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*Original Article*

# Peroxisome proliferator-activated receptor γ Pro12Ala polymorphism decrease the risk of diabetic nephropathy in type 2 diabetes: a meta analysis

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**Abstract:** Background: The association between peroxisome proliferators-activated receptor γ (PPARγ) Pro12Ala polymorphism and T2DN risk is inconclusive and contradictory. Therefore, we performed a meta-analysis. Methods: All relevant studies were searched by using the PubMed and EMBASE. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Effect model selection was on the basis of heterogeneity test. Results: A total of 20 case-control studies with 9357 subjects were included in this meta-analysis. We found that PPARγ Pro-12Ala polymorphism significantly associated with decreased T2DN risk (OR = 0.74; 95% CI 0.59-0.94; *P* = 0.01). In the subgroup analysis by race, Caucasian with PPARγ Pro12Ala polymorphism showed decreased T2DN risk (OR = 0.63; 95% CI 0.46-0.88; *P* = 0.006). But Asian with PPARγ Pro12Ala polymorphism did not show decreased T2DN risk (OR = 0.87; 95% CI 0.62-1.22; *P* = 0.41). Conclusions: In conclusion, our meta-analysis study confirmed that PPARγ Pro12Ala polymorphism might contribute to the risk for T2DN.

**Keywords:** Diabetic nephropathy, peroxisome proliferators-activated receptor γ, polymorphism

## Introduction

The prevalence of Type 2 diabetes mellitus (T2DM) and the metabolic syndrome has increased dramatically and globally over last decades. Type 2 diabetes results from insulin resistance and metabolic syndrome is also known as insulin resistance syndrome, linking to obesity, hyperglycemia, dyslipidemia and hypertension. Diabetic nephropathy (DN) is a major cause of end-stage renal disease (ESRD) and high mortality in T2DM patients [1]. T2DN is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors.

Peroxisome proliferators-activated receptor γ (PPARγ) is a ligand-activated nuclear transcription factor, which plays a central role in orchestrating gene expression in response to exogenous ligands. PPARγ is located in all three types of glomerular cells with a prominent expression in podocytes [2]. A number of in vivo and in vitro studies demonstrated that PPARγ benefits all kinds of kidney cells including the glomerular mesangial cells, endothelial cells, podocytes, and tubular epithelial cells under the diabetic condition [3] with more research emphasis on the podocytes [4]. Zhu et al. reported that PPARγ activation remarkably improved the mitochondria dysfunction induced by aldosterone in podocytes [5]. Pegg et al. found that combination of an EGFR inhibitor and a PPARγ agonist mitigates high-glucose-induced fibrosis and inflammation and reverses the upregulation of transporters and channels involved in sodium and water retention in human proximal tubule cells [6].

A series of studies have investigated the association between the PPARγ Pro12Ala polymorphism and T2DN susceptibility, but provided controversial or inconclusive results [7-24]. A previous meta-analysis investigated the asso-

**Table 1.** Characteristics of included studies

| First author | Year | Ethnicity | Age | Gender | Case (n) | Control (n) | Hardy-Weinberg equilibrium |
|---|---|---|---|---|---|---|---|
| Mori | 2001 | Asian | Adult | Mixed | 608 | 1024 | Yes |
| Herrmann | 2002 | Caucasian | Adult | Mixed | 197 | 203 | Yes |
| Caramori | 2003 | Caucasian | Adult | Mixed | 104 | 212 | Yes |
| Wu | 2004 | Asian | Adult | Mixed | 220 | 108 | Yes |
| Maeda | 2004 | Asian | Adult | Mixed | 61 | 79 | Yes |
| Pollex | 2007 | Caucasian | Adult | Mixed | 97 | 62 | Yes |
| Erdogan | 2007 | Asian | Adult | Mixed | 43 | 48 | Yes |
| Wei | 2008 | Asian | Adult | Mixed | 82 | 99 | Yes |
| Li | 2008 | Asian | Adult | Mixed | 165 | 94 | Yes |
| Wu | 2009 | Asian | Adult | Mixed | 175 | 214 | Yes |
| De Cosmo | 2009 | Caucasian | Adult | Mixed | 93 | 1026 | Yes |
| Liu | 2010 | Asian | Adult | Mixed | 532 | 228 | Yes |
| Lapice | 2010 | Caucasian | Adult | Mixed | 55 | 695 | Yes |
| Zhu | 2011 | Asian | Adult | Mixed | 41 | 37 | Yes |
| De Cosmo 1 | 2011 | Caucasian | Adult | Mixed | 251 | 580 | Yes |
| De Cosmo 2 | 2011 | Caucasian | Adult | Mixed | 254 | 369 | Yes |
| De Cosmo 3 | 2011 | Caucasian | Adult | Mixed | 232 | 482 | Yes |
| Zhang | 2012 | Asian | Adult | Mixed | 141 | 255 | Yes |
| Bhaskar | 2013 | Asian | Adult | Mixed | 54 | 67 | Yes |
| Azab | 2014 | Caucasian | Adult | Mixed | 25 | 45 | Yes |

ciation between PPARγ Pro12Ala polymorphism and T2DN risk [25]. However, some new studies have been reported. Thus, we decided to perform this update meta-analysis.

## Methods

### *Publication search*

All relevant studies were searched by using the PubMed and EMBASE (The last retrieval date was Sep 21, 2014, using the search terms: "Diabetic nephropathy" and "PPAR gamma" or "PPARγ" or "peroxisome proliferators-activated receptor γ"). All searched studies were retrieved and only published studies with full-text articles were included. When more than publications with duplicate samples, only the newest study was used in this research.

### *Inclusion and exclusion criteria*

The inclusion criteria were as follows: (1) the research was a case-control study or a cohort study; (2) the study investigated the association between PPARγ Pro12Ala polymorphism and T2DN risk; (3) the PPARγ Pro12Ala genotype of individual groups was provided. The exclusion criteria were as follows: (1) no usable data reported; (2) animal studies; (3) reviews or abstracts; (4) duplicates.

### *Data extraction*

Two authors extracted the data independently. These data included: the first author, year, ethnicity, age, gender, and sample size.

### *Statistical analysis*

Statistical analysis was conducted using Stata software 11.0 (StataCorp, College Station, Texas, USA) and RevMan 5.1. Hardy-Weinberg equilibrium (HWE) test in healthy control group was conducted using $\chi^2$ test. Odds ratio (OR) with a 95% confidence interval (CI) was presented for the association between PPARγ Pro12Ala polymorphism and T2DN risk, and significant level was 0.05. *Q*-statistic and $I^2$-statistic were used to measure statistical heterogeneity and significant level was 0.10. Effect model selection was on the basis of heterogeneity test. Fixed effect model was selected when no significant heterogeneity, or else the random effect. Subgroup analyses based on race were done. Sensitivity analysis was conducted. Publication bias was test using Begg's test and funnel plot (significant level was 0.05).

## Results

### *Study characteristics*

The characteristics of the included studies were listed in **Table 1**. Eleven studies were conducted in Asian populations, and 9 studies were performed in Caucasian populations. One study reported three independent cohorts, respectively. Thus, a total of 20 case-control studies with 9357 subjects were included in this meta-analysis.

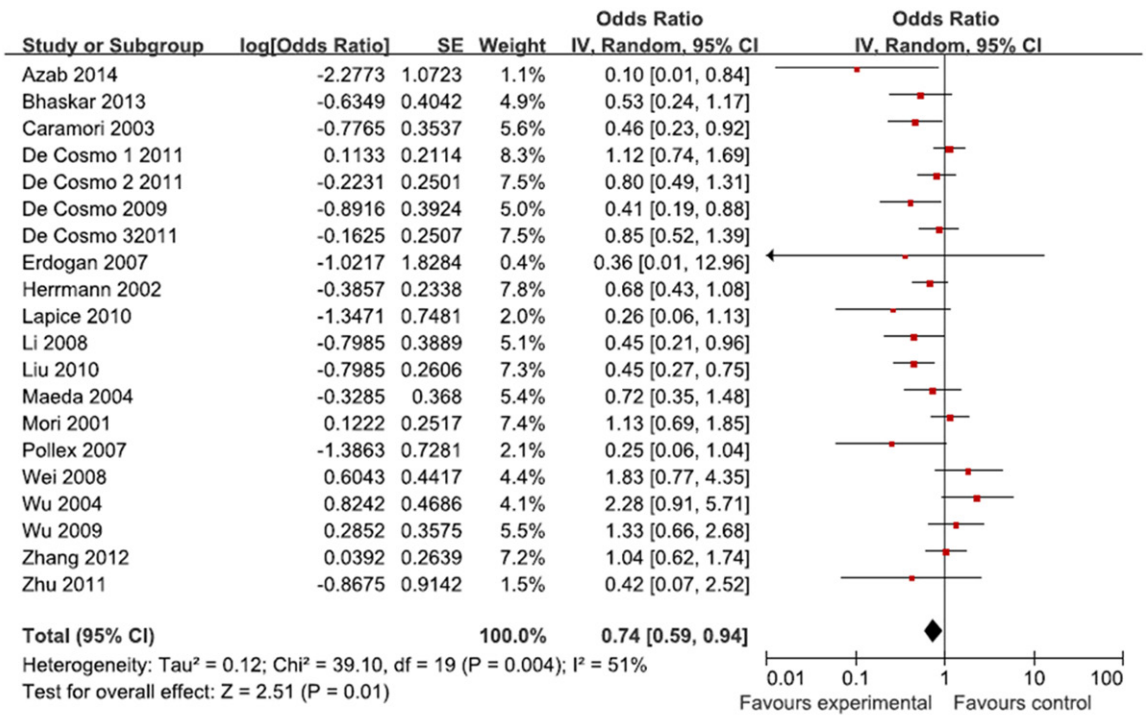


**Figure 1.** Results of the published studies of the association between PPARγ Pro12Ala polymorphism and T2DN risk.

*Quantitative data synthesis*

As shown in **Figure 1**, we found that PPARγ Pro12Ala polymorphism significantly associated with decreased T2DN risk (OR = 0.74; 95% CI 0.59-0.94; *P* = 0.01). In the subgroup analysis by race, Caucasian with PPARγ Pro12Ala polymorphism showed decreased T2DN risk (OR = 0.63; 95% CI 0.46-0.88; *P* = 0.006). But Asian with PPARγ Pro12Ala polymorphism did not show decreased T2DN risk (OR = 0.87; 95% CI 0.62-1.22; *P* = 0.41). To determine the stableness of the result, we performed the sensitivity analysis by omitting one study at a time. We found that single study did not impact the pooled OR, indicating that the results of our research were statistically robust (**Figure 2**).

Funnel plot and Begg's test were conducted to assess the publication bias. The shape of funnel plot was symmetry (**Figure 3**). Egger's test did not detect obvious publication bias (*P* = 0.10).

## Discussion

Within the kidney, PPARγ is mainly localized in the medullary collecting duct, with low expression in many other nephron segments, such as the glomeruli and proximal tubules, and in renal cells including glomerular mesangial cells, podocytes, and proximal epithelial cells [26, 27]. PPARg activation by TZDs is associated with the attenuation of diabetic nephropathy in patients with type 2 diabetes and in various type 2 diabetic rodent models [28]. In streptozotocin (STZ)-induced type 1 diabetic rodents, PPARg activation also ameliorates proteinuria independent of glycemic control [29]. Moreover, 3-month treatment of type 2 diabetic patients with rosiglitazone resulted in a significant reduction in albuminuria levels [30].

This present meta-analysis of 20 case-control studies evaluated the association between PPARγ Pro12Ala polymorphism and T2DN risk. We found that PPARγ Pro12Ala polymorphism significantly associated with decreased T2DN risk. In the subgroup analysis by race, Caucasian with PPARγ Pro12Ala polymorphism showed decreased T2DN risk. But Asian with PPARγ Pro12Ala polymorphism did not show decreased T2DN risk.

The association between PPARγ Pro12Ala polymorphism and other diseases were reported.

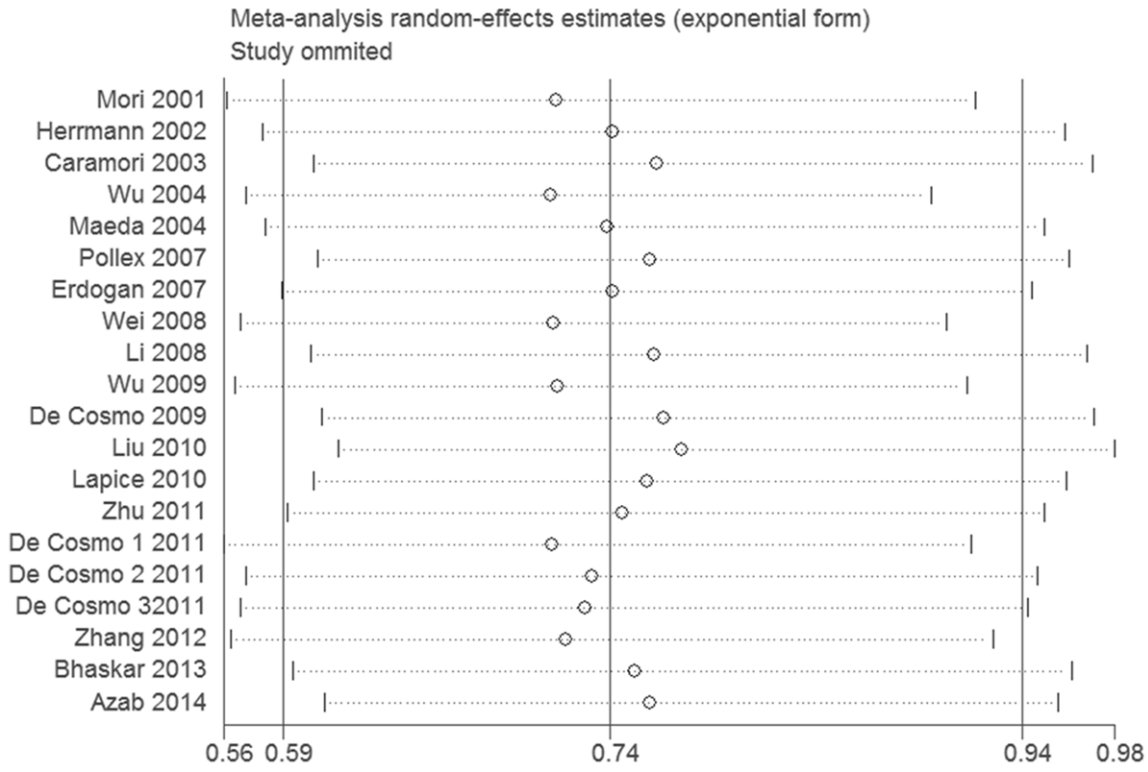


**Figure 2.** Sensitivity analysis of the association between PPARγ Pro12Ala polymorphism and T2DN risk.

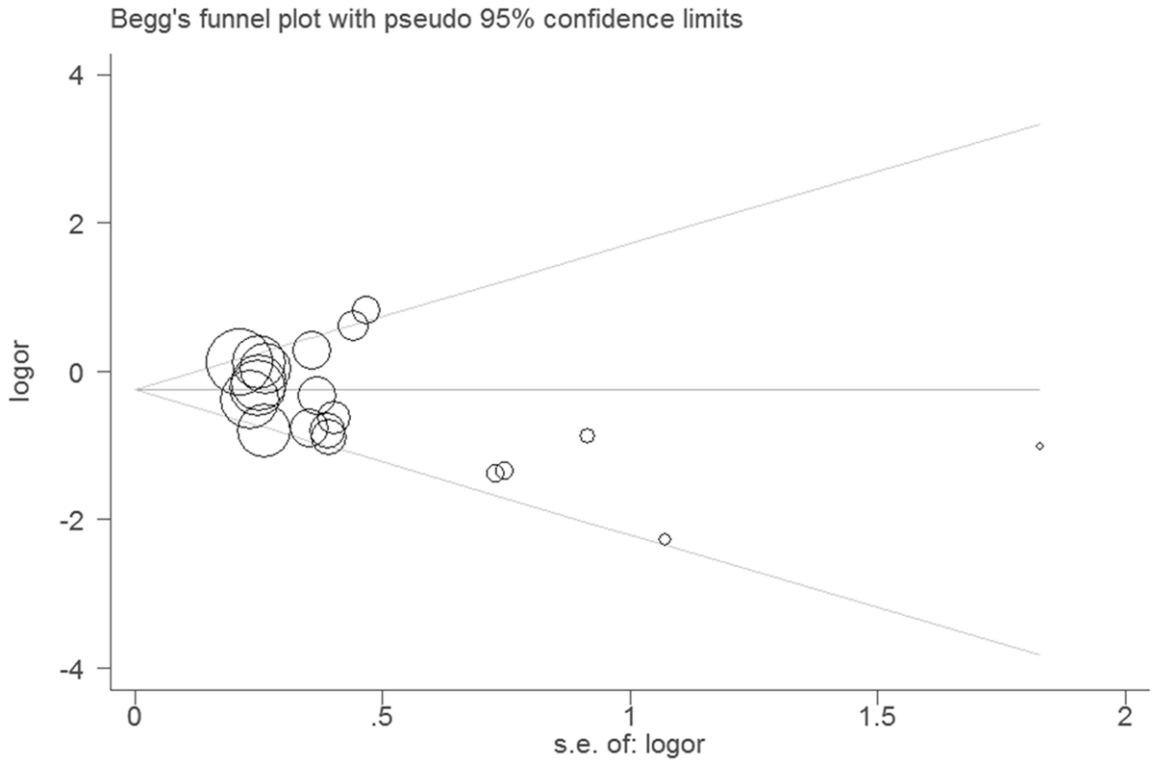


**Figure 3.** Funnel plot of the association between PPARγ Pro12Ala polymorphism and T2DN risk.

Mao et al. reported that PPARγ Pro12Ala modestly affects the risk of breast cancer [31]. Zhang et al. reported that Pro12Ala may affect the single component of metabolic syndrome [32]. Wu et al. suggested that PPARγ C161T polymorphism might play a moderate protective effect on developing CAD among Chinese [33]. Ma et al. indicated that a significant association exists between the Pro12Ala polymorphism and diabetic retinopathyin T2DM with ethnic differences [34].

In conclusion, our meta-analysis study confirmed that PPARγ Pro12Ala polymorphism might contribute to the risk for T2DN.

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## Disclosure of conflict of interest

None.

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## References

[1] Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab 2008; 4: 444-52.

[2] Guan Y, Breyer MD. Peroxisome proliferator-activated receptors (PPARs): novel therapeutic targets in renal disease. Kidney Int 2001; 60: 14-30.

[3] Qian Y, Feldman E, Pennathur S, Kretzler M, Brosius FC 3rd. From fibrosis to sclerosis: mechanisms of glomerulosclerosis in diabetic nephropathy. Diabetes 2008; 57: 1439-45.

[4] Miceli I, Burt D, Tarabra E, Camussi G, Perin PC, Gruden G. Stretch reduces nephrin expression via an angiotensin II-AT(1)-dependent mechanism in human podocytes: effect of rosiglitazone. Am J Physiol Renal Physiol 2010; 298: F381-90.

[5] Zhu C, Huang S, Yuan Y, Ding G, Chen R, Liu B, Yang T, Zhang A. Mitochondrial dysfunction mediates aldosterone-induced podocyte damage: a therapeutic target of PPARγ. Am J Pathol 2011; 178: 2020-31.

[6] Pegg K, Zhang J, Pollock C, Saad S. Combined Effects of PPARγ Agonists and Epidermal Growth Factor Receptor Inhibitors in Human Proximal Tubule Cells. PPAR Res 2013; 2013: 982462.

[7] Caramori ML, Canani LH, Costa LA, Gross JL. The human peroxisome proliferator-activated receptor gamma2 (PPAR-gamma2) Pro12Ala polymorphism is associated with decreased risk of diabetic nephropathy in patients with type 2 diabetes. Diabetes 2003; 52: 3010-3013.

[8] Herrmann SM, Ringel J, Wang JG, Staessen JA, Brand E. Peroxisome proliferator-activated receptor-gamma2 polymorphism Pro12Ala is associated with nephropathy in type 2 diabetes: The Berlin Diabetes Mellitus (BeDiaM) Study. Diabetes 2002; 51: 2653-2657.

[9] Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, Takeda J, Inoue I, Seino Y, Yasuda K, Hanafusa T, Yamagata K, Awata T, Kadowaki T, Hara K, Yamada N,Gotoda T, Iwasaki N, Iwamoto Y, Sanke T, Nanjo K, Oka Y, Matsutani A, Maeda E, Kasuga M. The Pro12→Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. Diabetes 2001; 50: 891-894.

[10] Wu S. Study on the Relationship of Polymorphism of PPAR-g2 and Type 2 Diabetes and Diabetic Nephropathy. Tianjin: Tianjin Medical University; 2004.

[11] Maeda A, Gohda T, Funabiki K, Horikoshi S, Tomino Y. Peroxisome proliferator-activated receptor gamma gene polymorphism is associated with serum triglyceride levels and body mass index in Japanese type 2 diabetic patients. J Clin Lab Anal 2004; 18: 317-321.

[12] Pollex RL, Mamakeesick M, Zinman B, Harris SB, Hegele RA, Hanley AJ. Peroxisome proliferator-activated receptor gamma polymorphism Pro12Ala is associated with nephropathy in type 2 diabetes. J Diabetes Complications 2007; 21: 166-171.

[13] Erdogan M, Karadeniz M, Eroglu Z, Tezcanli B, Selvi N, Yilmaz C. The relationship of the peroxisome proliferator-activated receptor-gamma 2 exon 2 and exon 6 gene polymorphism in Turkish type 2 diabetic patients with and without nephropathy. Diabetes Res Clin Pract 2007; 78: 355-359.

[14] Wei F, Wang J, Wang C, Huo X, Xue Y, Bai L. The relationship between the pro12Ala polymorphism in PPAR-g2 gene and diabetic nephropathy in Baotou. Chinese J Diabetes 2008; 16: 679-680.

[15] Li L, Liu L, Zheng T, Wang N, Wang F. Peroxisome proliferator activated receptor g2 gene P12A polymorphism and type 2 diabetic nephropathy in Han population in Shanghai. J Shanghai Jiaotong Univ 2008; 28: 376-379.
[16] Wu LS, Hsieh CH, Pei D, Hung YJ, Kuo SW, Lin E. Association and interaction analyses of genetic variants in ADIPOQ, ENPP1, GHSR, PPARgamma and TCF7L2 genes for diabetic nephropathy in a Taiwanese population with type 2 diabetes. Nephrol Dial Transplant 2009; 24: 3360-3366.
[17] De Cosmo S, Motterlini N, Prudente S, Pellegrini F, Trevisan R, Bossi A, Remuzzi G, Trischitta V, Ruggenenti P; BENEDICT Study Group. BENEDICT Study Group. Impact of the PPARgamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: evidence from BENEDICT. Diabetes 2009; 58: 2920-2929.
[18] Liu L, Zheng T, Wang F, Wang N, Song Y, Li M, Li L, Jiang J, Zhao W. Pro12Ala polymorphism in the PPARG gene contributes to the development of diabetic nephropathy in Chinese type 2 diabetic patients. Diabetes Care 2010; 33: 144-149.
[19] Lapice E, Pinelli M, Riccardi G, Vaccaro O. Pro12Ala polymorphism in the PPARG gene contributes to the development of diabetic nephropathy in Chinese type 2 diabetic patients: comment on the study by Liu et al. Diabetes Care 2010; 33: e114.
[20] Zhu W, Ji Y, Bu L, Yang Q. The correlativity study of peroxisome proliferator activated receptor g2 gene polymorphism with susceptibility of diabetic nephropathy in type 2 diabetes mellitus. J Radio-immunology 2011; 24: 296-298.
[21] De Cosmo S, Prudente S, Lamacchia O, Lapice E, Morini E, Di Paola R, Copetti M, Ruggenenti 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.
[22] Zhang H, Zhu S, Chen J, Tang Y, Hu H, Mohan V, Venkatesan R, Wang J, Chen H. Peroxisome Proliferator-Activated Receptor g Polymorphism Pro12Ala Is Associated With Nephropathy in Type 2 Diabetes. Diabetes Care 2012; 35: 1388-1393.
[23] Bhaskar LV, Mahin S, Ginila RT, Soundararajan P. Role of the ACE ID and PPARG P12A Polymorphisms in Genetic Susceptibility of Diabetic Nephropathy in a South Indian Population. Nephrourol Mon 2013; 5: 813-7.
[24] 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: 743-9.
[25] Wang L, Teng Z, Cai S, Wang D, Zhao X, Yu K. The association between the PPARγ2 Pro12Ala polymorphism and nephropathy susceptibility in type 2 diabetes: a meta-analysis based on 9,176 subjects. Diagn Pathol 2013; 8: 118.
[26] Guan Y, Zhang Y, Schneider A, Davis L, Breyer RM, Breyer MD. Peroxisome proliferator-activated receptor-gamma activity is associated with renal microvasculature. Am J Physiol Renal Physiol 2001; 281: F1036-46.
[27] Nicholas SB, Kawano Y, Wakino S, Collins AR, Hsueh WA. Expression and function of peroxisome proliferator-activated receptor-gamma in mesangial cells. Hypertension 2001; 37: 722-7.
[28] Yang J, Zhang D, Li J, Zhang X, Fan F, Guan Y. Role of PPARgamma in renoprotection in Type 2 diabetes: molecular mechanisms and therapeutic potential. Clin Sci (Lond) 2009; 116: 17-26.
[29] Flaquer M, Lloberas N, Franquesa M, Torras J, Vidal A, Rosa JL, Herrero-Fresneda I, Grinyó JM, Cruzado JM. The combination of sirolimus and rosiglitazone produces a renoprotective effect on diabetic kidney disease in rats. Life Sci 2010; 87: 147-53.
[30] Zheng F, Guan Y. Thiazolidinediones: a novel class of drugs for the prevention of diabetic nephropathy? Kidney Int 2007; 72: 1301-3.
[31] Mao Q, Guo H, Gao L, Wang H, Ma X. Peroxisome proliferator-activated receptor $\gamma^2$ Pro12Ala (rs1801282) polymorphism and breast cancer susceptibility: a meta-analysis. Mol Med Rep 2013; 8: 1773-8.
[32] 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-γ2 gene on metabolic syndrome risk: a meta-analysis. Gene 2014; 535: 79-87.
[33] Wu Z, Lou Y, Jin W, Liu Y, Lu L, Lu G. The C161T polymorphism in the peroxisome proliferator-activated receptor gamma gene (PPARγ) is associated with risk of coronary artery disease: a meta-analysis. Mol Biol Rep 2013; 40: 3101-12.
[34] Ma J, Li Y, Zhou F, Xu X, Guo G, Qu Y. Meta-analysis of association between the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 gene and diabetic retinopathy in Caucasians and Asians. Mol Vis 2012; 18: 2352-60.