Review Article

Association of Peroxisome Proliferator-Activated Receptors (PPARs) with Diabetic Retinopathy in Human and Animal Models: Analysis of the Literature and Genome Browsers

Špela Tajnšek,1 Danijel Petrovič,2 Mojca Globočnik Petrovič,3,4 and Tanja Kunej1

1University of Ljubljana, Biotechnical Faculty, Department of Animal Science, Slovenia
2University of Ljubljana, Faculty of Medicine, Institute of Histology and Embryology, Slovenia
3Eye Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia
4University of Ljubljana, Faculty of Medicine, Slovenia

Correspondence should be addressed to Mojca Globočnik Petrovič; mgpetrovic@yahoo.com and Tanja Kunej; tanja.kunej@bf.uni-lj.si

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Diabetic retinopathy (DR) is a condition that develops after long-lasting and poorly handled diabetes and is presently the main reason for blindness among elderly and youth. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that are involved in carbohydrate and fatty-acid metabolism and have also been associated with DR. Three PPAR isoforms are known: PPARγ, PPARα, and PPARδ. In the present study, we retrieved articles reporting associations between PPARs and DR from PubMed database and compiled the data in two catalogues, for human and animal models. Extracted data was then complemented with additional relevant genomic information. Seven retrieved articles reported testing an association between PPARs with DR in human. Four of them concluded association of PPARγ and PPARα with DR in European and Asian populations, having a protective role on DR development. One study reported pathogenic role of PPARγ, while two articles reported no association between PPARγ and DR among Indian and Chinese populations. Six retrieved articles reported testing of involvement of PPARγ and PPARα in DR in animal models, including mouse and rat. The review includes case-control studies, meta-analysis, expression studies, animal models, and cell line studies. Despite a large number of documented sequence variants of the PPAR genes available in genome browsers, researchers usually focus on a small set of previously reported variants. Data extraction from Ensembl genome browser revealed several sequence variants with predicted deleterious effect on protein function which present candidates for further experimental validation. Results of the present analysis will enable more holistic approach for understanding of PPARs in DR development. Additionally, developed catalogues present a baseline for standardized reporting of PPAR-phenotype association in upcoming studies.

1. Introduction

Diabetic retinopathy (DR) is a condition that develops due to bad glycemic control in subjects with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). Long-lasting poor blood glucose control, smoking, and hypertension can contribute to DR development [1, 2]. The disease progresses from nonproliferative (NPDR) to proliferative (PDR) stage where at first microvascular irregularities such as hemorrhage, ischemia, and microaneurysms lead to neoangiogenesis [2]. Microvascular changes start due to lower concentrations of oxygen in the retina of the eye after the disease progresses, and at final stages, PDR can lead to vision loss. Diabetic retinopathy had become the main reason for blindness in American adults. In year 2012, there were approximately 93 million people living with diabetic retinopathy, 17 million with PDR, and 21 with diabetic macular edema, and the number is expected to increase in the future [3, 4].
Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that regulate the expression of several genes and are affecting lipid and carbohydrate metabolism. PPARs consist of three subtypes: PPARA, PPARD, and PPARG [5]. Peroxisome proliferator-activated receptor gamma (PPARG) also known as GLM1, CIMT1, NR1C3, PPARG1, PPARG2, or PPARgamma is a nuclear receptor that binds hypolipidemic drugs and unsaturated fatty acids and affects adipocyte differentiation, gluconeogenesis, oxidation of fatty acids, lipogenesis, cholesterol metabolism, and synthesis of ketone bodies [5–9]. The gene is located on chromosome HSA3. In the eye, the gene is heterogeneously expressed in photoreceptor outer segments, choriocapillaries, retina, retinal pigmented epithelium, cornea, and lacrimal gland [10–12]. Three RNA isoforms of expressed PPAR have been identified: γ1, γ2, and γ3. PPAR-γ2 protein has additional stretch of 28 amino acids on N-terminal, and this extension seems to change PPAR-γ2 sensitivity to insulin action [13]. Proline variant of Pro12Ala (rs1801282) polymorphism of the PPARG gene is associated with increased resistance to insulin action whereas the alternative allele has the opposite properties [14]. Peroxisome proliferator-activated receptor alpha (PPARA) also known as PPARα, NR1C1, hPPAR, or PPARalpha is responsible for ketogenesis, lipid transport, lipogenesis, cholesterol metabolism, fatty acid transport, and oxidation [15]. It is located on the HSA22. PPARA is expressed in the retina; however, its levels have been shown to be reduced in the retinas with DR [16, 17]. Decreased PPARA expression in diabetic retinas contributes to retinal inflammation and neovascularization in DR, and activation of PPARA has anti-inflammatory and antiapoptotic effects in oxygen-induced retinopathy (OIR) and diabetic animal models through suppression of NF-κB signaling [16, 17].

Peroxisome proliferator-activated receptor delta (PPARD) also known as FAAR, NUC1, NUCI, NR1C2, NUCII, or PPARβ is located on HSA6. It affects fatty acid transport and oxidation, adipocyte differentiation, adaptive thermogenesis, cell survival, and ubiquitination [18]. Among the three PPAR subtypes, it is the least studied and understood, especially its effects on inflammation and proliferation associating DR.

To our knowledge, the complete database related with reported associations between PPARs and DR does not yet exist. The aim of this study was therefore to conduct an overview of articles reporting an association between three PPARs and DR/PDR in human and animal models.

2. Materials and Methods

Using keywords “PPAR” and/or “PPARG” and/or “PPARA” and/or “PPARD” and/or “polymorphism” and/or “diabetic retinopathy”, we explored the PubMed database for articles describing association between PPARs and DR in human and animal models. Inclusion criteria for the type of study in humans were case-control study, meta-analysis, or expression study. Retrieved articles included in previously published meta-analysis were excluded from the analysis. Time span for article search was set from January 1999 to December 2017. Retrieved articles were checked for the following information: retinopathy type, sequence variant, gene name, diabetes type, species, number of tested samples, result of the study, and method. The data extracted from publications was afterwards complemented with additional information such as gene ID (https://www.ncbi.nlm.nih.gov/gene), gene location (https://www.ncbi.nlm.nih.gov/gene), taxonomy ID (https://www.ncbi.nlm.nih.gov/taxonomy), disease ontology ID (DOID; http://disease-ontology.org/), reference SNP (rs) identification number, PubMed identification number (PMID) of the reference, and statistical significance (Figure 1). Ensembl genome browser release 96 was used to retrieve additional information related with sequence variants, predicted effect on protein function
using six bioinformatics tools, and clinical significance from ClinVar database [19].

3. Results

We developed two tables consisting of data extracted from 13 retrieved articles published between 1/2012 and 12/2017 reporting associations between PPAR polymorphisms and DR in human (Table 1) and animal models (Table 2) (Figure 2). In humans, six articles reported testing association between PPARG and DR/PDR and one reported PPARA and DR association. We did not retrieve any articles related with PPARD-DR association. Six studies were performed in animal models, including four articles describing involvement of PPARA in DR and two involvement of PPARG in DR.

3.1. Studies in Humans. Out of seven retrieved articles describing association between PPARs and DR/PDR in humans, six articles were related with the PPARG gene and one study with the PPARA gene.

One study reported that PPARG may play an important role in the pathogenesis of PDR. The PPARG concentrations in the aqueous humor and vitreous fluid were significantly higher in PDR patients than in controls, and the level of PPARG increased in the advanced clinical stage. Additionally, a correlation between PPARG and vascular endothelial growth factor (VEGF) concentrations was identified [20]. Two out of seven studies reported no association between PPARs and DR [21, 22]. Three studies identified association (protective effect or decreased DR risk) between PPARG and DR/PDR (Figure 2) [23–25]. Qi et al. studied polymorphism rs1800206 of the PPARG gene and concluded that carriers of homozygous mutant allele have decreased DR risk in comparison to wild-type homozygotes in Chinese Han population [26].

Most participants in the studies had type 2 diabetes mellitus (T2DM), and some participants had type 1 diabetes mellitus (T1DM). The developed catalogue includes five case-control studies, one meta-analysis [23], and one expression study [20]. Case-control studies included 17 to 812 participants. Meta-analysis study consisted of more than 4000 participants from eight studies. Studies were performed on different populations, such as European Caucasian, Asian (Chinese Han), and Pakistani. Methods used for genotyping and expression analysis were quantitative real time, PCR-ligase detection reaction (LDR), quantitative PCR, PCR-RFLP, and real-time PCR.

3.2. Studies in Animal Models. Six studies used animal models for testing association between PPARs and DR/PDR: mouse, rat, and cattle. In some studies, more than one animal model and additional animal cell lines were used. For imitating DR or diabetes in mice and rat, animals were made diabetic with streptozotocin (STZ) or underwent through OIR. Most studies based on an animal model used knockout mice (KO) approach. In most studies, they used C57Bl/6J mouse model or Brown Norway rats [16, 17, 27–30]. Additionally, bovine retinal endothelial cells (BRECs) were also used [28].

Various methods were used for testing association between PPARs and DR in animal models, for example, TUNEL assay, quantitative real-time PCR, retinal leakage assay, vascular leakage assay, fluorescent microscopy, immuno-fluorescence, western blot, and protein-based detection methods detecting over/underexpression of the protein.

Most of the reports in humans were designed as association studies between PPAR polymorphisms and DR; however, in animal models, most performed gene expression analyses in diabetic and nondiabetic animals (Table 2). Hu et al. [17] used animal model for testing an involvement of PPARA and DR and concluded that PPARA knockout mice developed more severe DR which resulted in retinal vascular leakage, leukostasis, pericyte loss, capillary degeneration, and overexpressed inflammatory factors, whereas PPARA overexpression reduced vascular leakage and inflammation. PPARA protective effects have been proven by Ding et al. [30]. PPAR+/- knockout mice had greater leukostasis and leakage than wild-type mice [27], and suppression of PPARG has been shown to be involved in the pathogenesis of diabetic retinopathy and OIR [28].

4. Discussion

PPARs are important factors in DR/PDR due to their protective function on the disease development. Our results revealed that reports in this study field are very heterogeneous. Most studies in humans analyzed polymorphism Pro12Ala (rs1801282) located in the PPARG gene. In contrary, some studies were performed on cell lines and animal models. For example, Chen et al. [29] reported that PPARA is a target of microRNA-21, which downregulates expression of PPARG and worsens DR condition.

Our study revealed that researchers use different synonyms for the same gene (for example, PPARG, PPARy, CIMT1, and NR1C3), for the same gene variant (Pro12Ala, rs1801282, c.34C>G), or for methodology. In several studies, patients with DR were not divided into NPDR and PDR cases. Additionally, in some studies, it is not clear whether a gene is associated with PDR or is associated only with NPDR.

The results of the association studies related with PPARs and its association with DR/PDR differ among populations (Table 1). For example, polymorphism Pro12Ala is the most studied polymorphism of the PPARG gene. Tariq et al. reported that polymorphism Pro12Ala is not associated with DR in Pakistani population [25]; however, Wang et al. reported that it is associated with DR in Chinese population [24].

According to the latest release of the Ensembl database, there are a high number of polymorphisms located within PPAR genes in humans and animals. However, our results show that researchers focused on only few sequence variants of the PPAR gene family. Several bioinformatics tools could be used for prioritization of stronger candidate sequence variants for experimental validation. Ensembl browser enables comparison of six bioinformatics tools designed for predicting the effect of sequence variants on protein function: SIFT, PolyPhen, CADD, REVEL, MetaLR, and MutationAssessor. Figure 3 presents a part of the variant table from the Ensembl genome browser. For example, most of the tools predict
| Gene symbol | Gene ID | Gene location | Sequence variant | rs ID of the polymorphism | Diabetes type | Retinopathy type | DOID | Population | Number of samples (cases/controls) | Statistical significance | Method | Main result of the study | Type of study | Reference | PMID |
|-------------|---------|---------------|------------------|--------------------------|---------------|-----------------|------|------------|----------------------------------|-------------------------|---------|--------------------------|-------------|-----------|------|
| PPARG       | 5468    | 3p25.2        | /                | /                        | T1DM T2DM     | PDR             | 13207 | Japan*     | 17 (12 PDR, 5 controls)            | \( p < 0.0005 \)         | Quantitative real-time PCR, ELISA, immunohistochemistry analysis | Higher expression of PPARG in PDR versus controls | Expression study | Katome et al. [20] | 25468312 |
| PPARG       | 5468    | 3p25.2        | rs1801282        | rs3856806 rs12497191     | T2DM DR, PDR  | 8947, 13207     | Chinese         | 792 T2DM (448 DR, 344 diabetes without DR) | \( OR (95\% CI) = 1.40 (0.85-2.29); p = 0.22 \) | PCR-LDR | No significant association between polymorphisms in the PPARG gene and DR or PDR | Case-control study | Zhang et al. [22] | 25274455 |
| PPARG       | 5468    | 3p25.2        | Pro12Ala         | /                        | T2DM DR       | 8947            | Caucasian Asian | 5170 (2720 DR cases, 2450 controls) | \( OR (95\% CI) = \frac{1.40 (0.85-2.29)}{p = 0.012} \) | Statistics | Protective effect of Pro12Ala on DR in T2DM with ethnic differences | Meta-analysis | Ma et al. [23] | 22993484 |
| PPARG       | 5468    | 3p25.2        | C1341T Intr C>A; Pro12Ala Intron C>T | rs3856806 rs709158 rs1805192 rs4684847 | T2DM DR       | 8947            | Chinese         | 500 T2DM (247 DR cases, 253 controls) | \( OR (95\% CI) = 0.86 (0.56-0.96), p = 0.012 \) | Quantitative PCR | Protective role of the 12Ala polymorphism against PDR in T2DM with lower DR risk; rs1805192 minor allele (Ala) of PPARG is significantly associated with lower DR risk; interaction between Ala-BMI interaction and overweight on DR | Case-control study | Wang et al. [24] | 26885119 |
| PPARG       | 5468    | 3p25.2        | rs1801282        | (c.34C>G, Pro12Ala)     | T2DM DR, PDR  | 8947, 13207     | Pakistani       | 573 (189 DR, 193 DNR, 200 controls) | \( OR = 0.4; 95\% CI = 0.2-0.8 \) | PCR-RFLP | No significant association between rs1800206 minor (V) allele and lower DR risk; interaction between rs1800206 and abdominal obesity | Case-control study | Tarki et al. [25] | 23559865 |
| PPARA       | 5465    | 22q13.31      | rs4253778         | rs1800206                | T2DM DR       | 8947            | Chinese Han     | 812 (402 DR, 410 control) | \( OR (95\% CI) = 0.78 (0.66-0.94) \) | Quantitative PCR | Association between rs1800206 minor (V) allele and lower DR risk; interaction between rs1800206 and abdominal obesity | Case-control study | Qi et al. [26] | 26671228 |

/ = data not available; * the country where the study was conducted; PPARA = peroxisome proliferator-activated receptor alpha; PPARG = peroxisome proliferator-activated receptor gamma; PPARD = peroxisome proliferator-activated receptor delta; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; DOID = disease ontology ID; PMID = PubMed ID; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; DNR = diabetes no retinopathy; LDR: ligase detection reaction.
| Gene symbol | Gene ID | Gene location | Species | Taxonomy ID | Sequence variant | Model | Retinopathy type model | DOID | Strain/details | Statistical significance | Method | Main result of the study | Type of study | Reference | PMID |
|-------------|---------|----------------|---------|-------------|------------------|-------|------------------------|------|-----------------|------------------------|--------|------------------------|--------------|-----------|------|
| Pparg       | 19016   | 6 E3           | Mouse   | 10090       | /                | Knockout, STZ   | DR    | C57BL/6               | p < 0.05 | Retinal leakage assay, fluorescent microscopy | Pparg signaling pathway inhibits diabetes-induced retinal leukostasis and leakage | Therapy with Pparg ligands may inhibit retinal leukostasis and retinal leakage in diabetes | Animal model | Muranaka et al. [27] | 17003451 |
| Pparg       | 25664   | 4q42           | Rat     | 10116       | /                | STZ              | DR    | Brown Norway          | p < 0.05 | Retinal leakage assay, fluorescent microscopy | The link between Pparg and retinal vascular inflammation in DR | Suppression of Pparg expression in high glucose-treated cells | Animal model | Muranaka et al. [27] | 17003451 |
| Pparg       | 19016   | 6 E3           | Mouse   | 10090       | /                | Knockout, STZ, OIR | DR    | C57BL/6J              | p < 0.05 | Immuno-fluorescence, western blot | Upregulated miR-21 and downregulated Ppara in OIR | Y-0452 exerts antiangiogenic effects in OIR retinas through Ppara-dependent mechanism | Cell line, animal model | Chen et al. [29] | 28270521 |
| Ppara       | 281993  | 22q24          | Cattle  | 9913        | /                | Cells            | DR    | BREC                  | p < 0.05 | Western blot | Y-0452 (Ppara agonist) alleviated the retinal apoptosis | Protective effect of Ppara against retinal pericyte loss in DR | Cell line, animal model | Deng et al. [16] | 28979999 |
| Ppara       | 19013   | 15 E2          | Mouse   | 10090       | /                | Knockout, OIR   | DR    | C57BLKS/6            | p < 0.05 | qRT-PCR            | Overexpression of Ppara in the retina alleviated vascular leakage and inflammation | Protective effect of Ppara against retinal pericyte loss in DR | Cell line, animal model | Deng et al. [16] | 28979999 |
| Ppara       | 25747   | 7q34           | Rat     | 10116       | /                | STZ              | DR    | Brown Norway          | p < 0.05 | Vascular leakage assay | Y-0452 (Ppara agonist) alleviated the retinal apoptosis | Protective effect of Ppara against retinal pericyte loss in DR | Cell line, animal model | Deng et al. [16] | 25108226 |
| Ppara       | 19013   | 15 E2          | Mouse   | 10090       | /                | Knockout, STZ   | DR    | C57BL/6J              | p < 0.05 | TUNEL assay         | Overexpression of Ppara in the retina alleviated vascular leakage and inflammation | Overexpression of Ppara in the retina alleviated vascular leakage and inflammation | Animal model | Hu et al. [17] | 24003152 |
| Ppara       | 25747   | 7q34           | Rat     | 10116       | /                | STZ              | DR    | Brown Norway          | p < 0.05 | Quantitative real-time RT-PCR | Overexpression of Ppara in the retina alleviated vascular leakage and inflammation | Overexpression of Ppara in the retina alleviated vascular leakage and inflammation | Animal model | Hu et al. [17] | 24003152 |

/ = data not available; Pparg = peroxisome proliferator-activated receptor gamma; Ppara = peroxisome proliferator-activated receptor alpha; STZ = streptozotocin; OIR = oxygen-induced retinopathy; DR = diabetic retinopathy; BREC = bovine retinal endothelial cells; DOID = disease ontology identification number.
benign effect of the polymorphism rs1801282 (Pro12Ala) on protein function and two predict tolerated/neutral effect. On the contrary, for several other polymorphisms, predicted effect on protein function is damaging (red color) or possibly damaging (orange). Out of 286 sequences with available bioinformatics predictions, only polymorphism rs121909246 has predicted deleterious effect by all six bioinformatics tools.

Additionally, according to the ClinVar database, this polymorphism has a pathogenic effect. However, several other missense polymorphisms of the PPARG gene have not yet been tested for association with diseases, including DR. For some of the polymorphisms, minor allele frequency (MAF) and clinical significance from ClinVar database are given. Currently, the Ensembl browser lists 10 sequence variants
PPARs are important protective factors of DR/PDR among certain populations and have potential for therapeutic targets. To the best of our knowledge, this is the first overview on the topic on PPARs associated with DR/PDR in human and animal models. The study presents a baseline for further studies, for example, meta-analyses and bioinformatics prioritization of new candidates for functional studies.

Additional Points

Executive Summary. (i) Literature review of studies testing an association between PPARs and diabetic retinopathy in human and animal models. (ii) Results showed that published results are opposing and data presentation of results in publications is heterogeneous. (iii) Developed catalogues summarizing PPAR-DR associations present a baseline for standardized reporting of PPAR-phenotype association in upcoming studies. (iv) Prioritization of novel candidate sequence variants for further experimental validation using six bioinformatics tools revealed several substitutions with predicted deleterious effect on protein function.

Conflicts of Interest

We declare that there are no conflicts of interests.

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