

Role of peroxisome proliferator-activated receptors gene polymorphisms in type 2 diabetes and metabolic syndrome

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Abstract

Metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) are the serious public health problems worldwide. Moreover, it is estimated that

MetS patients have about five-fold greater risk of the T2DM development compared with people without the syndrome. Peroxisome proliferator-activated receptors are a subgroup of the nuclear hormone receptor superfamily of ligand-activated transcription factors which play an important role in the pathogenesis of MetS and T2DM. All three members of the peroxisome proliferator-activated receptor (PPAR) nuclear receptor subfamily, PPAR α , PPAR β/δ and PPAR γ are critical in regulating insulin sensitivity, adipogenesis, lipid metabolism, and blood pressure. Recently, more and more studies indicated that the gene polymorphism of PPARs, such as Leu¹⁶²Val and Val²²⁷Ala of PPAR α , +294T > C of PPAR β/δ , Pro¹²Ala and C1431T of PPAR γ , are significantly associated with the onset and progressing of MetS and T2DM in different population worldwide. Furthermore, a large body of evidence demonstrated that the glucose metabolism and lipid metabolism were influenced by gene-gene interaction among PPARs genes. However, given the complexity pathogenesis of metabolic disease, it is unlikely that genetic variation of a single locus would provide an adequate explanation of inter-individual differences which results in diverse clinical syndromes. Thus, gene-gene interactions and gene-environment interactions associated with T2DM and MetS need future comprehensive studies.

Key words: Polymorphisms; Metabolic syndrome; Type 2 diabetes mellitus; Peroxisome proliferator-activated receptors

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Core tip: Recently, more and more studies indicated that the gene polymorphism influence of peroxisome proliferator-activated receptors (PPARs), including PPAR α , PPAR β/δ and PPAR γ , acted as a pivotal role in the onset and progressing of metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). We reviewed the recent advances in the relationships between PPARs polymorphisms and MetS and T2DM. Also, we discussed

the effects of gene-gene interaction among *PPARs* genes on the MetS and T2DM herein.

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INTRODUCTION

Globally, about 25% and 5.4% of adult population have been estimated to have metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), respectively^[1]. MetS is defined as a constellation of metabolic disorders including insulin resistance, central obesity, dyslipidemia and hypertension. The underlying cause of the MetS has been linked to the disorders of glucose metabolism including insulin resistance and glucose intolerance^[2,3]. One study in Nigeria reported that the prevalence of the MetS in T2DM patients is up to 86%^[4]. The study in Cameroon indicated that 71.7% T2DM patients diagnosed with the MetS^[5]. Thus, it is estimated that MetS patients have about five-fold greater risk of the T2DM development compared with people without the syndrome^[6].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that are part of the superfamily includes receptors for steroid hormones, thyroid hormones, retinoic acid and fat-soluble vitamin A and D. The primary role of PPARs is to regulate glucose, fatty acid and lipoprotein metabolism, energy balance, cell proliferation and differentiation, inflammation and atherosclerosis^[7]. PPAR α , the first member of the PPAR family identified in 1990, is mainly expressed in tissues in which fatty acid catabolism is important^[8,9]. Since that time, two additional members of the family, PPAR β/δ and PPAR γ , have been identified^[10,11]. Recently, more and more studies on the associations of PPARs polymorphisms and disorders of glucose metabolism and abnormal lipid metabolism have been published, indicating that the gene polymorphism influence of PPARs acted as a pivotal role in the development of MetS and T2DM^[12-15]. This review is aimed to summarize the recent advances in the relationships between PPARs polymorphisms and the metabolic disorders that related with MetS and T2DM. Moreover, the effects of gene-gene interaction among *PPARs* genes on the MetS and T2DM also will be discussed.

PPAR α

PPAR α gene is located on chromosome 22q12.2-13.1, and it is the first member of the *PPAR* isotypes to be cloned and was named based on its ability to be

activated by peroxisome proliferator chemicals. PPAR α is robustly expressed in tissues with elevated fatty acid catabolism and regulates transcription of multiple genes involved in glucose metabolism, such as the liver, heart and skeletal muscle, where it functions as a major regulator of fatty acid homeostasis^[8,9]. Along with regulation of lipid and glucose metabolism, PPAR α is as an attractive candidate gene for the risk of MetS and T2DM^[7].

Role of *PPAR α* gene polymorphisms in T2DM

Until now, more than 20 different base substitutions have been identified in the *PPAR α* gene. Among of them, Leu¹⁶²Val (rs1800206) has been shown to be significantly related with the risk of T2DM in different population^[16-20]. Flavell *et al.*^[17] reported that the variant of Leu¹⁶²Val variant was associated with increased plasma levels of total-cholesterol, HDL-cholesterol, and apoA-I, indicating that PPAR α gene variation influences the onset and progression of T2DM. Furthermore, the PPAR α haplotype significantly influenced age at diagnosis, with the C-L-C and C-V-C haplotypes [rs135539 (intron 1)-Leu¹⁶²Val (rs1800206)-rs4253778 (intron 7)] accelerating onset of diabetes by 5.9 and 10 years, respectively, as compared with the common A-L-G haplotype, and was associated with an odds ratio for early-onset diabetes (age at diagnosis \leq 45 years) of 3.75. Intron 1 C-allele (rs135539) carriers also progressed more rapidly to insulin monotherapy (AA 9.4 ± 1.5 and AC + CC 5.3 ± 1.1 years). In another study, Andrulionyte *et al.*^[19] reported that the presence of the G (162V) allele of rs1800206 in *PPAR α* gene increased the risk of developing diabetes. Moreover, haplotypes C-G-C and A-G-C, based on SNPs rs135539, rs1800206, and rs4253778, increased the risk of developing diabetes by 4.58-fold and 3.18-fold, respectively, compared with the C-C-C haplotype. Additionally, it should be noted that the Leu¹⁶²Val polymorphism has different effects on gene transcription. Evans *et al.*^[20] demonstrated that the Leu¹⁶²Val polymorphism was associated with a lower body mass index (BMI) in two independently recruited groups of patients with T2DM, suggesting that Leu¹⁶²Val polymorphism in PPAR α protects T2DM patients from the overweight which is frequently associated with their condition.

Role of *PPAR α* gene polymorphisms in MetS

Leu¹⁶²Val polymorphism not only plays a pivotal role in the T2DM development, but also significantly associated with the risk of MetS. In young Caucasians males, Uthurralt *et al.*^[21] found Leu¹⁶²Val polymorphism of PPAR α to be a strong determinant of serum triglyceride levels, where carriers of the V allele showed 78% increase in triglycerides relative to L homozygotes. Moreover, men with the V allele showed lower HDL, but women did not. Recently, Smalinskiene *et al.*^[22] reported that males with the G (162V) allele of rs1800206 in *PPAR α* gene had higher OR of elevated

triglyceride levels vs carriers of *PPARα* genotype CC, indicating that *PPARα* Leu¹⁶²Val polymorphism gene influences the onset and development of MetS.

Val²²⁷Ala, a non-synonymous variant at the *PPARα* locus encoding a substitution of valine for alanine at amino acid residue 227, is another important *PPARα* polymorphism reported that associated with MetS development^[23-28]. In Japanese population, significant interactions between *PPARα* Val²²⁷Ala polymorphism and triglyceride levels and AST/ALT ratios were found in drinkers^[23,24]. Chan *et al*^[26] reported that the level of weight, BMI, hip circumference, waist circumference, waist-hip ratio, percentage of body fat, abdominal wall fat thickness in Chinese subjects with Val²²⁷Ala variant were significantly lower than that in Val²²⁷Ala wide type. Additionally, in Chinese females, the presence of the A227 allele was significantly associated with lower serum concentrations of total cholesterol and triglycerides^[26,27]. Moreover, Chan's results also showed that the Val²²⁷Ala polymorphism modulates the association between dietary polyunsaturated fatty acid intake and serum high density lipoprotein concentration^[26].

In addition, the other variants of *PPARα* gene associated with MetS were also demonstrated in previous studies^[29-33]. A Rotterdam study observed that the minor alleles of the *PPARα* rs4253728 and rs4823613 polymorphisms are associated with a better total and LDL-cholesterol-lowering response to simvastatin, possibly through influence on CYP3A4^[33]. Therefore, better understanding the associations between *PPARα* polymorphisms and lipo-protein metabolism would be helpful for the prevention and treatment of MetS.

PPAR α

PPAR δ , also known as *PPAR β* , has 441 amino acid residues. Its coding gene is located in 6p 21.1-21.2, which includes 11 exons. *PPAR δ* is widely expressed in the liver, kidneys, cardiac and skeletal muscle, adipose tissue, brain, colon and vasculature^[34,35]. Animal studies found that *PPAR δ* knockout mice showed glucose intolerance on normal chow, and were prone to obesity on high-fat diet^[36,37]. *PPAR δ* activation in the liver also appears to decrease hepatic glucose output, thereby contributing to improved glucose tolerance and insulin sensitivity^[36,37]. Meanwhile, treatment with *PPAR δ* -specific agonist enhanced β -oxidation, decreased free fatty acid, and improved insulin sensitivity in mice and moderately obese men^[38,39]. Hence, *PPAR δ* has emerged as a key role for the development of MetS and T2DM in recent years.

Role of *PPAR δ* gene polymorphisms in T2DM

PPAR δ is an important candidate gene for T2DM. About ten years ago, Vanttinen *et al*^[40] reported that a statistically significant increase in insulin-stimulated whole-body and skeletal muscle glucose uptake

in carriers of the alleles of three variants in *PPAR δ* (rs6902123, rs2076167 and rs1053049), and the association was strongest for the rs6902123 variant. After that, the results from "The STOP-NIDDM Trial" demonstrated an increased risk of conversion to overt T2DM in carriers of the rs6902123 variant^[41]. Similar to these findings, Lu *et al*^[42] observed that rs6902123 was significantly associated with risk of T2DM and impaired fasting glucose in Chinese Han population. The minor C allele of rs6902123 was associated with increased levels of fasting glucose and HbA1c. In addition, a previous study revealed that the haplotype, composed of -13454G>T, -87T>C, 2022+12G>A, 2629T>C, and 2806C>G, is closely related to fasting plasma glucose and BMI of normal people in Korea^[43]. Also, Hu *et al*^[44] and Yu *et al*^[45] reported that gene polymorphism of *PPAR δ* , -87T>C, is significantly associated with higher fasting plasma glucose concentrations in both normal glucose tolerant and diabetic subjects.

However, with 886 middle age Chinese female T2DM patients, Villegas *et al*^[46] did not find a main gene effect of *PPAR δ* on T2DM or an interaction between the genes with BMI or exercise participation and the risk of T2DM. The similar result was also observed in another study of 7495 middle age white people that sequenced the *PPAR δ* gene and found no association between variants and T2DM^[47]. The reason for this disparity is not clear. It should be considered that that both genetic and environmental heterogeneity, including differences in their interaction, could give rise to population-specific discrepancies in the association of allelic variants and insulin resistance and thereby account for the inconsistent findings.

Role of *PPAR δ* gene polymorphisms in MetS

Based on the analysis of a *PPAR δ* null mouse model, it was demonstrated that *PPAR δ* gene-deficient mice who bypassed the lethal placental defect displayed a lean phenotype, with a significantly smaller amount of fat mass. In addition, the muscle-specific *PPAR δ* transgenic mice displayed increased mitochondrial-rich, oxidative type-1 myofibers with enhanced oxidative enzymatic activities^[36,37,48,49]. Skogsberg *et al*^[50] screened the 5'-untranslated region of the human *PPAR δ* gene and found that a +294T > C (also named -87T > C, rs2016520) polymorphism in nucleotide 15 of exon 4 (located 87 nucleotides upstream of the start codon), was significantly associated with plasma levels of LDL and cholesterol in two cohorts of healthy men. In a Canada study, Robitaille *et al*^[51] reported that *PPAR δ* +294T > C polymorphism may be associated with a lower risk to exhibit the MetS and this association is influenced by dietary fat intake. Also, Aberle *et al*^[52] showed that a highly significant association between the +294T > C and lower HDL- cholesterol levels in dyslipidemic female subjects. Moreover, MetS patients with CC genotype had significantly higher total and LDL-cholesterol

levels than those with TT and TC genotypes. The risk variant of PPAR δ +294T >C marker was associated with higher LDL-cholesterol and increased serum total cholesterol^[53]. Additionally, several other studies demonstrated that the PPAR δ +294T >C polymorphism was associated with modifications of serum lipid concentrations in healthy subjects and the risk of CAD in dyslipidemic women and hypercholesterolemic men and cholesterol metabolites in Alzheimer's disease patients^[54,55].

However, previous studies of PPAR δ +294T >C polymorphism provided conflicting results regarding association with MetS. In another study in Scottish males, Skogsberg *et al.*^[56] reported that the +294C allele did not influence LDL-cholesterol concentrations. Gouni-Berthold *et al.*^[57] demonstrated that the presence of the C allele had no effect on triglyceride, HDL-cholesterol, and LDL-cholesterol levels, both in diabetic and non-diabetic German controls, or both in men and in women. In a Chinese study, Wei *et al.*^[58] showed that serum total cholesterol, HDL-cholesterol, LDL-cholesterol, ApoA1, and ApoB levels were not correlated with +294T >C polymorphism in nondrinkers. In addition, Grarup *et al.*^[47] also did not replicate the associations of +294T >C polymorphism with metabolic traits in 7495 middle-aged white people. Therefore, more studies focused on the impact of PPAR δ gene polymorphism on the MetS development should be performed in different populations in future.

PPAR γ

The gene of PPAR γ (isoforms PPAR γ 1, PPAR γ 2 and PPAR γ 3) is located on chromosome 3p25 encodes a nuclear transcription factor involved in the expression of hundreds of genes. PPAR γ gene contains 9 exons, spans more than 100 kb. Since 1997, more and more evidences indicated that both common and rare polymorphisms of the genes of PPAR γ acted as key roles in the regulation of lipid and glucose metabolism^[59-62]. Rare mutations of PPAR γ (loss-of-function mutations) exhibit a limited impact due to their low frequency but are associated with severe phenotypes such as hypertension, T2DM and MetS^[63]. Conversely, common polymorphisms of PPAR γ significantly associated with the risk of T2DM development, obesity and cardiovascular diseases in the general population due to their relatively high frequency^[64].

Role of PPAR γ gene polymorphisms in T2DM

PPAR γ was the first gene reproducibly associated with T2DM. The association between the substitution of alanine by proline at codon 12 of PPAR γ 2 (Ala12 allele) and the risk for T2DM has been widely studied since Yen *et al.*^[65], first reported this polymorphism. In a recent study on the association between Pro¹²Ala polymorphism with both T2DM and the development of diabetic nephropathy, the results demonstrated

that the Pro/Pro genotype was the most common in diabetic patients as well as in controls followed by Pro/Ala genotype and Ala/Ala genotypes was the least common one. The allelic frequency of Pro was significantly higher in diabetic patients than controls and also significantly higher in diabetics with nephropathy than without nephropathy^[66]. In South Africa population, Vergotine *et al.*^[67] reported that the Pro¹²Ala of PPAR γ 2 is significantly associated with insulin resistance and this polymorphism interacts with IRS1 Gly⁹⁷²Arg, to increase the risk of T2DM. In addition, Wang *et al.*^[68] demonstrated that the presence of the Ala allele may contribute to improved insulin secretory capacity and may confer protection from T2DM and obesity in the Chinese population. Moreover, a meta-analysis confirmed the association between the PPAR γ 2 Pro12 allele and T2DM, and suggested that patients who carry the Pro12 allele have a 1.27-fold higher risk for developing T2DM than Ala12 carriers. This seemingly modest effect translates into a staggering 25% population-attributable risk because of the higher frequency of the Pro12 allele, especially in Japanese and European populations^[69].

Compared to the effects of the common Pro¹²Ala variant, rare mutations of PPAR γ gene affecting the ligand-binding domain of PPAR γ , such as 185Stop, Arg⁴²⁵Cys, and Pro⁴⁶⁷Leu, also associated with decreased transcriptional activity, improves glucose homeostasis and insulin sensitivity^[70-72]. Additionally, the other PPAR γ polymorphisms such as Cys¹¹⁴Arg, Cys¹³¹Tyr and Cys¹⁶²Trp could restrict wild-type PPAR γ action *via* a non-DNA binding, transcriptional interference mechanism. Heterozygous carriers of these new mutations are severely insulin resistant also been reported in the previous studies^[73,74].

Role of PPAR γ gene polymorphisms in MetS

The functional mutation Pro¹²Ala has also been reported to be associated with MetS in several populations^[75,76]. Tellechea *et al.*^[75] reported that individuals carrying the Ala12 allele of PPAR γ have a high risk for MetS and IR, especially among nonsmokers from Buenos Aires, Argentina. Also, The Québec Family Study observed that Ala12 carriers had a higher BMI, WC, fat mass than Pro/Pro homozygotes, suggesting that this polymorphism can modulate the association between dietary fat intake and components of the MetS^[76]. However, studies investigating the association between Pro¹²Ala polymorphisms and the risk of MetS in different populations have been inconsistent. In a large French population-based study, Meirhaeghe *et al.*^[77] found no association between Pro¹²Ala polymorphism of PPAR γ and MetS. Based on the analysis of 423 subjects with MetS and families without MetS, Yang *et al.*^[78] reported that Pro¹²Ala polymorphism was not associated directly with MetS, although MetS patients with Ala allele have higher fasting blood sugar (FBS) and higher left ventricular voltage. Similar to these findings, Ala carriers of middle-aged Swedish individuals did

not show statistically significantly different levels of fasting blood glucose, triglycerides, HDL-cholesterol, waist circumference or BP when compared with Pro¹²Pro homozygotes, suggesting that Pro12Ala polymorphism in *PPAR γ* gene does not have a major role in determining MetS prevalence^[79]. More recently, a meta-analysis included 4456 cases and 10343 controls from 10 case-control studies, indicated that no significant statistical difference was observed between the variant and metabolic syndrome, even if stratified by ethnicity, definition of metabolic syndrome, source of control groups, and quality score of selected studies^[80].

Another polymorphism, the C1431T silent substitution (rs3856806) in the 6th exon of *PPAR γ* , has also been shown to be associated with MetS in the different populations^[78,81]. In Iranian population, a significant difference in the frequencies of the C1431T genotypes was observed between MetS and control subjects. The T allele carriers had a significantly increased risk of MetS compared to the CC genotype even after correction for multiple-testing and adjustment for age, sex and genotype^[81]. In Chinese population, the association of C1431T polymorphism with MetS has also been observed. There were significant differences in terms of gender, FBS, LDL-cholesterol levels, triglyceride between CC genotype and CT +TT genotype groups in patients with MetS^[78]. However, not all studies had similar results. In Meirhaeghe's French population study, polymorphisms of C1431T were not individually associated with MetS. However connected with the other three polymorphisms, -681C>G, P2-689C>T, Pro¹²Ala, haplotypes are significantly associated with the risk for MetS^[82].

GENE-GENE INTERACTION AMONG *PPAR α* , *PPAR δ* AND *PPAR γ*

Until now, increasing evidences suggested that gene-gene interaction among *PPAR α* , *PPAR δ* and *PPAR γ* influenced the onset and progressing of T2DM and MetS^[41,83-88]. Andrulionyte *et al*^[41] reported that SNP rs6902123 of *PPAR δ* alone and in combination with the Pro¹²Ala polymorphism of *PPAR γ* 2 predicted the conversion from impaired glucose tolerance (IGT) to T2DM. More recently, our results indicated that there was a significant association between plasma Lp(a) level and gene-gene interaction among the polymorphisms rs1800206, rs135539 in *PPAR α* and rs10865710, rs1805192, and rs4684847 in *PPAR γ* , suggesting that *PPAR α/γ* gene may influence the risk of T2DM and MetS by regulating Lp(a) level^[83,84]. In addition, the results from our another study demonstrated that gene-gene interaction among *PPAR $\alpha/\delta/\gamma$* polymorphisms contribute to the risk of hypertriglyceridemia independently or in an interactive manner^[86,87]. Thus, gene-gene interactions among SNPs in *PPAR α* , *PPAR δ* and *PPAR γ* should be further investigated in future in order to better understand the small single gene effects that

cannot be detected by single-locus studies.

CONCLUSION

Although the molecular mechanisms are still uncovered, more and more studies indicated that the gene polymorphism influence of PPARs acted as a pivotal role in the development of MetS and T2DM. Therefore, identification of polymorphic variants of PPARs in different populations and the genotypic associations between SNPs and gene-gene interactions would be helpful for the prevention and treatment of T2DM and MetS. However, given the complexity pathogenesis of metabolic disease, it is unlikely that genetic variation of a single locus would provide an adequate explanation of inter-individual differences which results in diverse clinical syndromes. To this end, gene-gene interactions and gene-environment interactions associated with T2DM and MetS needs future comprehensive studies.

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