 2 diabetes mellitus: the Women's Genome Health Study. *Atherosclerosis* 214, pp. 107- 109.

Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jørgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjögren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ; Wellcome Trust Case Control Consortium, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M & Altshuler D. (2008). Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet.* 40(5), pp. 638-45.

Zimmerman AW & Veerkamp JH. (2002). New insights into the structure and function of fatty acid-binding proteins. *Cell Mol Life Sci.* 59(7), pp. 1096-116.

Zinman B, Hanley AJ, Harris SB, Kwan J& Fantus G. (1999). Circulating tumor necrosis factor α concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 84, pp. 272–8.