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RESEARCH ARTICLE

ASSOCIATION OF PEROXISOME PROLIFERATED ACTIVATED RECEPTOR (PPAR) AND FATTY ACID BINDING PROTEIN (FABP2) GENE POLYMORPHISMS ON T2DM AND INSULIN RESISTANCE ON DIFFERENT POPULATIONS

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ABSTRACT

Type 2 Diabetes mellitus (T2DM) is a highly prevalent chronic degenerative disease, which is indicated by insulin resistance (IR) in insulin-target tissues, and aberrant insulin secretion from pancreatic β-cells. Several common polymorphic genetic variants have been concerned in type 2 diabetes and insulin resistance, though the results of previous researches performed on different ethnic groups and populations are greatly contradicting. Two of the most common polymorphisms studied widely are the Ala54Thr variant of Fatty Acid Binding Protein 2 (FABP2) gene, and the Pro12Ala variant of Peroxisome Proliferator Activated Receptor Gamma (PPARγ) gene. A number of other non-genetic factors also significantly affect insulin resistance, like body composition, regular levels of physical exercises, gender and age. In this review, we discuss both genetic and non genetic factors, the relationship between insulin resistance and T2DM, how the polymorphisms in two candidate genes FABP2 and PPARγ affect the T2DM, IR and other diseases in different populations and ethnic groups.

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INTRODUCTION

Diabetes is a chronic disease with high prevalence throughout the world. It results when the pancreas do not produce enough insulin or when the body cannot efficiently use the insulin produced. The etiology of the disease encompasses numerous metabolic alterations (obesity, lipid profile, hypertension) that are also involved with a variable influence on the progression of the disease. Having access to genetic basis of diabetes, will greatly assist in the proper therapeutic production and eventually prevention of disease complications, progression, and development. As a complex disease, diabetes continues to escape the medical and research communities. However, and unfortunately, the growing epidemic persistently increases the gap between treatments and treated (Miramontes González *et al*., 2014). The number of people worldwide with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild *et al*., 2004). In people over 65 years old, the prevalence was 26.9% in 2007 (National Diabetes Fact Sheet, 2011). This number signifies huge societal costs when it comes to mortality morbidity and healthcare systems.

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T2DM Mellitus (T2D), the most common type of diabetes (comprising 90% of patients worldwide), a complex metabolic disorder of multifactorial pathogenesis (Stumvoll *et al*., 2005). It is a vital health issue because of its persistently increasing rate of morbidity and mortality. It is one of the key challenges to public health.

Insulin resistance

Insulin resistance (IR) is a condition in which the normal response to a certain amount of insulin is decreased. As a consequence of this reduction, elevated levels of insulin are required for it to be more effective. So, the pancreas compensates by producing higher levels of insulin. This creates resistance and it occurs in response to the body's own insulin (endogenous) or when insulin is administered by injection (exogenous). With insulin resistance, the pancreas continues to produce higher levels of insulin until the pancreas can no longer produce sufficient amount of insulin to meet the body's requirements, then blood sugar increases. Insulin resistance hence poses to be a risk factor for progression of diabetes and heart disease. It is characterized by decreased glucose uptake and altered lipid metabolism (Cline *et al*., 1999),

(Dresner *et al*., 1999), (Kelley *et al*., 2002), (Rothman *et al*., 1992), (Russell 1999). It is a precursor for the initial stages of T2DM, a metabolic disorder commonly linked with obesity, ectopic fat depots, and physical inactivity, and ultimately develops toward failure of the pancreatic β-cells. The association among insulin resistance and the buildup of lipids in tissues suggests that these lipids are both markers and mediators of metabolic dysfunction, particularly in skeletal muscle, that is the major location of insulin-stimulated glucose clearance (Chibalin AV *et al*., 2008), (Kelley *et al*., 1999), (Levin *et al*., 2007), (McGarry 1998), (McGarry *et al*., 2001), (Muoio *et al*., 2006), (Savage *et al*., 2007), (Young *et al*., 2002).

Relationship between insulin resistance and diabetes

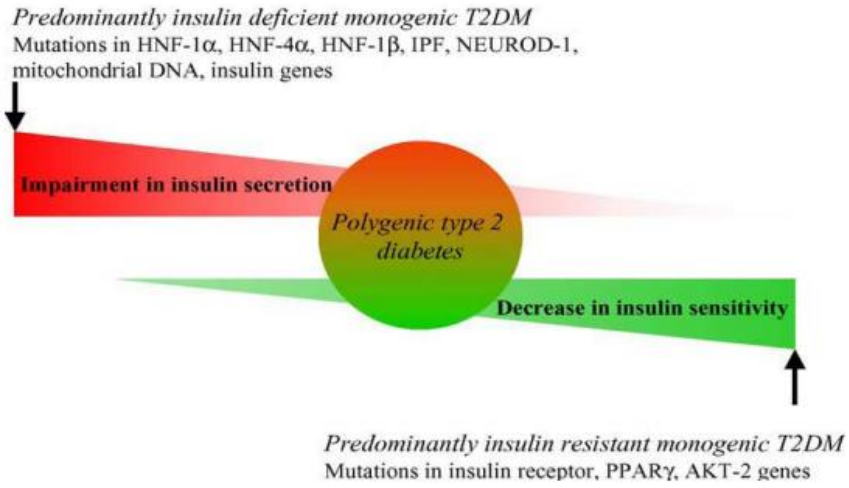
T2DM is the type of diabetes that occurs later in life or with obesity at any age. It results from a decrease in glucose-induced insulin secretion and reduced efficiency in insulin action (insulin resistance). It is also characteristic of obesity and lipodystrophy (Ferré 2004) Insulin resistance heralds the progression of T2DM, sometimes by years. In those who will eventually develop T2DM, the blood glucose and insulin levels are normal for many years, until at some point, they develop insulin resistance. At this point, high insulin levels are often coupled with other diseases such as obesity, cholesterol aberration, and hypertension. When all these problems happen simultaneously, it is called the metabolic syndrome. One function of insulin is to bind on the insulin receptors on cell surfaces (mainly muscle and fat) which removes and uses glucose from the blood. This is one method by which insulin controls the level of blood glucose.

sugar rises abnormally above certain levels, T2DM is present (Stoppler *et al*., 2014).

The association between insulin resistance and diabetes is clear. For instance insulin resistance is a key contributor to the pathogenesis of type-2 diabetes (T2DM) and a main player in various other metabolic disorders including hypertension, dyslipidaemia and atherosclerosis (Khan *et al*., 2000). T2DM patients have at least 50% (and sometimes up to 100%) normal β-cell mass, and their fasting plasma insulin concentrations are increased (Khan c roland, 2000), yet these patients are sometimes considered insulin-deficient because normal pancreases would have secreted considerably larger amounts of insulin when confronted with similar degree of hyperglycemia (Weire *et al*., 2001).

Major complications due to diabetes

The main complications of diabetes are cardiovascular problems like heart diseases, hypertension, diabetic neuropathies, renal complications, skin ulcers, and oral problems. Diabetes leads to reduced life expectancy; about 50% die of cardiovascular disease (CVD). The CVDs that accompany diabetes include angina, myocardial infarction (heart attack), stroke, peripheral arterial disease, and congestive heart failure. (Mathew E *et al*., 2010). It could be due to the direct toxic effects of hyperglycemia, and in addition the impact of hypertension, dyslipidemia and abnormalities of small blood vessels.



This figure is taken from (Maciej *et al*., 2005)

Fig. 1. Main contributing factors to T2DM- insulin resistance

The resistance of the cells persistently increases over time. As long as the pancreas produces enough insulin to overcome this resistance, blood glucose levels remain normal. However when the pancreas is unable to produce enough insulin for the body, the blood glucose levels begin to rise. Initially, this happens after meals (when glucose levels are at their highest and more insulin is needed) but eventually while fasting too. When blood

T2DM is linked with a cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglycerides.

Many reports have been published on T2DM genetics with the latest ones showing the effect of SNP's in a variety of genes

that correspond to the risk prediction of T2DM such as, gene variants of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) and Fatty Acid Binding Protein-2 (FABP2).

In this review, we will focus on two candidate genes Peroxisome Proliferator Activated Protein- Gamma (PPAR-γ) and Fatty Acid Binding Protein 2 (FABP2), in which the genetic polymorphisms have been well known to be functional and shown in more than one study for their association with T2DM, in various ethnic groups and populations.

FABP-2

Fatty acid-binding protein (FABP) 2 is an intracellular protein expressed only in the intestine (Sacchettini JC *et al*.,1990). FABP2 plays a major role in the absorption and intracellular transport of dietary long chain fatty acids. Because glucose and fatty acid metabolism are closely related occurrences, FABP2 soon became a significant candidate gene for T2DM (Abbas *et al*., 2013).

The gene for FABP2 is located in the long arm of chromosome 4. The G-to-A polymorphism of codon 54 results in the substitution of threonine (Thr) for alanine (Ala) (Baier *et al*., 1995). In vitro experiments have shown that this substitution enhances the affinity of FABP2 for long-chain fatty acids and is linked with increased triglyceride transport in human intestinal cells (Baier *et al*., 1996), (Prochazka *et al*., 1993).

FABP2 variants, insulin resistance and T2DM

The relation between Type 2 DM and the Ala54Thr polymorphism of the FABP2 gene, might be explained by the result of this mutation on the free fatty acid metabolism. Mutations in this gene elevate fatty acid absorption and enhance fatty acid oxidation. The link between FABP2 mutation and T2DM can be explained by the Randle cycle (Randle *et al*., 1963) that is based upon the competition between free fatty acid and glucose at the level of striated muscle is a potential mechanism of insulin resistance (Boullu-Sanchis *et al*., 1999).

Several studies have evaluated FABP2 gene polymorphisms and their association with insulin resistance and have revealed several FABP2 gene variants in humans. The first of these variants was discovered in 1993 (Prochazka *et al*., 1993). A microsatellite region in intron 2 of the FABP2 gene was found to have 7 alleles including the wild-type allele and trinucleotide repeats of 10–15 consecutive ATT sequences (Humphreys *et al*., 1994), (Prochazka *et al*., 1993). Novel sites with sequence variation were found in 1995 by Baier *et al* who scanned the four exons of FABP2 and discovered SNPs at three positions (Baier *et al*., 1995). Two of the SNPs, a thymine (T) for cytosine (C) substitution in codon 71 and an adenine (A) for guanine (G) substitution in codon 118, that were present in coding regions of the gene, but are silent mutations. However, a third SNP, an A for G substitution in codon 54 of exon 2, was found to be a missense mutation. A consequence of this variant is a threonine (Thr) for alanine (Ala) amino acid substitution in the translation product and, thus, changes the structure and potentially the role of FABP2. The latest identified FABP2 variant is an A for G SNP in the 3' non-coding region of FABP2 (Pihlajamaki *et al*., 1997), (Rissanen *et al*., 1997), (Snustad *et al*., 2000). Hypothetically, this variant does not affect the gene product. However, the function of the nucleotide sequences that flank the coding regions of genes are not completely understood, and they are probably involved in the regulation of gene expression (Snustad *et al*., 2000).

Therefore, among all these mutations in the FABP2 gene, only the Ala54Thr SNP has a certain effect on primary protein structure; thus, this variant seems the most probable candidate to change the protein's function. Even though it is uncertain that a silent mutation in the coding region and a mutation in the non coding region can affect the role, their presence cannot be neglected because the function of these gene regions is mainly unknown (Weiss *et al*., 2002).

The Ala 54 to Thr 54 FABP2 polymorphism is common, with a Thr54 allelic frequency of 30% in most populations. This amino acid substitution had an effect of being associated with high insulin resistance, and fasting insulin concentrations (Baier *et al*., 1995).

FABP2 Ala54Thr polymorphism has been linked with an increased fasting insulin concentration, increased rate of lipid oxidation, reduced insulin-stimulated glucose uptake and increased concentrations of fasting and postprandial triglyceride-rich lipoprotein (Agren *et al*., 2001), (Lefevre *et al*., 2005), (Marin *et al*., 2005), (Berthier *et al*., 2001), (Yamada *et al*., 1997). It has been suggested that the Ala54Thr polymorphism might potentially be linked with the risk for atherosclerosis since it causes a compositional alteration in LDL particles (Pihlajamaki *et al*.,1997), an altered postprandial lipemia (Agren *et al*., 2001).

The fatty acid binding protein 2 (FABP2) gene codes for intestinal FABP, which is a member of a family of small intracellular lipid-binding proteins. FABP plays a significant role in many steps of unsaturated and saturated long chain fatty acids (LCFAs), protection of the cell from the cytotoxic effects of FFAs, and modulation of the enzyme additive involved in lipid metabolism (Besnard 1996), (Van Nieuwenhoven Fa *et al*., 1996).

Carriers of the *Thr54* allele in *FABP2* have a 2-fold greater affinity for the long-chain fatty acids than those with the *Ala54*-containing *FABP2* (Agren *et al*., 2001), which maintain the function of the *FABP2* Ala54Thr polymorphism in the etiology of metabolic disorders. On the other hand, elevated levels of a circulating cytokine expressed in adipocytes-where it is a significant modulator of gene expression-called tumor necrosis factor (TNF) α are a potential risk factor for the progression of obesity and other obesity related disorders (Hotamisligil *et al*.,1995). Reports confirm suggesting that a higher ω-6-to- ω -3 fatty acid ratio in the diet is linked with increased circulating levels of TNF α (Blok *et al*., 1997), (Hodge *et al*., 1998), (Sasaki *et al*., 2000). TNF α has an effect on lipid metabolism and might cause hypertriglyceridemia by lessening the activity of hepatic lipoprotein lipase and by enhancing hepatic de novo fatty acid synthesis (Zinman *et al*., 1999). Circulating levels of TNF α have also been described to decrease the activity of

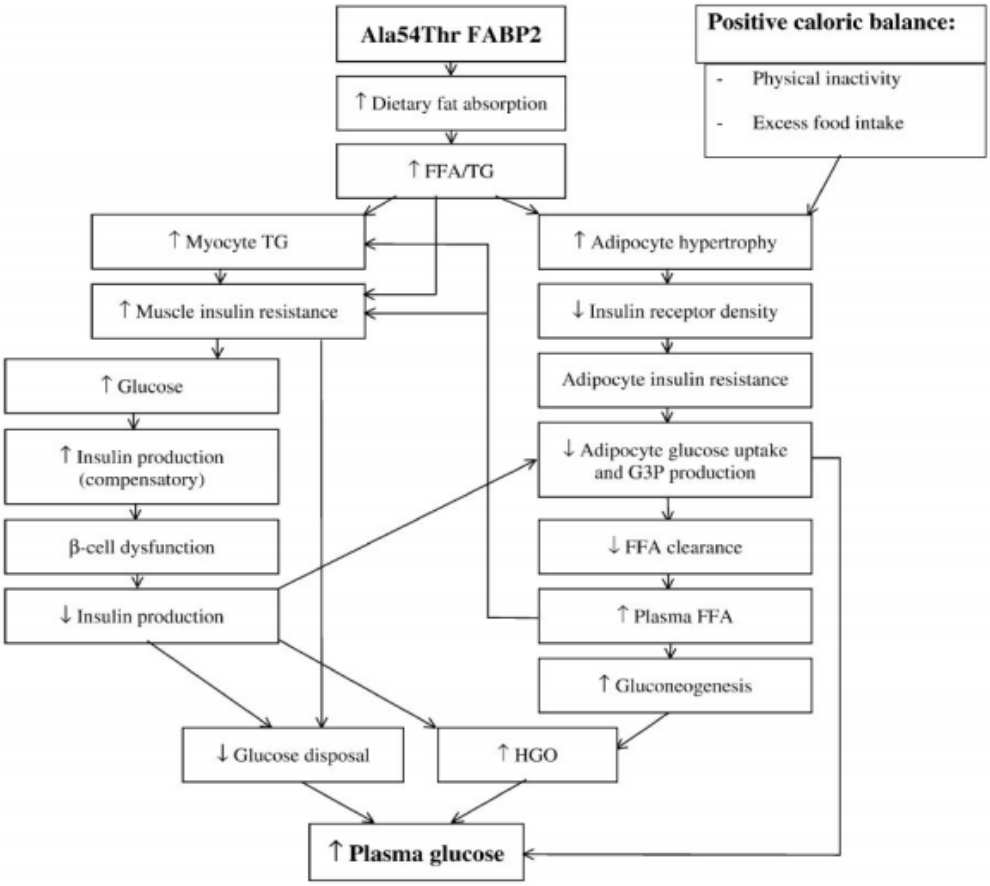
insulin receptor tyrosine kinase and stimulate GLUT4 transporter down-regulation in adipocytes in a way that links insulin resistance and T2DM (Hotamisligil *et al*., 1994).

PPAR γ

PPARs (isoforms α, δ, and γ) are ligand-activated transcription factors that form a heterodimer with retinoid X receptor (RXR). It has been studied that agonists of PPAR acquire anti-diabetogenic, anti-inflammatory, and antioxidant effects. PPAR-γ gene, that encodes the nuclear receptor PPAR-γ, was the first gene reproducibly associated with T2DM (Deeb *et al*., 1998).

PPAR-γ gene is located on chromosome 3p25 and contains 9 exons, spans more than 100 kilobases, and two protein isoforms are produced; PPARγ-1 and PPARγ-2, as a consequence of alternative mRNA splicing (Fajas L *et al*., 1997). PPARs comprise of a different sub-family of the nuclear receptors that are activated by naturally occurring fatty acids (Balasubramanyam *et al*., 2000).

gene that enhances ligand independent activation (Altshuler *et al*., 2000). This polymorphism has been reported to be linked with obesity. Using a family based design to control for population stratification, it was found that Ala allele of this polymorphism was linked with a decreased risk of T2DM (Deeb *et al*., 1998). In a meta analysis performed by Ludovico, it was found that those who had an alanine allele possessed less risk to T2DM among the Asians and Caucasians (Ludovico *et al*., 2007). However, contradictory results have been reported within the same study in another place where Ala12 variant was linked with a reduced risk for the progression of diabetes (Altshuler *et al*., 2000), (Mori *et al*., 2001), (Ghoussaini *et al*., 2005). Shortly, it became clear that most negative reports had been underpowered and after joining the data from all published studies in a meta-analysis it became clear that Pro12Ala variant was linked with T2DM (Altshuler *et al*., 2000), (Gouda *et al*., 2010), (Tonjes *et al*., 2006). PPAR-γ holds an important function in glucose homeostasis and is the molecular target for a rank of insulin-sensitizing drugs called thiazolidinediones (TZDs).



This image was taken from: Weiss EP *et al*., 2002

Fig. 2. Combined hypothesis of Ivy *et al* (1999) and Baier *et al* (1995) to explain the connection between Ala54Thr FABP2 and insulin resistance/T2DM

Ever since Yen CJ discovered this polymorphism, the link between the alanine to proline substitution at codon 12 of PPAR- γ and the risk for T2DM has been extensively studied (Yen *et al*., 1997). A common Pro12Ala polymorphism has been discovered within an exclusive domain of the PPARγ-2 TZDs is PPARγ2 ligands and extensively used to treat T2DM (Florian *et al*., 2006), they had least activity towards PPAR-α or PPAR-β. The PPAR- γ levels are 10–30 times higher in fat than in muscle or liver, but this receptor is still expressed in these latter tissues. Effects on insulin action in

other tissues would then happen as a result of modification in signalling molecules produced by fat, such as free fatty acids, TNF-α, leptin, or others (Perspectives in Diabetes PPAR-γ: Adipogenic Regulator and TZDs Receptor) (Spiegelman *et al*., 1998). PPAR- γ activation controls one or more genes that regulate systemic insulin sensitivity like TNF-α and leptin.

PPARγ role in insulin resistance

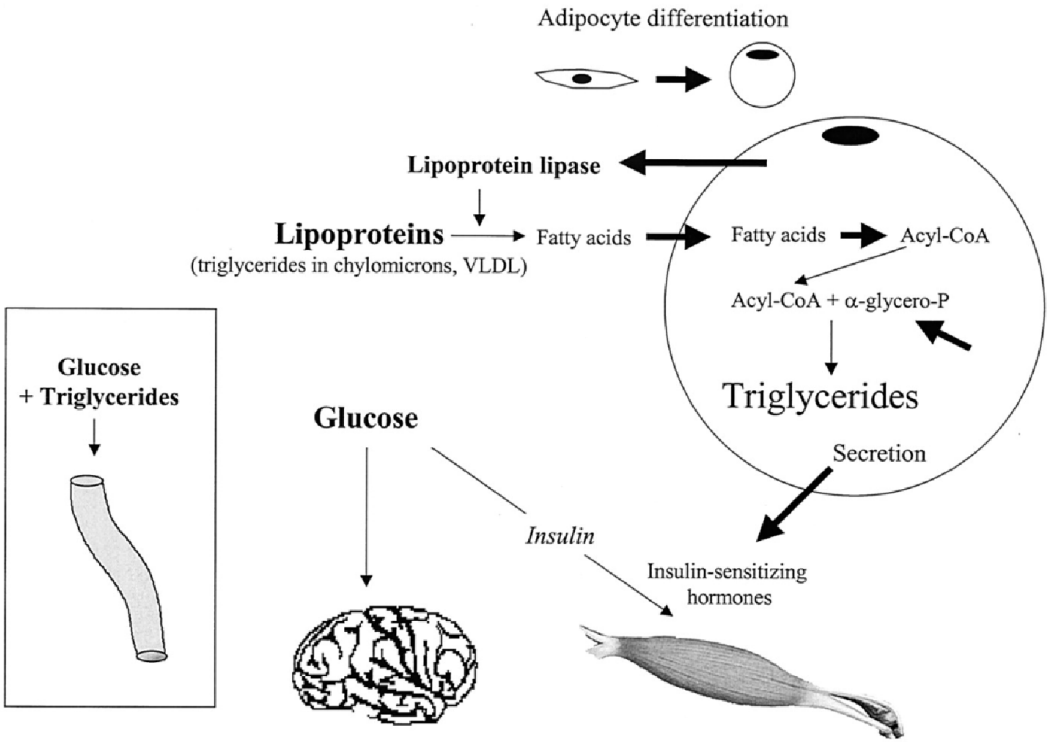
PPAR γ is greatly expressed in adipose tissue, where it plays crucial functions, such as regulating adipocyte differentiation, lipid storage, glucose metabolism and the transcriptional regulation of a variety of genes involved in these metabolic processes. Few of the main target genes of PPAR γ include the fat-specific ap2 gene, LPL, fatty acid transport, fatty acid binding protein, ABC-A1 (Azhar *et al*., 2010), (Semple *et al*., 2006). The most popular of PPAR γ polymorphisms is rs1805192 (Yen *et al*., 1994). Rs3856806 variant has been reported to be linked with traits, which alter the associations observed with the rs1805192 (Wu *et al*., 2011). Currently, many studies have reported that rs1805192 and rs3856806 polymorphisms were connected with obesity, insulin sensitivity and T2DM (Clement *et al*., 2000), (Hara *et al*., 2000), (Doney *et al*., 2002). Nevertheless, the links between rs1805192 or rs3856806 polymorphisms and lipid serum levels in the general population were seldom studied, and the conclusions were contradictory.

Because PPAR-γ is present in adipose tissue but almost negligible in muscle, (which is the main insulin-sensitive tissue) it raises the question of the association between adipose tissue and peripheral insulin sensitivity. A probable justification is that activation of PPAR-γ causes the channeling of fatty acids into adipose tissue and hence to a decrease in their plasma concentration. Lessening the fatty acid availability for muscles would alleviate insulin resistance (Ferré 2004).

Mutations in PPAR-γ that consequence in a functionally dominant negative form of the protein have been linked with severe insulin resistance in a limited number of patients (Barroso *et al*., 1999). This fits in with the common hypothesis that PPAR-γ is significant for sustaining normal insulin sensitivity. Yet, a more common polymorphism (Pro12Ala), which is linked with a lessened transcriptional activity in in vitro experiments, is associated with enhanced insulin sensitivity (Deeb *et al*., 1998). However, it should be emphasized that this polymorphism is also linked with a lower BMI.

PPARs are involved in the continual regulation of lipid metabolism, and their activity is altered by endogenous lipid-derived ligands. PPAR-γ, by elevating triglyceride storage and improving insulin sensitivity, is somewhat a "well-fed-lipid storing-glucose utilizing" regulator (Fig. 3). Evidently, their activation is a way to improve conditions such as T2DM, that are described by high concentrations of plasma lipids and by insulin resistance. PPAR-γ works by elevating lipid flux into storage and by inducing secretion of useful hormones. Few agonists with both PPAR- γ selectivity are currently being tested and appear to combine positive effects on insulin sensitivity and on lipid parameters (Ferré 2004).

The peroxisome proliferator-activated receptor-γ gene (PPARG) has been implicated in the etiology of T2DM mellitus and insulin resistance and has been examined in numerous epidemiologic studies. A study done on the Russian population (Chistiakov *et al*., 2010) suggest that Pro12Ala variant is considered as an independent risk marker that makes subjects more vulnerable to T2D and that carriers of the Pro12 allele and those homozygous for the Pro/Pro are more prone to developing T2DM.



This image was taken from Ferre, 2004

Fig. 3. Steps of fat storage and glucose utilization stimulated by PPAR-γ activation

Table 1. The effect of PPARγ Pro12Ala polymorphism on different populations- association with diabetes, IR and other diseases

#	Reference	Population	Major findings	Other diseases related with T2DM and the respective gene polymorphism	Association of polymorphism with diabetes/IR: Yes/no
1	(Chistiakov *et al*., 2010)	Russian	Carriers of the Pro12 allele and individuals homozygous for Pro/Pro allele had notably greater threat of developing T2DM -Pro12Ala polymorphism could be considered as an independent risk marker giving vulnerability to T2D in a Russian population.	The Pro/Pro genotype demonstrated association with elevated levels of fasting insulin in non-diabetic controls and increased serum triglycerides in T2D patients.	yes
2	(Motavallian *et al*., 2013)	Iranian	Polymorphism of PPAR-γ2 gene was reported to be associated with T2DM. - Ala allele is significantly present in non-diabetic individual's Iranian population.	NA	yes
	(Mirzaei *et al*., 2009)		-No association was seen among Pro12Ala polymorphism in PPAR-γ gene and T2DM.	Discovered an association between the Ala polymorphism of PPAR-γ2 gene and obesity	no
3	(González *et al*. 2014)	Caucasian, of Spanish decent	-No major correlation found among the PPAR-γ Pro12Ala polymorphism and T2D. -No direct influence of the PPAR-γ Pro12Ala polymorphism genetic variation in the development of diabetes disease found.	NA	no
4	(Wang *et al*. 2013)	Chinese Han	The Ala allele of the Pro12Ala polymorphism was linked with a considerably lower risk of T2DM.	Presence of the Ala allele may give enhanced insulin secretory capacity and may give protection from T2DM and obesity in the Chinese population.	yes
5	(Ho J. S. K *et al*., 2012)	Hong Kong	The PPARG Pro12 risk allele contributed to increased risk for both T2D.	The PPARG Pro12 risk allele contributed to increased risk for Coronary Heart Disease.	yes
6	(Malecki *et al*., 2003)	Polish	Not able to confirm earlier reports that the Pro allele gave an increased risk for development of T2DM. -The results of the stratified analysis propose a conflicting trend in late onset T2DM.	NA	no
7	(Bhatt *et al*., 2012)	Asian Indians	The Ala/Ala genotype of the PPAR-γ2 gene is linked with Insulin resistance without diabetes	Reported for the first time that truncal subcutaneous adiposity is linked with the Ala/Ala genotype. In general, PPAR-γ2 gene expression is increased in the adipose tissue of obese subjects.	yes
8	(SOSKIĆ *et al*., 2010)	Serbian population	No association between Pro12Ala polymorphism and T2DM was found. A non-important increase in the risk for T2DM onset was found for Ala12 allele carriers. -A significantly minor fasting INS concentration was linked with 12Ala allele carriers was seen only in the group of T2DM women.	NA	no
9	(Tavares V *et al*., 2005)	Brazilian population	Subjects with the Ala12 allele of the PPAR-gamma2 gene could be more sensitive to insulin than those carriers of the Pro12 allele	NA	yes
10	(Buzzetti *et al*., 2004)	Italian population	-Study interpretation verified that X12Ala variant is importantly linked with greater insulin sensitivity.	NA	yes
11	(Ghoussaini M *et al*., 2005)	French population	-There is an association of PPAR-γ 2 Pro12 allele in the genetic risk for T2D, particularly in obese subjects, where this allele worsens insulin resistance and enhances fasting insulin levels	Pro12Ala polymorphism is not linked with childhood or adult obesity.	yes
12	(Baddii *et al*., 2008)	Qatar	No association is seen between the $Pro_{12}Ala$ polymorphism in PPAR γ2 gene and the type2 diabetes.	NA	no

Two studies done on Iranian population reported contradicting results; Motavallian *et al* found out that the polymorphism of PPAR-γ2 gene is associated with T2DM (Motavallian *et al*., 2013). However, another study from Mirzaei *et al* done on Iranian population reported that there was no association between Pro12Ala polymorphism in the PPARγ2 gene and T2DM (Mirzaei *et al*., 2009).

Many other reports have confirmed that the Pro12Ala variant of the PPARγ2 gene is associated with T2DM. In Hong Kong, the PPARγ2 variant was a causative agent to increasing the risk of T2DM, along with coronary heart disease (Ho *et al*., 2012). Furthermore, Tavaeres *et al.* and Buzzetti *et al.* reported that those who had the Ala 12 allele of the PPARγ2 gene, were more insulin sensitive in the Brazilian and Italian populations, respectively (Tavares *et al*., 2005), (Buzzetti *et al*., 2004). Likewise the Ala/Ala genotype was associated with Insulin resistance in Asian Indians, and the PPARγ2 gene expression in general is elevated in the adipose tissue of obese subjects (Bhatt *et al*., 2012).

Ghossaini *et al* confirmed that the Pro 12 allele is a genetic risk for T2DM especially in obese French subjects. However, this polymorphism is not associated with childhood or adult obesity in the French Caucasian. (Ghoussaini *et al*., 2005)

Conversely, there have been many contradicting reports. Malecki *et al.* were not able to confirm the hypothesis that the Pro allele confers a risk for T2DM in the Polish population (Malecki *et al*., 2003). Also, there was no association found between the Pro12Ala polymorphism in the Serbian population and a considerably lower fasting INS concentration linked with 12Ala allele carriers was seen only in the group of T2DM women (SOSIK *et al*.,2010). There was no direct influence of the PPAR-γ Pro12Ala polymorphism genetic variation in the development of diabetes disease found in the Caucasian population of a Spanish decent, or the Qatar population. (Miramontes Gonzalez *et al*., 2014), (Badii *et al*., 2008) Interestingly, Wang *et al*. also reported that in the Chinese population, the Ala allele of the Pro12Ala polymorphism was associated with a considerably lower risk of T2DM, which proposes that the Ala allele may help to enhance the ability of insulin secretion and it may give protection from T2DM and obesity (Wang *et al*., 2013).

The FABP2 gene has been anticipated as a possible candidate gene for insulin resistance as the intestinal FABP (FABP2) plays a key role in the absorption and intracellular transport of dietary LCFA (Weiss *et al*., 2002). Many studies reported have confirmed that Ala54Thr polymorphism enhances the affinity of FABP2 for LCFA and is linked with elevated triglyceride transport in human intestinal cells (Baier *et al*., 1996), (Prochazka *et al*., 1993). Many experiments earlier have reported important correlating links among the FABP2 gene and of insulin resistance prevalence (Baier *et al*., 1995), (Yamada *et al*., 1997), (Chiu *et al*., 2001), (Mitchell, BD *et al*., 1995), but Rissanen *et al*. found a contradicting association in Finnish population (Rissanen *et al*.,1997). Baier *et al*. reported the important correlations among the common FABP2 Ala54Thr polymorphism (rs1799883) and elevated fasting insulin concentration, fasting fatty acid oxidation, and lessened insulin sensitivity in Pima Indians, a population that has a major prevalence of obesity and T2DM (Baier *et al*., 1995). In addition, the linkage analysis of the FABP2 locus with insulin resistance was also reported in a study in Mexican Americans who were of a mixed American-Indian and -European ancestry (Mitchell *et al*., 1995), Sib-pair analyses were unsuccessful in finding any linkage of the FABP2 locus or the Ala54Thr polymorphism with diabetes-related phenotypes in other ethnic groups, like in the Japanese (Ito *et al*., 1999).

An experiment performed by Lei HH *et al* on the African American reported that the FABP2 variant may not be linked with the risk of T2DM (Lei *et al*., 1999). Similarly, Tahvanainen *et al* and Al harbi *et al* reported that the Ala54Thr polymorphism doesn't pose a risk to increase the chances of T2DM in European and Saudi Arabia population, respectively (Tahvanainen *et al*., 2000). Another study done on the Tongan population reported that there was no association of this polymorphism to diabetes or obesity (Helvi Vidgren *et al*., 2003)

On the contrary, several studies contradict these previous findings, a study done on the Indian population of Guadelope report that there is significant relation between the Ala54Thr polymorphism of the FABP2 gene and T2DM. This relation could be a link with the high cardiovascular risk shown by the Asian Indian populations (Boullu-Sanchis *et al*., 1999). Another study done on Indians reported that in the fasting state, the NEFA (None Esterfied Fatty Acid) level in blood are decreased and have more insulin resistance (Pratley *et al*., 2000)

Xiang *et al* reported that in the Chinese population, the glucose stimulated insulin secretion (GSIS) reserve of islet beta-cells is more reserved in individuals that have FABP2-Thr54(+) genotype than in those with FABP2-Thr54(-) genotype, suggesting that FABP2 variant causes the progression of NDDM by secreting insufficient insulin (Xiang *et al*., 1999). A number of conflicting and inconclusive studies have investigated the possible association of the FABP2 Ala54Thr polymorphism with insulin resistance.

Apart from ethnic differences, several other factors determine the association of FABP2 and PPARγ polymorphisms with insulin resistance, T2DM and other complications that arise from them. The homozygous Thr54/Thr54 genotype has found the associations with higher fasting insulin levels and also TNF-α levels in 33 adult obese women (Cecilia Albala, *et al*., 2004) However, the findings of this study would need to be confirmed in studies involving a larger number of subjects. As gender and ethnicity probably were important variables in determining associative risk with insulin resistance and T2DM. The FABP2 gene was found to be associated with increased fat oxidation and hyperinsulinemia in normal healthy Korean men (Kim *et al*., 2010)

Weiss *et al*. reported that FABP2 genotype is greatly associated with insulin sensitivity in postmenopausal women. Also, he concluded that this link is independent of the identified associations between insulin sensitivity and regular physical activity levels, and body composition (Weiss *et al*., 2001).

Table 2. The effect of FABP2 gene -Ala54Thr substitution on different populations- association with diabetes, IR and other diseases

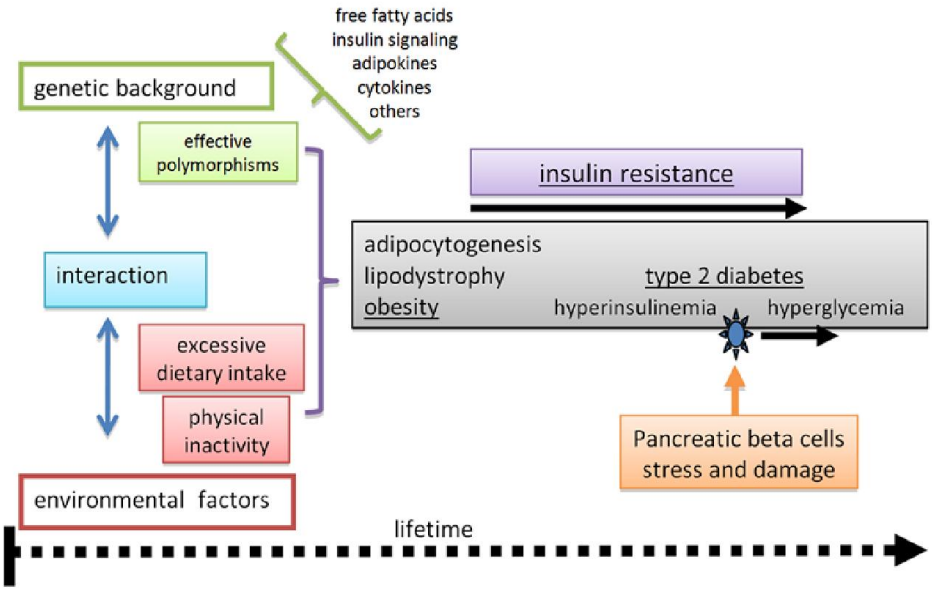
#	Reference	Population	Major findings	Other diseases related with T2DM and the respective gene polymorphism	Association of polymorphism with diabtes/IR: Yes/no
1	(Chui *et al*., 2001)	Caucasians	The A54T polymorphism of the FABP2 was linked with insulin resistance Multivariate analysis confirmed that this variant was an independent risk factor for insulin resistance. -On the contrary, this polymorphism had no impact on Beta cells function.	NA	yes
2	(Ito *et al*., 1999)	Japanese	The allele encoding threonine in the FABP2 does not predispose to Type 2 DM or insulin resistance.	NA	no
3	(Rissanen *et al*., 1997)	Finnish	-No variants found in the FABP2 gene particular for patients with NIDDM. - The AlaMThr polymorphism was not linked with high fasting or postchallenge insulin levels or with insulin resistance. - Nondiabetic individuals with the Thr54 allele happened to be more insulin sensitive than those with the Ala54Ala genotype. - Furthermore, no effect of this variant on lipid oxidation rate was seen either in nondiabetic or diabetic subjects.	NA	no
	(Pihlajamäki *et al*., 1997)		Insulin sensitivity was not linked with the codon 54 polymorphism of the FABP2 gene	FABP2 gene is not expected to be a major gene in FCHL. But, the polymorphism in codon 54 of this gene could influence lipid oxidation rate or lipid and lipoprotein levels in subjects with FCHL.	no
4	(Baier *et al*., 1995)	Pima Indians	FABP2 Ala54Thr genotypes was reported to be linked with insulin resistance	FABP2 Ala54Thr genotypes was reported to be linked with increased fatty acid-binding and increased fat oxidation	yes
5	(Lei *et al*., 1999)	African-Americans	-These variants in the FABP2 genes are not linked with the risk of T2DM, severe obesity, or marked hyperinsulinemia, but that their independent and joint effects may be associated with small increases in BMI.	NA	no
6	(Pratley *et al*., 2000)	Indian	(NEFA) level in blood are lessened in fasting state and have greater insulin resistance	NA	yes
7	(Mitchell *et al*., 1995)	Mexican-American	This gene is associated with diabetes and its related problems	NA	yes
8	(Helvi Vidgren *et al*., 2003)	Tongan	No association found with obesity and diabetes	NA	no
9	Xiang *et al*., (1999)	China	Suggests that FABP2-codon 54 variation may contribute to the inadequate insulin secretion in the development of NIDDM in Chinese.	NA	yes
10	(Tahvanainen *et al*., 2000)	Europeans	In this study FABP2 Ala54Thr polymorphism was not found to be associated with lipid or glucose metabolism.	NA	no
11	(Alharbi *et al*., 2014)	Saudi Arabia	Ala54Thr variant in FABP2 gene is not probable contributor to the risk of T2DM and related traits. However TT genotype is a threat factor for the disease in males.	NA	no
12	(Boullu-Sanchis *et al*., 1999)	Guadelope (Indian descendants)	There is a statistically important association between the Ala54Thy polymorphism of the FABP2 gene and Type 2 DM. This association confirms with the physiological function of the FABP2 gene and with the fact that these populations are especially vulnerable to cardiovascular diseases.	NA	yes

Table 3. The effect of FABP2 and PPAR polymorphisms on gender, age and other factors- association with diabetes, IR and other diseases

#	Reference	Gene	Factor-(population/age/gender)	Major finding for diabetes or IR	Other major findings
1	(Gonza´lez Sa´nchez *et al*., 2002)	PPAR	Spanish population	Women but not men carriers of the Ala12 allele are more insulin sensitive and have improved lipid profiles compared to the subjects with the Pro12Pro genotype in the Spanish population.	There is an association between Ala12 carriers, lesser total triglycerides levels, lower fasting insulin levels and an enhanced insulin sensitivity by HOMA-IR, together with gender differences as these reports were present only in women
2	(Galluzzi *et al*., 2001)	FABP2	Framinghams offspring	-No association found between the FABP2 polymorphism and T2DM	In women, carriers of the thr54 allele had considerably higher 2-h postchallenge plasma insulin levels compared to noncarriers. In men, no significant associations was reported with the FABP2 polymorphism.
3	(Albala *et al*., 2007)	FABP2	Chilean elders >60	- an association among the Ala54Thr polymorphism of FABP2 with diabetes, revealed a genetic dosage effect regarding its link with diabetes in Chilean elders.	NA
4	(Weiss *et al*., 2001)	FABP2	Unrelated healthy postmenopausal white women	FABP2 genotype is strongly linked with insulin sensitivity in postmenopausal women.	This assosciation is independent of the identified associations among insulin sensitivity and habitual physical activity levels, body composition, and HRT status.
5	(Weiss *et al*., 2007)	FABP2	Sedentary non smoking men and postmenopausal women (age: 50-75 years old)	In nondiabetic sedentary middle-aged to older adults who follow a low-fat diet, carriers of the Thr54 allele of the FABP2 gene are more susceptible to have abnormal glucose tolerance, enhanced fasting plasma concentrations of glucose, and lower insulin action than do FABP2 Ala54 homozygotes	Those subjects have higher postprandial lipid oxidation rates compared to Ala54 homozygotes.
6	(Kim *et al*., 2010)	FABP2	Healthy young Korean men	The Ala54Thr substitution in the FABP2 gene is linked with increased fat oxidation and hyperinsulinemia in normal Korean men, however these effects are not mediated by higher intestinal fatty acid absorption.	NA
7	(Cecilia Albala *et al*., 2004)	FABP2 gene – Ala54Thr substitution	Premenopausal Chilean women (20-50 years old)	Ala54Thr polymorphism of the FABP2 gene is linked with insulin resistance.	Ala54Thr polymorphism of the FABP2 gene is associated with obesity The effect of this polymorphism might be mediated by elevated production of TNFα.
8	(De Luis *et al*., 2010)	FABP2 gene	Naïve patients with T2DM and obese patients.	C reactive protein, insulin and HOMA were higher in mutant group than wild group.	NA

Similarly, he found that in the middle aged to older population, carriers of the Thr54 allele of the FABP2 gene are more vulnerable to have abnormal glucose tolerance, higher fasting plasma concentrations of glucose, and lower insulin action than do FABP2 Ala54 homozygotes (Weiss *et al*., 2007). Interestingly, in the Framingham offspring study, the women carriers of the thr54 allele had considerably higher 2-h post-challenge plasma insulin levels than non-carriers. However in men, they did not find any important associations with the FABP2 polymorphism (Galluzzi *et al*., 2001). Albala *et al*. found a link between the Ala54Thr polymorphism of FABP2 with diabetes in Chilean elders, where all the subjects were above 60 years old (Albala *et al*., 2007).

Remarkably, among the Spanish population, Gonzalez *et al* reported that women not men carriers of the Ala12 allele of the



(This figure was taken from: Evrim Komurcu-Bayrak 2012)

Fig. 4. General overview of genetic and environmental factors contributing to the development of insulin resistance and T2DM. 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 T2DM

PPAR gene are more insulin sensitive and have better lipid profiles than the subjects with Pro12Pro genotype. Furthermore they found that an association in women between Ala12 carriers lower total triglycerides levels, lower fasting insulin levels and a higher insulin sensitivity by HOMA-IR together with gender differences since these findings were present only in women (Gonzalez *et al*., 2002).

Another study done on naïve patients with T2DM and obese patients by De Luis *et al* established the association of the Thr54/Ala54 and Thr54/Thr54 FABP2 genotypes with higher levels of C reactive protein, insulin and HOMA. The levels of all three were higher in the mutant compared to the wildtype (De Luis *et al*., 2010). Higher HOMA values indicate higher insulin resistance (Evrim, 2012).

Conclusion

Insulin resistance and T2DM is mainly a genetic condition and initiates from the interactions of various genes and environmental factors. Figure 4 summarizes the main aspects that contribute to the progression of insulin resistance and T2DM. Interestingly, the molecular mechanism of insulin resistance is not completely understood till date. Until now, the aim of many studies was to use a candidate gene approach to discover genes that are linked with insulin resistance and various genes have been reported in many association-based studies, FABP2 and PPARɣ being two key ones. However, majority of the time, results of these studies have shown conflicting conclusions, as seen in this review. These varying results may probably be because of dissimilarities in the study populations and design of these experiments. Not enough meta-analyses have been performed to reveal the effect of many candidate gene polymorphisms on insulin resistance.

Alternatively, the utilization of genome-wide association (GWA) studies will discover new polymorphisms that are linked to insulin resistance. This awareness will permit the determination of the genetic predisposition to the insulin resistance and new approaches to treat and prevent the clinical phenotypes such as T2DM, obesity, hypertension and metabolic syndrome (Evrim, 2012). We conclude that insulin resistance is a predisposition of T2DM, and both are highly controlled by the polymorphisms of two key genes- the Pro12Ala variant of the PPARγ gene, and the Ala54Thr variant of the FABP2 gene in many populations. Nevertheless, many other studies have shown to be conflicting with this hypothesis, confirming that the association of the variants of these 2 genes with T2DM is ethnicity, gender and age based which could be because of different environmental and lifestyle exposures.

Significance

The detection of DNA polymorphisms in human populations is an important approach to understand how functional genetic variants affect the predisposition of diseases (Evrim, 2012). A step to find out the likelihood of the disease utilizes polymorphisms as marker for a disease in an affected DNA population by comparing it to a control DNA population. Consequently, the polymorphisms shown to be linked with the diseased might be directly useful or associated to the possible contributing variant. Presently, there are above 10 million single nucleotide polymorphisms (SNPs) including insertion/deletion variants in public databases that probably offer a marker group for disease-gene association studies. Even though this is a large number of variants, it's not necessary that all of them contribute to some disease since these studies were done on very limited number of subjects. This is the reason why the determination of genetic polymorphism and variations

in exons of an individual's genome is significant for disease-gene association studies. Nonetheless, this approach isn't practical for complex polygenic disease such as insulin resistance and T2DM. Hence GWA studies are being used lately to discover the genetic background of complex polygenic diseases.

This is why the discovery genetic variation in regions of functional DNA sequence in the genomes of individuals with disease is important for disease-gene association studies. Till date, many proposals have been presented to clarify 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 *et al*., 2010), (Erion *et al*., 2010), (Muoio *et al*., 2008). Given the critical functions of pathways in the pathogenesis of liver and muscle insulin resistance, knowing the molecular mechanism of insulin resistance is significant to develop noval and more effective therapies for metabolic syndromes (Evrim, 2012).

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