MATHEWS Open Access Journals

ISSN: 2474-6932

Mini Review | Mathews Journal of Ophthalmology

Candidate Genes in Mexican Population with Diabetic Retinopathy

Perla M. Madrigal-Ruiz[1], María Elena Aguilar-Aldrete[2], Sergio Alberto Ramirez-Garcia[3], Luis J. Flores-Alvarado[1], Dalia A. Madrigal-Ruiz[1], Rosalba Ruiz-Mejía[1], Nory O. Dávalos-Rodríguez[1]

[1]Department of Molecular Biology and Genomic Medicine from University of Guadalajara, Jalisco, Mexico.

[2]Department of Public Health from University of Guadalajara, Jalisco Mexico.

[3]Institute of Research of Public Health of the University of the Sierra Sur, Oaxaca, México.

Corresponding Author: Nory O. Dávalos-Rodríguez, Department of Molecular Biology and Genomic Medicine from University of Guadalajara, Jalisco, Mexico, **Tel:** +01(33) 1058-5200; **Email:** sergio7genetica@Hotmail.com

Received Date: 03 Jan 2018

Accepted Date: 20 Jan 2018

Published Date: 22 Jan 2018

Citation: Madrigal-Ruiz PM, Aguilar-Aldrete ME, Ramirez-Garcia SA, Flores-Alvarado LJ, et al. (2018). Candidate Genes In Mexican Population with Diabetic Retinopathy. M J Opht. 3(1): 019.

ABSTRACT

Diabetic retinopathy is a complex trait since it depends on environmental and genetic factors for its development. Among them, the early therapy with insulin, the degree of metabolic control, time evolution of diabetes and different genetic polymorphisms. We conducted an exhaustive search of the literature, and in the Mexican population we only found five genes associated with diabetic retinopathy; APOE, CYP19A1, *ALR2, HLA-DR7, and ADRB3*. We concluded that, considering the molecular heterogeneity of the DM2 and DR in Mexican population, is required more studies with candidate genes. A new frontier for research in DR, are the variant of the *ELMO1, CUBN and LRP2* genes

KEYWORDS

Aldose Reductase; Apolipoprotein; Diabetic Retinopathy; Microvascular Complications; Polymorphism.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is one the most significant health problems worldwide, affects more than 415 million people worldwide, and it is estimated to increase to 642 million by 2040[1-2]. In 2015, Mexico was the second Latin American country and sixth in the world in prevalence of this disorder with nearly 11.5 million of patients, and its costs to the health care system continue to rise, It is related to themorbidity and mortality associated with microvascular complications such as retinopathy[2-3]. Diabetic retinopathy (DR) is a leading cause of visual impairment in patients at productive age [3-4]. DR prevalence is of 22–37 % in individuals with diabetes [3-4]. Damage of the retina microvasculature is a result of prolonged exposure to metabolic changes induced by diabetes [3-4]. Based on the severity of symptoms, DR is classified into two categories; non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The key sign of NPDR, as a result of hypoxia and venous bleeding, are microaneurysms, vascular leakage, hard exudates, intraretinal microvascular abnormalities and cotton wool spots. Retinal neovascularization induced by ischemia is the main characteristic of PDR [3-4]. The DR diagnostic methods for early identification of diabetic patients with significantly elevated risk of development DR and optimal prevention and intervention of metabolic control of DM patients are needed [3-4]. The exploration of candidate genes through the search of genetic markers such as polymorphisms is a good option, because clinical risk factors for DR, such as duration of disease, and glucose control, do not adequately predict disease progression in patients, suggesting the influence of a genetic component.

In these sense, multiple studies have investigated genotype-phenotype correlations in DR, included genes encoding vascular endothelial growth factor (related to the vascular endothelial dysfunction), aldose reductase (related to the polyol pathway), the receptor for advanced glycation end products, genes associated with inflammation, such as RAAS (renin–angiotensine–aldosterone system), glucose induced pathways, remodeling of extracellular matrix (ECM), and angiogenesis genes [3]. In general, reported results have been conflicting,

due to factors including small sample sizes, variations in study design, differences in clinical end points, and underlying genetic differences between study groups. At this time, there is no confirmed association with any risk allele reported or principal gene in NPDR and PDR [3-4]. Nineteen markers are proposed in the personalizedtherapy of DR, a new trend at therapeutic response in patients, by identifying genotypic and phenotypic factors, may result in less optimal response to conventional therapy, and consequently, lead to poorer outcome, mainly polymorphism in the gene VEGF [5].

Considering this entire context, the objective of this work was to make an exhaustive review of the literature, looking for association studies with genes in diabetic retinopathy in the Mexican population, which allow us to know the molecular epidemiology of this disease in Mexico. We searched the article bases in PudMed, Scielo, Google academic, Proquest, Science Direct, HighWire Press, Imbiomed, Medigraphic data bases, as well as looking at google academic and complete or preliminary studies presented at congresses or scientific meetings.

In Mexican population, only six association studies, have focused on finding genetic markers for predisposition for DR; Such genes are related to polyol pathway, dyslipidemia, angiogenesis, remodeling ECM and antigen presentation [3-4]. There have been various studies in relation to retinopathy and diabetic ophthalmopathy like macular edema. This last, in populations from Western from Mexico, the epsilon4 allele of the APOE gene is a potential risk factor for the severity of retinal hard exudates ($p<0.05$) and visual loss (AV< 0.5 Log MAR, $p=0.057$) [6]. The relationship of the APOE gene with the deterioration of visual acuity has not been previously reported in other populations, and should be considered by clinicians worldwide, since the variants of this gene are also closely related to dyslipidemia and diabetes, and they can be sensitive markers in monitoring and prognosis of the diabetic patient for the control as well as detection of the diabetic ophthalmopathy.

Carrillo et al., also studied a factor correlated to levels of total lipids. Also, heterozygous genotype from the polymorphism p.P207S of CYP19A1 gene is related to moderate macular edema in diabetic patients. This genetic variant is related to high levels of cholesterol and triglyceridesin Mexican Mestizos [7]. The same author and his collaborators reported association in diabetic retinopathy to ALR2 gene (encodes for aldose reductase). Carriers with repeats longer than 23 from the polymorphism (AC)n, show a risk of 5.16. This suggests that long allele's carriers for this genetic marker are at increased odds ratio [8]. Certainly the polymorphism in the CYP19A1 gene has not been studied in other populations, it is very important, since it has its locus in the region that codes for the active site of the aromatase enzyme, which is very important to maintain the conversion of androgens to estrogens, which, as we already know, influence the dyslipidemia state, but also regulate vascular processes, which are part of the etiology of diabetic retinopathy. For this reason, this variant will have to be considered in future replication studies at the level of genetic epidemiology.

On the other hand, Mexican Mestizos with diabetic retinopathy showed less frequency of HLA-D11 compared with the control group ($p = 0.043$). NPDR patients with 10 or more years of DM2 showed an increase of HLA-DR7 ($p = 0.01$), finds odds less than one unit. These results suggest that the carriers of the HLA-DR7 protects against the development of proliferative disease in the diabetic Mexican population [9]. The genetic markers of HLA in retinopathy have only been reviewed in the Mexican and Turkish population, in which presumably HLA-DR7 andHLA-D11marker coincides, which suggests an important participation of the immune component, which is not only linked to the presentation and formation of immune complexes, but also with the inflammatory response and fibrogenesis, which can explain the association with the development of proliferative retinopathy[10]. The markers in HLA genes at the clinical level are very useful, because they are also markers widely used for their sensibility, specificity and are accessible for molecular detection. Considering the association with PDR, they should be analyzed in replication epidemiological studies in other populations.

In México, population of the Western, the genotypes Arg64Arg Trp64Arg from gene encoding for adrenergic beta receptor type 3 are related to mixed dyslipidemia and proliferative retinopathy in diabetics [11]. A marker in ADRB3 gene is very little studied in relation to diabetes mellitus type 2 and its complications worldwide, however it must be retaken by clinicians in the management as well as prognosis, and prevention of complications such as DR, for two reasons. The first one, that is associated with components of the metabolic syndrome (hyperglycemia and hypertension), which are precipitating factors of DR [12]. The second one is related to body composition and lifestyles, which makes it a useful marker for the clinician, which should not only be considered in research studies, but in the clinical management of the diabetic patient [13].

The first analysis in México involving VEGF polymorphisms (rs3025021, rs3025035 and rs2010963) and proliferative diabetic retinopathy found lack of association to PDR. Based on these results, we can infer that different populations have different genetic background and for this reason there is a variation in the rate of associations for the same polymorphisms

[14]. However, even though these polymorphisms are not associated, replication studies are required in other populations in Mexico, since they present a great ethnic and genetic diversity, but other markers in genes related to angiogenesis must also be analyzed. Also BglII/NdeIα2 integrin gene polymorphisms found lack of association to PDR [15]. The study of ECM genes as well as α2 integrin gene in Mexico is limited, more studies are required. We are currently studying variants at the gene ELMO1, which is an important regulator of cytokinesis, ciliogenesis and fibrogenesis, some of these variants are already associated with diabetes mellitus type 2, which can be very important because ELMO1 could be associated with proliferative retinopathy, given that when there is endothelial dysfunction, it is activated by hyperglycemia, also during vasculogenesis or vascular damage [16-17]. Furthermore, this gene is related to diabetic nephropathy [18]. Certainly, the pathological processes, in which ELMO1 is involved, are closely related to diabetic retinopathy, which is why he positions it very well as a candidate gene, a new frontier not explored worldwide.

Certainly at the clinical level there is a direct relationship between the development of microalbuminuria, established nephropathy and DR. With this pathophysiological relationship, it could suggest that some genes participating in albuminuria or predisposition for kidney damage, may also be associated with DR [19]. As well as SNP in the LPR2 and CUBN genes, which have already studied their association with diabetes and diabetic nephropathy. The analysis of its variants, p.I2984V (rs1801239) and p.G3002E (rs1801240) of CUBN and the polymorphisms p.H498Q, p.R4220P, p.I4210L, rs17848169 (p.N2632D) of LRP2 gene in the DR is a new frontier of research.

CONCLUSION

We conclude that considering the molecular heterogeneity of the DM2 and DR, in Mexican population is required more association studies with different candidate genes, there are five genes associated APOE, CYP19A1, ALR2, HLA-DR7, and ADRB3, Two marker lack association in VEGF andα2 integrin genes. A new frontier for research in DR, are de variant of the ELMO1, CUBN and LRP2 genes. Studies will be needed also at the interaction gene-gene, in diabetic eye disease because a single gene or genetic variant cannot explain the risk of development of DR which actually is expected.

REFERENCES

1. Mercader JM, Liao RG, Bell AD, Dymek Z, et al. (2017). A Loss-of-Function Splice Acceptor Variant in IGF2 Is Protective for Type 2 Diabetes.Diabetes. 66(11): 2903-2914.
2. García EG, Leal E, Peralta-Leal V, Durán-González J, et al. (2017). Genetic Epidemiology of Type 2 Diabetes in Mexican Mestizos. Biomed Res Int. 39: 378-393.
3. Priščáková P, Minárik G and Repiská V. (2016). Candidate gene studies of diabetic retinopathy in human.MolBiol Rep. 43(12):1327-1345.
4. Hampton BM, Schwartz SG, Brantley MA and Flynn HW . (2015). Update on genetics and diabetic retinopathy. Clin-Ophthalmol. 23(9): 2175-2193.
5. Agarwal A, Soliman MK, Sepah YJ, Do DV, et al. (2014). Diabetic retinopathy: variations in patient therapeutic outcomes and pharmacogenomics. PharmgenomicsPers Med.12(7): 399-409.
6. Santos A, Salguero ML, Gurrola C, Muñoz F, et al. (2002). The epsilon 4 allele of apolipoprotein E gene is a potential risk factor for the severity of macular edema in type 2 diabetic Mexican patients. Ophthalmic Genet. 23(1): 13-19.
7. Flores-Alvarado LJ, Ramirez-Garcia SA, Ferman PD, Davalos-Rodriguez NO, et al. (2014). Molecular Heterogeneity of Type 2 Diabetes Mellitus in Mexican Population and its Impact of the Public Health on Policies in Primary Care. MedChem. 4: 791-797.
8. Carrillo C, González M and Santos A. (2006). AC polymorphism gene for aldose reductase and susceptibility to diabetic retinopathy in patients with type 2 diabetes mellitus. Report of the meeting of the study group of diabetes mellitus A.C (16 stedn). Guadalajara, Jalisco, México.
9. Quiroz-Mercado H, Suárez-Licona A, Fromow-Guerra J, López-Carasa, et al. (2002). Human lymphocyte antigen DR7 protects against proliferative retinopathy with type II diabetes mellitus.ArchMed Res. 33(2): 123-127.
10. Birinci A, Birinci H, Abidinoglu R, Durupinar B, et al. (2002). Diabetic retinopathy and HLA antigens in type 2 diabetes mellitus.Eur J Ophthalmol. 12(2): 89-93.
11. Muñoz JF, Santos A, Vázquez M, Carrillo C, et al. (2001). Genotipos del receptor b3-adrenérgicoen pacientes con retinopatíadiabética no proliferativa y suinfluenciasobre el perfil de lípidos en el Occidente de México. RevMexPatolClin. 48: 7-16.
12. Mirrakhimov A, Kerimkulova A, Lunegova O, Moldokeeva CB, et. al. (2011). An association between TRP64ARG polymorphism of the B3 adrenoreceptor gene and some metabolic disturbances. Cardiovasc Diabetol.10: 89.
13. Bea JW, Lohman TG, Cussler EC, Going SB, et al. (2010). Lifestyle modifies the relationship between body composition and adrenergic receptor geneticpolymorphisms, ADRB2, ADRB3 and ADRA2B: a secondary analysis of a randomized controlled trial of physical activity among postmenopausal women. Behav Genet. 40(5): 649-659.

14. Gonzalez-Salinas R, Garcia-Gutierrez MC, Garcia-Aguirre G, Morales-Canton V, et al. (2017). Evaluation of VEGF gene polymorphisms and proliferative diabetic retinopathy in Mexicanpopulation. Int J Ophthalmol. 10(1): 135-139.
15. Cepeda AC, Esquivel-Contreras MT, Duran-Iñiguez F, Salinas-Santander MA, et al. (2015). High prevalence of diabetic retinopathy and lack of association with integrin α2 gene polymorphisms in patients with type 2 diabetes from Northeastern Mexico. Exp Ther Med. 10(2): 435-444.
16. Turki A, Mzoughi S, Mtitaoui N, Khairallah M, et al. (2017). Gender differences in the association of ELMO1 genetic variants with type 2 diabetes in Tunisian Arabs. J EndocrinolInvest. 10.1007/s40618-017-0734-7.
17. Ramirez-Garcia SA, Charles-Niño C, Mazariegos-Rubí M, Topete-González LR, et al. (2015). Asociación del gen ELMO1 (SNP rs1345365) con el desarrollo de diabetes mellitus tipo 2 en población mestiza Mexicana. InvestClin. 56(4): 341-355.
18. Mehrabzadeh M, Pasalar P, Karimi M, Abdollahi M, et al. (2016). Association between ELMO1 gene polymorphisms and diabetic nephropathy in an Iranian population. J Diabetes Metab Disord. 15: 43.
19. Flores Alvarado LJ, Ramirez-Garcia SA, Ortega-Pacheco D, Ramírez-Bohórquez E, et al. (2017). Candidate Genes for Diabetic Nephropathy in Mexican Population. Austin J Nephrol Hypertens. 4(2): 1069.