

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

Chen Dong, Hui Zhou, Chong Shen, Lu-Gang Yu, Yi Ding, Yong-Hong Zhang, Zhi-Rong Guo

Chen Dong, Hui Zhou, Yong-Hong Zhang, Zhi-Rong Guo, Department of Epidemiology, School of Public Health, Soochow University, Suzhou 215123, Jiangsu Province, China

Hui Zhou, Lu-Gang Yu, Yi Ding, Suzhou Industrial Park Centers for Disease Control and Prevention, Suzhou 215123, Jiangsu Province, China

Chong Shen, Department of Epidemiology and Biostatistics, School of Public Health, Nanjing Medical University, Nanjing 210000, Jiangsu Province, China

**Author contributions:** Dong C and Guo ZR proposed the manuscript concept and surveyed the literature; Zhou H, Shen C, Yu LG, Ding Y and Zhang YH generated relevant background and expanded the manuscript.

**Conflict-of-interest:** All of authors declared that they have no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Zhi-Rong Guo, MD, Department of Epidemiology, School of Public Health, Soochow University, 199 Ren'ai Road, Industrial Park District, Suzhou 215123, Jiangsu Province, China. [guozhirong28@163.com](mailto:guozhirong28@163.com)

Telephone: +86-512-65880079

Fax: +86-512-65884830

Received: August 28, 2014

Peer-review started: August 28, 2014

First decision: December 17, 2014

Revised: December 27, 2014

Accepted: February 9, 2015

Article in press: February 11, 2015

Published online: May 15, 2015

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 $\alpha$ , PPAR $\beta/\delta$  and PPAR $\gamma$  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 Leu<sup>162</sup>Val and Val<sup>227</sup>Ala of PPAR $\alpha$ , +294T > C of PPAR $\beta/\delta$ , Pro<sup>12</sup>Ala and C1431T of PPAR $\gamma$ , 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

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Recently, more and more studies indicated that the gene polymorphism influence of peroxisome proliferator-activated receptors (PPARs), including PPAR $\alpha$ , PPAR $\beta/\delta$  and PPAR $\gamma$ , 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

### Abstract

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

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

Dong C, Zhou H, Shen C, Yu LG, Ding Y, Zhang YH, Guo ZR. Role of peroxisome proliferator-activated receptors gene polymorphisms in type 2 diabetes and metabolic syndrome. *World J Diabetes* 2015; 6(4): 654-661 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v6/i4/654.htm> DOI: <http://dx.doi.org/10.4239/wjd.v6.i4.654>

## 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<sup>[1]</sup>. 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<sup>[2,3]</sup>. One study in Nigeria reported that the prevalence of the MetS in T2DM patients is up to 86%<sup>[4]</sup>. The study in Cameroon indicated that 71.7% T2DM patients diagnosed with the MetS<sup>[5]</sup>. Thus, it is estimated that MetS patients have about five-fold greater risk of the T2DM development compared with people without the syndrome<sup>[6]</sup>.

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<sup>[7]</sup>. PPAR $\alpha$ , the first member of the PPAR family identified in 1990, is mainly expressed in tissues in which fatty acid catabolism is important<sup>[8,9]</sup>. Since that time, two additional members of the family, PPAR $\beta/\delta$  and PPAR $\gamma$ , have been identified<sup>[10,11]</sup>. 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<sup>[12-15]</sup>. 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 $\alpha$

*PPAR $\alpha$*  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 $\alpha$  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<sup>[8,9]</sup>. Along with regulation of lipid and glucose metabolism, PPAR $\alpha$  is as an attractive candidate gene for the risk of MetS and T2DM<sup>[7]</sup>.

### Role of *PPAR $\alpha$* gene polymorphisms in T2DM

Until now, more than 20 different base substitutions have been identified in the *PPAR $\alpha$*  gene. Among of them, Leu<sup>162</sup>Val (rs1800206) has been shown to be significantly related with the risk of T2DM in different population<sup>[16-20]</sup>. Flavell *et al.*<sup>[17]</sup> reported that the variant of Leu<sup>162</sup>Val variant was associated with increased plasma levels of total-cholesterol, HDL-cholesterol, and apoA-I, indicating that PPAR $\alpha$  gene variation influences the onset and progression of T2DM. Furthermore, the PPAR $\alpha$  haplotype significantly influenced age at diagnosis, with the C-L-C and C-V-C haplotypes [rs135539 (intron 1)-Leu<sup>162</sup>Val (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  $9.4 \pm 1.5$  and AC + CC  $5.3 \pm 1.1$  years). In another study, Andrulionyte *et al.*<sup>[19]</sup> reported that the presence of the G (162V) allele of rs1800206 in *PPAR $\alpha$*  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 Leu<sup>162</sup>Val polymorphism has different effects on gene transcription. Evans *et al.*<sup>[20]</sup> demonstrated that the Leu<sup>162</sup>Val polymorphism was associated with a lower body mass index (BMI) in two independently recruited groups of patients with T2DM, suggesting that Leu<sup>162</sup>Val polymorphism in PPAR $\alpha$  protects T2DM patients from the overweight which is frequently associated with their condition.

### Role of *PPAR $\alpha$* gene polymorphisms in MetS

Leu<sup>162</sup>Val 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.*<sup>[21]</sup> found Leu<sup>162</sup>Val polymorphism of PPAR $\alpha$  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.*<sup>[22]</sup> reported that males with the G (162V) allele of rs1800206 in *PPAR $\alpha$*  gene had higher OR of elevated

triglyceride levels vs carriers of *PPARα* genotype CC, indicating that *PPARα* Leu<sup>162</sup>Val polymorphism gene influences the onset and development of MetS.

Val<sup>227</sup>Ala, 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<sup>[23-28]</sup>. In Japanese population, significant interactions between *PPARα* Val<sup>227</sup>Ala polymorphism and triglyceride levels and AST/ALT ratios were found in drinkers<sup>[23,24]</sup>. Chan *et al*<sup>[26]</sup> 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 Val<sup>227</sup>Ala variant were significantly lower than that in Val<sup>227</sup>Val type. Additionally, in Chinese females, the presence of the A227 allele was significantly associated with lower serum concentrations of total cholesterol and triglycerides<sup>[26,27]</sup>. Moreover, Chan's results also showed that the Val<sup>227</sup>Ala polymorphism modulates the association between dietary polyunsaturated fatty acid intake and serum high density lipoprotein concentration<sup>[26]</sup>.

In addition, the other variants of *PPARα* gene associated with MetS were also demonstrated in previous studies<sup>[29-33]</sup>. 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<sup>[33]</sup>. Therefore, better understanding the associations between *PPARα* polymorphisms and lipo-protein metabolism would be helpful for the prevention and treatment of MetS.

## PPARα

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

## Role of *PPARδ* gene polymorphisms in T2DM

*PPARδ* is an important candidate gene for T2DM. About ten years ago, Vanttinen *et al*<sup>[40]</sup> 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 *PPARδ* (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<sup>[41]</sup>. Similar to these findings, Lu *et al*<sup>[42]</sup> 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<sup>[43]</sup>. Also, Hu *et al*<sup>[44]</sup> and Yu *et al*<sup>[45]</sup> reported that gene polymorphism of *PPARδ*, -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*<sup>[46]</sup> did not find a main gene effect of *PPARδ* 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 *PPARδ* gene and found no association between variants and T2DM<sup>[47]</sup>. The reason for this disparity is not clear. It should be considered 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 *PPARδ* gene polymorphisms in MetS

Based on the analysis of a *PPARδ* null mouse model, it was demonstrated that *PPARδ* 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 *PPARδ* transgenic mice displayed increased mitochondrial-rich, oxidative type-1 myofibers with enhanced oxidative enzymatic activities<sup>[36,37,48,49]</sup>. Skogsberg *et al*<sup>[50]</sup> screened the 5'-untranslated region of the human *PPARδ* 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*<sup>[51]</sup> reported that *PPARδ* +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*<sup>[52]</sup> 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 *PPARδ* +294T >C marker was associated with higher LDL-cholesterol and increased serum total cholesterol<sup>[53]</sup>. Additionally, several other studies demonstrated that the *PPARδ* +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<sup>[54,55]</sup>.

However, previous studies of *PPARδ* +294T >C polymorphism provided conflicting results regarding association with MetS. In another study in Scottish males, Skogsberg *et al.*<sup>[56]</sup> reported that the +294C allele did not influence LDL-cholesterol concentrations. Gouni-Berthold *et al.*<sup>[57]</sup> 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.*<sup>[58]</sup> 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.*<sup>[47]</sup> 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 *PPARδ* gene polymorphism on the MetS development should be performed in different populations in future.

## PPAR $\gamma$

The gene of *PPAR $\gamma$*  (isoforms *PPAR $\gamma$ 1*, *PPAR $\gamma$ 2* and *PPAR $\gamma$ 3*) is located on chromosome 3p25 encodes a nuclear transcription factor involved in the expression of hundreds of genes. *PPAR $\gamma$*  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 $\gamma$*  acted as key roles in the regulation of lipid and glucose metabolism<sup>[59-62]</sup>. Rare mutations of *PPAR $\gamma$*  (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<sup>[63]</sup>. Conversely, common polymorphisms of *PPAR $\gamma$*  significantly associated with the risk of T2DM development, obesity and cardiovascular diseases in the general population due to their relatively high frequency<sup>[64]</sup>.

### Role of *PPAR $\gamma$* gene polymorphisms in T2DM

*PPAR $\gamma$*  was the first gene reproducibly associated with T2DM. The association between the substitution of alanine by proline at codon 12 of *PPAR $\gamma$ 2* (Ala12 allele) and the risk for T2DM has been widely studied since Yen *et al.*<sup>[65]</sup>, first reported this polymorphism. In a recent study on the association between Pro<sup>12</sup>Ala 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<sup>[66]</sup>. In South Africa population, Vergotine *et al.*<sup>[67]</sup> reported that the Pro<sup>12</sup>Ala of *PPAR $\gamma$ 2* is significantly associated with insulin resistance and this polymorphism interacts with IRS1 Gly<sup>972</sup>Arg, to increase the risk of T2DM. In addition, Wang *et al.*<sup>[68]</sup> 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 $\gamma$ 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<sup>[69]</sup>.

Compared to the effects of the common Pro<sup>12</sup>Ala variant, rare mutations of *PPAR $\gamma$*  gene affecting the ligand-binding domain of *PPAR $\gamma$* , such as 185Stop, Arg<sup>425</sup>Cys, and Pro<sup>467</sup>Leu, also associated with decreased transcriptional activity, improves glucose homeostasis and insulin sensitivity<sup>[70-72]</sup>. Additionally, the other *PPAR $\gamma$*  polymorphisms such as Cys<sup>114</sup>Arg, Cys<sup>131</sup>Tyr and Cys<sup>162</sup>Trp could restrict wild-type *PPAR $\gamma$*  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<sup>[73,74]</sup>.

### Role of *PPAR $\gamma$* gene polymorphisms in MetS

The functional mutation Pro<sup>12</sup>Ala has also been reported to be associated with MetS in several populations<sup>[75,76]</sup>. Tellechea *et al.*<sup>[75]</sup> reported that individuals carrying the Ala12 allele of *PPAR $\gamma$*  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<sup>[76]</sup>. However, studies investigating the association between Pro<sup>12</sup>Ala polymorphisms and the risk of MetS in different populations have been inconsistent. In a large French population-based study, Meirhaeghe *et al.*<sup>[77]</sup> found no association between Pro<sup>12</sup>Ala polymorphism of *PPAR $\gamma$*  and MetS. Based on the analysis of 423 subjects with MetS and families without MetS, Yang *et al.*<sup>[78]</sup> reported that Pro<sup>12</sup>Ala 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 Pro<sup>12</sup>Pro homozygotes, suggesting that Pro<sup>12</sup>Ala polymorphism in *PPAR $\gamma$*  gene does not have a major role in determining MetS prevalence<sup>[79]</sup>. 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<sup>[80]</sup>.

Another polymorphism, the C1431T silent substitution (rs3856806) in the 6th exon of *PPAR $\gamma$* , has also been shown to be associated with MetS in the different populations<sup>[78,81]</sup>. 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<sup>[81]</sup>. 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<sup>[78]</sup>. 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, Pro<sup>12</sup>Ala, haplotypes are significantly associated with the risk for MetS<sup>[82]</sup>.

## GENE-GENE INTERACTION AMONG *PPAR $\alpha$* , *PPAR $\delta$* AND *PPAR $\gamma$*

Until now, increasing evidences suggested that gene-gene interaction among *PPAR $\alpha$* , *PPAR $\delta$*  and *PPAR $\gamma$*  influenced the onset and progressing of T2DM and MetS<sup>[41,83-88]</sup>. Andrulionyte *et al.*<sup>[41]</sup> reported that SNP rs6902123 of *PPAR $\delta$*  alone and in combination with the Pro<sup>12</sup>Ala polymorphism of *PPAR $\gamma$* 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 $\alpha$*  and rs10865710, rs1805192, and rs4684847 in *PPAR $\gamma$* , suggesting that *PPAR $\alpha$ / $\gamma$*  gene may influence the risk of T2DM and MetS by regulating Lp(a) level<sup>[83,84]</sup>. 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<sup>[86,87]</sup>. Thus, gene-gene interactions among SNPs in *PPAR $\alpha$* , *PPAR $\delta$*  and *PPAR $\gamma$*  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.

## REFERENCES

- 1 **Mogre V**, Salifu ZS, Abedandi R. Prevalence, components and associated demographic and lifestyle factors of the metabolic syndrome in type 2 diabetes mellitus. *J Diabetes Metab Disord* 2014; **13**: 80 [PMID: 25054102 DOI: 10.1186/2251-6581-13-80]
- 2 **Civelek S**, Konukoglu D, Erdenen F, Uzun H. Serum neurotrophic factor levels in patients with type 2 diabetes mellitus: relationship to metabolic syndrome components. *Clin Lab* 2013; **59**: 369-374 [PMID: 23724627]
- 3 **Sora ND**, Marlow NM, Bandyopadhyay D, Leite RS, Slate EH, Fernandes JK. Metabolic syndrome and periodontitis in Gullah African Americans with type 2 diabetes mellitus. *J Clin Periodontol* 2013; **40**: 599-606 [PMID: 23557538 DOI: 10.1111/jcpe.12104]
- 4 **Osuji CU**, Nzerem BA, Dioka CE, Onwubuya EI. Metabolic syndrome in newly diagnosed type 2 diabetes mellitus using NCEP-ATP III, the Nnewi experience. *Niger J Clin Pract* 2012; **15**: 475-480 [PMID: 23238201 DOI: 10.4103/1119-3077.104530]
- 5 **Assah FK**, Ekelund U, Brage S, Mbanya JC, Wareham NJ. Urbanization, physical activity, and metabolic health in sub-Saharan Africa. *Diabetes Care* 2011; **34**: 491-496 [PMID: 21270205 DOI: 10.2337/dc10-0990]
- 6 **Saito I**. Epidemiological evidence of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease in Japan. *Circ J* 2012; **76**: 1066-1073 [PMID: 22453006 DOI: 10.1253/circj.CJ-11-1519]
- 7 **Grygiel-Górniak B**. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications--a review. *Nutr J* 2014; **13**: 17 [PMID: 24524207 DOI: 10.1186/1475-2891-13-17]
- 8 **Seok H**, Cha BS. Refocusing Peroxisome Proliferator Activated Receptor- $\alpha$ : A New Insight for Therapeutic Roles in Diabetes. *Diabetes Metab J* 2013; **37**: 326-332 [PMID: 24199160 DOI: 10.4093/dmj.2013.37.5.326]
- 9 **Gao M**, Bu L, Ma Y, Liu D. Concurrent activation of liver X receptor and peroxisome proliferator-activated receptor alpha exacerbates hepatic steatosis in high fat diet-induced obese mice. *PLoS One* 2013; **8**: e65641 [PMID: 23762402 DOI: 10.1371/journal.pone.0065641]
- 10 **Cohen RD**, Welch C, Xia Y, Lusis AJ, Reue K. Localization of mouse peroxisome proliferator-activated receptor delta (Ppard) on chromosome 17 near colipase (Clps). *Mamm Genome* 1996; **7**: 557-558 [PMID: 8672143 DOI: 10.1007/s00359900167]
- 11 **Greene ME**, Blumberg B, McBride OW, Yi HF, Kronquist K, Kwan K, Hsieh L, Greene G, Nimer SD. Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping. *Gene*

- Expr* 1995; **4**: 281-299 [PMID: 7787419]
- 12 **Mansour M.** The roles of peroxisome proliferator-activated receptors in the metabolic syndrome. *Prog Mol Biol Transl Sci* 2014; **121**: 217-266 [PMID: 24373239 DOI: 10.1016/B978-0-12-801011-1.00007-7]
  - 13 **Azhar S.** Peroxisome proliferator-activated receptors, metabolic syndrome and cardiovascular disease. *Future Cardiol* 2010; **6**: 657-691 [PMID: 20932114 DOI: 10.2217/fca.10.86]
  - 14 **Ma Y, Wang SQ, Xu WR, Wang RL, Chou KC.** Design novel dual agonists for treating type-2 diabetes by targeting peroxisome proliferator-activated receptors with core hopping approach. *PLoS One* 2012; **7**: e38546 [PMID: 22685582 DOI: 10.1371/journal.pone.0038546]
  - 15 **Seda O, Sedová L.** Peroxisome proliferator-activated receptors as molecular targets in relation to obesity and type 2 diabetes. *Pharmacogenomics* 2007; **8**: 587-596 [PMID: 17559348 DOI: 10.2217/14622416.8.6.587]
  - 16 **Doney AS, Fischer B, Lee SP, Morris AD, Leese G, Palmer CN.** Association of common variation in the PPARA gene with incident myocardial infarction in individuals with type 2 diabetes: a Go-DARTS study. *Nucl Recept* 2005; **3**: 4 [PMID: 16309557 DOI: 10.1186/1478-1336-3-4]
  - 17 **Flavell DM, Ireland H, Stephens JW, Hawe E, Acharya J, Mather H, Hurel SJ, Humphries SE.** Peroxisome proliferator-activated receptor alpha gene variation influences age of onset and progression of type 2 diabetes. *Diabetes* 2005; **54**: 582-586 [PMID: 15677519 DOI: 10.2337/diabetes.54.2.582]
  - 18 **Gouni-Berthold I, Giannakidou E, Müller-Wieland D, Faust M, Kotzka J, Berthold HK, Krone W.** Association between the PPARalpha L162V polymorphism, plasma lipoprotein levels, and atherosclerotic disease in patients with diabetes mellitus type 2 and in nondiabetic controls. *Am Heart J* 2004; **147**: 1117-1124 [PMID: 15199365 DOI: 10.1016/j.ahj.2003.12.005]
  - 19 **Andrulionyte L, Kuulasmaa T, Chiasson JL, Laakso M.** Single nucleotide polymorphisms of the peroxisome proliferator-activated receptor-alpha gene (PPARA) influence the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes* 2007; **56**: 1181-1186 [PMID: 17317762 DOI: 10.2337/db06-1110]
  - 20 **Evans D, Aberle J, Wendt D, Wolf A, Beisiegel U, Mann WA.** A polymorphism, L162V, in the peroxisome proliferator-activated receptor alpha (PPARalpha) gene is associated with lower body mass index in patients with non-insulin-dependent diabetes mellitus. *J Mol Med (Berl)* 2001; **79**: 198-204 [PMID: 11409711 DOI: 10.1007/s001090100189]
  - 21 **Uthurralt J, Gordish-Dressman H, Bradbury M, Tesi-Rocha C, Devaney J, Harmon B, Reeves EK, Brandoli C, Hansen BC, Seip RL, Thompson PD, Price TB, Angelopoulos TJ, Clarkson PM, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Gordon PM, Hoffman EP.** PPARalpha L162V underlies variation in serum triglycerides and subcutaneous fat volume in young males. *BMC Med Genet* 2007; **8**: 55 [PMID: 17705849 DOI: 10.1186/1471-2350-8-55]
  - 22 **Smalinskiene A, Petkeviciene J, Luksiene D, Jureniene K, Klumbiene J, Lesauskaite V.** Association between APOE, SCARB1, PPARa polymorphisms and serum lipids in a population of Lithuanian adults. *Lipids Health Dis* 2013; **12**: 120 [PMID: 23919842 DOI: 10.1186/1476-511X-12-120]
  - 23 **Naito H, Kamijima M, Yamanoshita O, Nakahara A, Katoh T, Tanaka N, Aoyama T, Gonzalez FJ, Nakajima T.** Differential effects of aging, drinking and exercise on serum cholesterol levels dependent on the PPARA-V227A polymorphism. *J Occup Health* 2007; **49**: 353-362 [PMID: 17951966 DOI: 10.1539/joh.49.353]
  - 24 **Naito H, Yamanoshita O, Kamijima M, Katoh T, Matsunaga T, Lee CH, Kim H, Aoyama T, Gonzalez FJ, Nakajima T.** Association of V227A PPARalpha polymorphism with altered serum biochemistry and alcohol drinking in Japanese men. *Pharmacogenet Genomics* 2006; **16**: 569-577 [PMID: 16847426 DOI: 10.1097/01.fpc.0000220565.90466.79]
  - 25 **Chen SH, Li YM, Yu CH, Jiang LL.** The association of Val227Ala polymorphism of the peroxisome proliferator activated receptor alpha (PPAR alpha) gene with non-alcoholic fatty liver disease. *Zhonghua Ganzangbing Zazhi* 2007; **15**: 64-65 [PMID: 17244467]
  - 26 **Chan E, Tan CS, Deurenberg-Yap M, Chia KS, Chew SK, Tai ES.** The V227A polymorphism at the PPARA locus is associated with serum lipid concentrations and modulates the association between dietary polyunsaturated fatty acid intake and serum high density lipoprotein concentrations in Chinese women. *Atherosclerosis* 2006; **187**: 309-315 [PMID: 16288935 DOI: 10.1016/j.atherosclerosis.2005.10.002]
  - 27 **Wu CT, Cheng YH, Chen FN, Chen DR, Wei MF, Chang NW.** Combined effects of peroxisome proliferator-activated receptor alpha and apolipoprotein E polymorphisms on risk of breast cancer in a Taiwanese population. *J Investig Med* 2012; **60**: 1209-1213 [PMID: 23076161 DOI: 10.231/JIM.0b013e31826be86a]
  - 28 **Chen S, Li Y, Li S, Yu C.** A Val227Ala substitution in the peroxisome proliferator activated receptor alpha (PPAR alpha) gene associated with non-alcoholic fatty liver disease and decreased waist circumference and waist-to-hip ratio. *J Gastroenterol Hepatol* 2008; **23**: 1415-1418 [PMID: 18853997 DOI: 10.1111/j.1440-1746.2008.05523.x]
  - 29 **Tanaka T, Ordovas JM, Delgado-Lista J, Perez-Jimenez F, Marin C, Perez-Martinez P, Gomez P, Lopez-Miranda J.** Peroxisome proliferator-activated receptor alpha polymorphisms and postprandial lipemia in healthy men. *J Lipid Res* 2007; **48**: 1402-1408 [PMID: 17363837 DOI: 10.1194/jlr.M700066-JLR200]
  - 30 **Chen ES, Mazzotti DR, Furuya TK, Cendoroglo MS, Ramos LR, Araujo LQ, Burbano RR, Smith Mde A.** Association of PPARalpha gene polymorphisms and lipid serum levels in a Brazilian elderly population. *Exp Mol Pathol* 2010; **88**: 197-201 [PMID: 19822141 DOI: 10.1016/j.yexmp.2009.10.001]
  - 31 **Kreutz RP, Owens J, Jin Y, Nystrom P, Desta Z, Kreutz Y, Breall JA, Li L, Chiang C, Kovacs RJ, Flockhart DA.** Cytochrome P450 3A4\*22, PPAR- $\alpha$ , and ARNT polymorphisms and clopidogrel response. *Clin Pharmacol* 2013; **5**: 185-192 [PMID: 24353446 DOI: 10.2147/CPAA.S53151]
  - 32 **Woillard JB, Kamar N, Coste S, Rostaing L, Marquet P, Picard N.** Effect of CYP3A4\*22, POR\*28, and PPARA rs4253728 on sirolimus in vitro metabolism and trough concentrations in kidney transplant recipients. *Clin Chem* 2013; **59**: 1761-1769 [PMID: 23974086 DOI: 10.1373/clinchem.2013.204990]
  - 33 **de Keyser CE, Becker ML, Uitterlinden AG, Hofman A, Lous JJ, Elens L, Visser LE, van Schaik RH, Stricker BH.** Genetic variation in the PPARA gene is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. *Pharmacogenomics* 2013; **14**: 1295-1304 [PMID: 23930676 DOI: 10.2217/pgs.13.112]
  - 34 **Schmidt A, Endo N, Rutledge SJ, Vogel R, Shinar D, Rodan GA.** Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids. *Mol Endocrinol* 1992; **6**: 1634-1641 [PMID: 1333051]
  - 35 **Kliwer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K, Evans RM.** Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* 1994; **91**: 7355-7359 [PMID: 8041794 DOI: 10.1073/pnas.91.15.7355]
  - 36 **Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R, Evans RM.** Effects of peroxisome proliferator-activated receptor delta on placental, adiposity, and colorectal cancer. *Proc Natl Acad Sci USA* 2002; **99**: 303-308 [PMID: 11756685 DOI: 10.1073/pnas.012610299]
  - 37 **Kostadinova R, Montagner A, Gouranton E, Fleury S, Guillou H, Dombrowicz D, Desreumaux P, Wahli W.** GW501516-activated PPAR $\beta/\delta$  promotes liver fibrosis via p38-JNK MAPK-induced hepatic stellate cell proliferation. *Cell Biosci* 2012; **2**: 34 [PMID: 23046570 DOI: 10.1186/2045-3701-2-34]
  - 38 **Bojic LA, Telford DE, Fullerton MD, Ford RJ, Sutherland BG, Edwards JY, Sawyez CG, Gros R, Kemp BE, Steinberg GR, Huff MW.** PPAR $\delta$  activation attenuates hepatic steatosis in Ldlr $^{-/-}$  mice by enhanced fat oxidation, reduced lipogenesis, and improved insulin sensitivity. *J Lipid Res* 2014; **55**: 1254-1266 [PMID: 24353446]

- 24864274 DOI: 10.1194/jlr.M046037]
- 39 **Greene NP**, Fluckey JD, Lambert BS, Greene ES, Riechman SE, Crouse SF. Regulators of blood lipids and lipoproteins? PPAR $\delta$  and AMPK, induced by exercise, are correlated with lipids and lipoproteins in overweight/obese men and women. *Am J Physiol Endocrinol Metab* 2012; **303**: E1212-E1221 [PMID: 22990076 DOI: 10.1152/ajpendo.00309.2012]
  - 40 **Vänttinen M**, Nuutila P, Kuulasmaa T, Pihlajamäki J, Hällsten K, Virtanen KA, Lautamäki R, Peltoniemi P, Takala T, Viljanen AP, Knuuti J, Laakso M. Single nucleotide polymorphisms in the peroxisome proliferator-activated receptor delta gene are associated with skeletal muscle glucose uptake. *Diabetes* 2005; **54**: 3587-3591 [PMID: 16306381 DOI: 10.2337/diabetes.54.12.3587]
  - 41 **Andrulionyte L**, Peltola P, Chiasson JL, Laakso M. Single nucleotide polymorphisms of PPARD in combination with the Gly482Ser substitution of PGC-1A and the Pro12Ala substitution of PPARG2 predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes* 2006; **55**: 2148-2152 [PMID: 16804087 DOI: 10.2337/db05-1629]
  - 42 **Lu L**, Wu Y, Qi Q, Liu C, Gan W, Zhu J, Li H, Lin X. Associations of type 2 diabetes with common variants in PPARD and the modifying effect of vitamin D among middle-aged and elderly Chinese. *PLoS One* 2012; **7**: e34895 [PMID: 22509365 DOI: 10.1371/journal.pone.0034895]
  - 43 **Shin HD**, Park BL, Kim LH, Jung HS, Cho YM, Moon MK, Park YJ, Lee HK, Park KS. Genetic polymorphisms in peroxisome proliferator-activated receptor delta associated with obesity. *Diabetes* 2004; **53**: 847-851 [PMID: 14988273 DOI: 10.2337/diabetes.53.3.847]
  - 44 **Hu C**, Jia W, Fang Q, Zhang R, Wang C, Lu J, Xiang K. Peroxisome proliferator-activated receptor (PPAR) delta genetic polymorphism and its association with insulin resistance index and fasting plasma glucose concentrations in Chinese subjects. *Diabet Med* 2006; **23**: 1307-1312 [PMID: 17116180 DOI: 10.1111/j.1464-5491.2006.02001.x]
  - 45 **Yu XJ**, Su BL, Wang XM, Feng HJ, Jin CJ. Association of peroxisome proliferator-activated receptor-delta polymorphisms with sugar metabolism indices and tumor necrosis factor alpha level. *Genet Mol Res* 2014; **13**: 5088-5093 [PMID: 25061733 DOI: 10.4238/2014.July.7.1]
  - 46 **Villegas R**, Williams S, Gao Y, Cai Q, Li H, Elasy T, Cai H, Edwards T, Xiang YB, Zheng W, Long J, Ou Shu X. Peroxisome proliferator-activated receptor delta (PPARD) genetic variation and type 2 diabetes in middle-aged Chinese women. *Ann Hum Genet* 2011; **75**: 621-629 [PMID: 21834910 DOI: 10.1111/j.1469-1809.2011.00669.x]
  - 47 **Grarup N**, Albrechtsen A, Ek J, Borch-Johnsen K, Jørgensen T, Schmitz O, Hansen T, Pedersen O. Variation in the peroxisome proliferator-activated receptor delta gene in relation to common metabolic traits in 7,495 middle-aged white people. *Diabetologia* 2007; **50**: 1201-1208 [PMID: 17431579 DOI: 10.1007/s00125-007-0668-2]
  - 48 **Genovese S**, Foreman JE, Borland MG, Epifano F, Gonzalez FJ, Curini M, Peters JM. A natural propenoic acid derivative activates peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta). *Life Sci* 2010; **86**: 493-498 [PMID: 20153754 DOI: 10.1016/j.lfs.2010.02.008]
  - 49 **Eisele NA**, Ruby T, Jacobson A, Manzanillo PS, Cox JS, Lam L, Mukundan L, Chawla A, Monack DM. Salmonella require the fatty acid regulator PPAR $\delta$  for the establishment of a metabolic environment essential for long-term persistence. *Cell Host Microbe* 2013; **14**: 171-182 [PMID: 23954156 DOI: 10.1016/j.chom.2013.07.010]
  - 50 **Skogsberg J**, Kannisto K, Cassel TN, Hamsten A, Eriksson P, Ehrenborg E. Evidence that peroxisome proliferator-activated receptor delta influences cholesterol metabolism in men. *Arterioscler Thromb Vasc Biol* 2003; **23**: 637-643 [PMID: 12615676 DOI: 10.1161/01.ATV.0000064383.88696.24]
  - 51 **Robitaille J**, Gaudet D, Pérusse L, Vohl MC. Features of the metabolic syndrome are modulated by an interaction between the peroxisome proliferator-activated receptor-delta -87T > G; C polymorphism and dietary fat in French-Canadians. *Int J Obes (Lond)* 2007; **31**: 411-417 [PMID: 16953259 DOI: 10.1038/sj.ijo.0803450]
  - 52 **Aberle J**, Hopfer I, Beil FU, Seedorf U. Association of peroxisome proliferator-activated receptor delta +294T/C with body mass index and interaction with peroxisome proliferator-activated receptor alpha L162V. *Int J Obes (Lond)* 2006; **30**: 1709-1713 [PMID: 16652134 DOI: 10.1038/sj.ijo.0803345]
  - 53 **Miao L**, Yin RX, Wu DF, Cao XL, Li Q, Hu XJ, Yan TT, Aung LH, Yang DZ, Lin WX. Peroxisome proliferator-activated receptor delta +294T > G; C polymorphism and serum lipid levels in the Guangxi Bai Ku Yao and Han populations. *Lipids Health Dis* 2010; **9**: 145 [PMID: 21176135 DOI: 10.1186/1476-511X-9-145]
  - 54 **Jguirim-Souissi I**, Jelassi A, Hrira Y, Najah M, Slimani A, Addad F, Hassine M, Hamda KB, Maatouk F, Rouis M, Slimane MN. +294T/C polymorphism in the PPAR-delta gene is associated with risk of coronary artery disease in normolipidemic Tunisians. *Genet Mol Res* 2010; **9**: 1326-1333 [PMID: 20645257 DOI: 10.4238/vol9-3gmr831]
  - 55 **Holzappel J**, Heun R, Lütjohann D, Jessen F, Maier W, Kölsch H. PPARD haplotype influences cholesterol metabolism but is no risk factor of Alzheimer's disease. *Neurosci Lett* 2006; **408**: 57-61 [PMID: 16979821 DOI: 10.1016/j.neulet.2006.08.029]
  - 56 **Skogsberg J**, McMahon AD, Karpe F, Hamsten A, Packard CJ, Ehrenborg E. Peroxisome proliferator activated receptor delta genotype in relation to cardiovascular risk factors and risk of coronary heart disease in hypercholesterolaemic men. *J Intern Med* 2003; **254**: 597-604 [PMID: 14641801 DOI: 10.1111/j.1365-2796.2003.01236.x]
  - 57 **Gouni-Berthold I**, Giannakidou E, Faust M, Berthold HK, Krone W. The peroxisome proliferator-activated receptor delta +294T/C polymorphism in relation to lipoprotein metabolism in patients with diabetes mellitus type 2 and in non-diabetic controls. *Atherosclerosis* 2005; **183**: 336-341 [PMID: 16285997 DOI: 10.1016/j.atherosclerosis.2005.03.016]
  - 58 **Wei XL**, Yin RX, Miao L, Wu DF. The peroxisome proliferator-activated receptor delta +294T > G; C polymorphism and alcohol consumption on serum lipid levels. *Lipids Health Dis* 2011; **10**: 242 [PMID: 22192471 DOI: 10.1186/1476-511X-10-242]
  - 59 **Choi SS**, Park J, Choi JH. Revisiting PPAR $\gamma$  as a target for the treatment of metabolic disorders. *BMB Rep* 2014; **47**: 599-608 [PMID: 25154720]
  - 60 **Chehaibi K**, Nouria S, Mahdouani K, Hamdi S, Rouis M, Slimane MN. Effect of the PPAR $\gamma$  C161T gene variant on serum lipids in ischemic stroke patients with and without type 2 diabetes mellitus. *J Mol Neurosci* 2014; **54**: 730-738 [PMID: 24841086 DOI: 10.1007/s12031-014-0326-3]
  - 61 **Zhao X**, Xu K, Shi H, Cheng J, Ma J, Gao Y, Li Q, Ye X, Lu Y, Yu X, Du J, Du W, Ye Q, Zhou L. Application of the back-error propagation artificial neural network (BPANN) on genetic variants in the PPAR- $\gamma$  and RXR- $\alpha$  gene and risk of metabolic syndrome in a Chinese Han population. *J Biomed Res* 2014; **28**: 114-122 [PMID: 24683409 DOI: 10.7555/JBR.27.20120061]
  - 62 **Domenici FA**, Brochado MJ, Martinelli Ade L, Zucoloto S, da Cunha SF, Vannucchi H. Peroxisome proliferator-activated receptors alpha and gamma2 polymorphisms in nonalcoholic fatty liver disease: a study in Brazilian patients. *Gene* 2013; **529**: 326-331 [PMID: 23891824 DOI: 10.1016/j.gene.2013.06.091]
  - 63 **Visser ME**, Kropman E, Kranendonk ME, Koppen A, Hamers N, Strees ES, Kalkhoven E, Monajemi H. Characterisation of non-obese diabetic patients with marked insulin resistance identifies a novel familial partial lipodystrophy-associated PPAR $\gamma$  mutation (Y151C). *Diabetologia* 2011; **54**: 1639-1644 [PMID: 21479595 DOI: 10.1007/s00125-011-2142-4]
  - 64 **Galbete C**, Toledo E, Martínez-González MA, Martínez JA, Guillén-Grima F, Martí A. Pro12Ala variant of the PPARG2 gene increases body mass index: An updated meta-analysis encompassing 49,092 subjects. *Obesity (Silver Spring)* 2013; **21**: 1486-1495 [PMID: 23666678 DOI: 10.1002/oby.20150]
  - 65 **Yen CJ**, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP,



- Burns DK, Roth J, Shuldiner AR. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 1997; **241**: 270-274 [PMID: 9425261 DOI: 10.1006/bbrc.1997.7798]
- 66 **Azab MM**, Abdel-Azeez HA, Zanaty MF, El Alawi SM. Peroxisome proliferator activated receptor  $\gamma$ 2 gene Pro12Ala gene polymorphism in type 2 diabetes and its relationship with diabetic nephropathy. *Clin Lab* 2014; **60**: 743-749 [PMID: 24839816]
- 67 **Vergotine Z**, Yako YY, Kengne AP, Erasmus RT, Matsha TE. Proliferator-activated receptor gamma Pro12Ala interacts with the insulin receptor substrate 1 Gly972Arg and increase the risk of insulin resistance and diabetes in the mixed ancestry population from South Africa. *BMC Genet* 2014; **15**: 10 [PMID: 24447396 DOI: 10.1186/1471-2156-15-10]
- 68 **Wang X**, Liu J, Ouyang Y, Fang M, Gao H, Liu L. The association between the Pro12Ala variant in the PPAR $\gamma$ 2 gene and type 2 diabetes mellitus and obesity in a Chinese population. *PLoS One* 2013; **8**: e71985 [PMID: 23991018 DOI: 10.1371/journal.pone.0071985]
- 69 **De Cosmo S**, Prudente S, Lamacchia O, Lapice E, Morini E, Di Paola R, Copetti M, Ruggerenti P, Remuzzi G, Vaccaro O, Cignarelli M, Trischitta V. PPAR $\gamma$ 2 P12A polymorphism and albuminuria in patients with type 2 diabetes: a meta-analysis of case-control studies. *Nephrol Dial Transplant* 2011; **26**: 4011-4016 [PMID: 21493814 DOI: 10.1093/ndt/gfr187]
- 70 **Barroso I**, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK, O'Rahilly S. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 1999; **402**: 880-883 [PMID: 1062252]
- 71 **Jenning EH**, Gurnell M, Kalkhoven E. Functional implications of genetic variation in human PPARgamma. *Trends Endocrinol Metab* 2009; **20**: 380-387 [PMID: 19748282 DOI: 10.1016/j.tem.2009.04.005]
- 72 **Semple RK**, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. *J Clin Invest* 2006; **116**: 581-589 [PMID: 16511590 DOI: 10.1172/JCI28003]
- 73 **Agostini M**, Gurnell M, Savage DB, Wood EM, Smith AG, Rajanayagam O, Garnes KT, Levinson SH, Xu HE, Schwabe JW, Willson TM, O'Rahilly S, Chatterjee VK. Tyrosine agonists reverse the molecular defects associated with dominant-negative mutations in human peroxisome proliferator-activated receptor gamma. *Endocrinology* 2004; **145**: 1527-1538 [PMID: 14657011 DOI: 10.1210/en.2003-1271]
- 74 **Agostini M**, Schoenmakers E, Mitchell C, Szatmari I, Savage D, Smith A, Rajanayagam O, Semple R, Luan J, Bath L, Zalin A, Labib M, Kumar S, Simpson H, Blom D, Marais D, Schwabe J, Barroso I, Trembath R, Wareham N, Nagy L, Gurnell M, O'Rahilly S, Chatterjee K. Non-DNA binding, dominant-negative, human PPARgamma mutations cause lipodystrophic insulin resistance. *Cell Metab* 2006; **4**: 303-311 [PMID: 17011503 DOI: 10.1016/j.cmet.2006.09.003]
- 75 **Tellechea ML**, Aranguren F, Pérez MS, Cerrone GE, Frechtel GD, Taverna MJ. Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma gene is associated with metabolic syndrome and surrogate measures of insulin resistance in healthy men: interaction with smoking status. *Circ J* 2009; **73**: 2118-2124 [PMID: 19745552 DOI: 10.1253/circj.CJ-09-0320]
- 76 **Robitaille J**, Després JP, Périus L, Vohl MC. The PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and components of the metabolic syndrome: results from the Québec Family Study. *Clin Genet* 2003; **63**: 109-116 [PMID: 12630956 DOI: 10.1034/j.1399-0004.2003.00026.x]
- 77 **Meirhaeghe A**, Amouyel P. Impact of genetic variation of PPARgamma in humans. *Mol Genet Metab* 2004; **83**: 93-102 [PMID: 15464424 DOI: 10.1016/j.ymgme.2004.08.014]
- 78 **Yang LL**, Hua Q, Liu RK, Yang Z. Association between two common polymorphisms of PPARgamma gene and metabolic syndrome families in a Chinese population. *Arch Med Res* 2009; **40**: 89-96 [PMID: 19237017 DOI: 10.1016/j.arcmed.2008.11.005]
- 79 **Montagnana M**, Fava C, Nilsson PM, Engström G, Hedblad B, Lippi G, Minuz P, Berglund G, Melander O. The Pro12Ala polymorphism of the PPARG gene is not associated with the metabolic syndrome in an urban population of middle-aged Swedish individuals. *Diabet Med* 2008; **25**: 902-908 [PMID: 18959602 DOI: 10.1111/j.1464-5491.2008.02510.x]
- 80 **Zhang R**, Wang J, Yang R, Sun J, Chen R, Luo H, Liu D, Cai D. Effects of Pro12Ala polymorphism in peroxisome proliferator-activated receptor- $\gamma$ 2 gene on metabolic syndrome risk: a meta-analysis. *Gene* 2014; **535**: 79-87 [PMID: 24012868 DOI: 10.1016/j.gene.2013.07.087]
- 81 **Roooki H**, Haerian MS, Azimzadeh P, Mirhafez R, Ebrahimi M, Ferns G, Ghayour-Mobarhan M, Zali MR. Associations between C1431T and Pro12Ala variants of PPAR $\gamma$  gene and their haplotypes with susceptibility to metabolic syndrome in an Iranian population. *Mol Biol Rep* 2014; **41**: 3127-3133 [PMID: 24464185 DOI: 10.1007/s11033-014-3172-z]
- 82 **Meirhaeghe A**, Cottel D, Amouyel P, Dallongeville J. Association between peroxisome proliferator-activated receptor gamma haplotypes and the metabolic syndrome in French men and women. *Diabetes* 2005; **54**: 3043-3048 [PMID: 16186413 DOI: 10.2337/diabetes.54.10.3043]
- 83 **Xie HJ**, Hai B, Wu M, Chen Q, Liu MM, Dong C, Guo ZR. Analysis on the association between PPAR $\alpha/\gamma$  polymorphisms and lipoprotein(a) in a Chinese Han population. *Mol Genet Genomics* 2014; **289**: 981-987 [PMID: 24880474 DOI: 10.1007/s00438-014-0866-9]
- 84 **Gu SJ**, Chen DH, Guo ZR, Zhou ZY, Hu XS, Wu M. Effect of obesity on the association between common variations in the PPAR gene and C-reactive protein level in Chinese Han population. *Endocrine* 2015; **48**: 195-202 [PMID: 24599720]
- 85 **Gu SJ**, Guo ZR, Zhou ZY, Hu XS, Wu M. PPAR  $\alpha$  and PPAR  $\gamma$  polymorphisms as risk factors for dyslipidemia in a Chinese Han population. *Lipids Health Dis* 2014; **13**: 23 [PMID: 24460649 DOI: 10.1186/1476-511X-13-23]
- 86 **Luo W**, Guo Z, Wu M, Hao C, Hu X, Zhou Z, Zhou Z, Yao X, Zhang L, Liu J. Association of peroxisome proliferator-activated receptor  $\alpha/\delta/\gamma$  with obesity, and gene-gene interaction, in the Chinese Han population. *J Epidemiol* 2013; **23**: 187-194 [PMID: 23545576 DOI: 10.2188/jea.JE20120110]
- 87 **Gu SJ**, Liu MM, Guo ZR, Wu M, Chen Q, Zhou ZY, Zhang LJ, Luo WS. Gene-gene interactions among PPAR $\alpha/\delta/\gamma$  polymorphisms for hypertriglyceridemia in Chinese Han population. *Gene* 2013; **515**: 272-276 [PMID: 23262340 DOI: 10.1016/j.gene.2012.11.078]
- 88 **Ding Y**, Guo ZR, Wu M, Chen Q, Yu H, Luo WS. Gene-gene interaction between PPAR $\delta$  and PPAR $\gamma$  is associated with abdominal obesity in a Chinese population. *J Genet Genomics* 2012; **39**: 625-631 [PMID: 23273766 DOI: 10.1016/j.jgg.2012.08.005]

P- Reviewer: Chen JX, Corso G, Kumiko S S- Editor: Tian YL

L- Editor: A E- Editor: Wu HL







Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

