HHS Public Access

Author manuscript

Curr Diab Rep. Author manuscript; available in PMC 2023 June 26.

Published in final edited form as:

Curr Diab Rep. ; 19(9): 67. doi:10.1007/s11892-019-1186-6.

Genetics of Diabetic Retinopathy

Jonathan Han, B.S.[1], **Leonardo Lando, M.D.**[2], **Dorota Skowronska-Krawczyk, Ph.D**[2], **Daniel L. Chao, M.D., Ph.D**[2]

[1]School of Medicine, University of California San Diego

[2]Shiley Eye Institute; Andrew Viterbi Department of Ophthalmology, University of California San Diego, 9415 Campus Point Dr La Jolla CA 92093

Abstract

Purpose of review: The goal of this paper is to review the latest findings in understanding the genetics of diabetic retinopathy. We highlight recent literature using a variety of molecular genetic techniques to identify variants which contribute to genetic susceptibility for diabetic retinopathy.

Recent findings: New GWAS and whole-exome sequencing approaches have been utilized to identify both common and rare variants associated with diabetic retinopathy. While variants have been identified in isolated studies, no variants have been replicated across multiple studies

Summary: The identification of genetic factors associated with diabetic retinopathy remains elusive. This is due to the multifactorial nature of the disease, small sample sizes for GWAS, and difficulty in controlling covariates of the disease. Larger populations as well as utilization of new sequencing and data analysis techniques may lead to new insights into genetic factors associated with diabetic retinopathy in the future.

Keywords

diabetic retinopathy; diabetic macular edema; genetics; GWAS; whole exome

Introduction

Diabetic retinopathy (DR) is among the leading causes of vision impairment and loss worldwide.[1] It is estimated as the seventh most common cause of blindness worldwide in 2015.[2] Numerous factors are known to contribute of DR. Glycemic exposure is the most well-known modifiable risk factor, with hypertension, hyperlipidemia, and BMI also recognized to be involved in the disease process.[3]

In addition, several studies have suggested that there is a significant genetic susceptibility to the development of DR. There is a high rate of concordance of DR among twins with

Correspondence to: Daniel L. Chao MD, PhD, Shiley Eye Institute; Andrew Viterbi Department of Ophthalmology, University of California San Diego, 9500 Gilman Dr MC 0946 La Jolla CA 93094, Phone: (8585) 534-6290, dlchao@ucsd.edu.

Conflict of Interest

Jonathan Han, Leonardo Lando, and Dorota Skowronska-Krawczyk declare that they have no conflict of interest.

Daniel L. Chao reports grants from the National Eye Institute and Brightfocus Foundation; being a consultant for Recens Medical, Zilia Health, and DTx Pharma; and being a co-founder and consultant for Visgenx.

both type 1 and type 2 diabetes mellitus.[4–6] Family members of those with DR are also 2–3 times more likely to develop the disease compared to those without affected family members.[7] The genetic contribution has been calculated to be as high as 27% for DR and 52% for proliferative DR (PDR).[8, 9]

In the last decade, there has been a large body of research focused on identifying genetic determinants of DR. Genetic linkage analyses, candidate-gene studies, genome-wide association studies, and next-generation sequencing have all brought a wealth of information regarding genes and loci that may attribute to the development of retinopathy. This review seeks to summarize the progress in identifying a genetic basis of DR and the challenges involved.

Genetic Linkage Analysis

Genetic linkage analysis relies on identifying parts of the genome which segregate with the phenotype, generally in families.[10] Statistical evidence for linkage is calculated as the logarithm of the odds (LOD) score, with 3.0 being the commonly accepted threshold to demonstrate genome-wide significance in linkage between two loci.

Most linkage analysis studies for DR were conducted during the 1980s and 1990s. The two largest studies were conducted in Pima Indian sibling pairs in Arizona and Mexican-Americans in Starr County, Texas.[11, 12] In the Pima Indian cohort, Imperatore et al. found limited evidence of linkage to DR susceptibility on chromosomes 3 and 9 with LOD scores of 1.36 and 1.46 respectively.[13] A follow up study in this same population identified a locus on chromosome 1 (LOD score of 3.1).[14] A separate study in the Mexican-American cohort in Starr County identified regions on chromosomes 3 and 12(LOD scores 2.41 and 2.47 respectively).[15] However, no additional studies have replicated these findings in other cohorts.

Linkage analysis is best suited for monogenic disease with Mendelian inheritance. In multifactorial disease such as DR, this approach has not been successful given the small effect size of each genetic variant and the common frequency of the genetic variants, which makes it likely that a given allele might be inherited via more than one parental lineage.[16] Additionally, regions identified in linkage analysis usually encompass regions that span multiple genes, while other approaches may be able to identify specific genes which are implicated in the disease. Therefore, linkage analysis studies have been largely replaced with other genetic analyses.

Candidate Gene Analysis

Candidate gene studies seek to demonstrate whether an allele or variant of a gene is present more often in disease than in health. A gene of interest is chosen based on available knowledge on how it may be involved in the disease's mechanism; the frequencies of variants in this gene, in the form of single nucleotide polymorphisms (SNPs), are compared between subjects with and without the disease.[17] A number of reviews have categorically indexed the wide array of genes currently associated with the pathogenesis of DR as discerned through candidate gene analysis.[12, 18, 19] Following these analyses, several genes have undergone extensive study, including vascular endothelial growth factor (VEGF),

aldose reductase, erythropoietin (EPO), and receptor for AGEs (RAGE). We will focus on the first two genes for the purposes of this review.

VEGF is well known for its role in neovascularization and is also implicated in the breakdown of the blood-retinal barrier seen in DR.[20] It has the greatest number of reported SNPs in the context of DR and has been strongly implicated in the pathogenesis of DR in patients with type 1 and type 2 diabetes, with presentations of either non-proliferative or proliferative DR.[19, 20] Indeed, many of the current treatments for DR utilize anti-VEGF therapies, demonstrating the notable role it plays in the pathophysiology of DR. In a review from 2014, Kuo et al. noted 14 distinct polymorphisms that had been the subject of candidate gene studies in the context of DR.[21] Of these SNPs, only one, rs2010963 (−634G>C) was found to have a statistically significant association in the reported metanalyses, with an increased risk for non-proliferative DR but not PDR. Interestingly, the genomic localization of the variant in the regulatory region of VEGF gene is highly suggestive of its potential molecular impact on the VEGF expression, confirmed by Chet et al. in their in vitro studies.[22] rs2010963 is the most studied VEGF polymorphism for DR, and since the above review, four additional meta-analyses evaluating its role have been published. Only one by Qiu et al. suggested an association between the SNP and DR while the other three did not find a significant relationship in any form of the disease.[23–26]

Aldose reductase is part of the polyol pathway which is responsible for the conversion of glucose to sorbitol to fructose (reviewed in article[27]). Accumulation of sorbitol in diabetes has been previously shown to damage and cause the death of retinal cells and pericytes as well as induce thickening of the basement membrane.[28] In a meta-analysis study covering twenty genes linked with DR, Abhary et al. found that variations in the *AKR1B1* gene were most significantly associated with DR in patients with type 1 and type 2 diabetes, although polymorphisms in several other genes of the pathway have also been tied to DR.[29, 19, 30] While a promising direction of study, aldolase reductase inhibitors have not yet demonstrated significant therapeutic effects on the disease.[31, 32]

While candidate gene studies are now less often utilized due to newer techniques with higher throughput, more recent studies have taken advantage of advances in DNA sequencing and availability of genetic databases. In 2011, Sobrin et al. assessed the Candidate gene Association Resource (CARe) which includes over 40,000 participants genotyped for 49,320 SNPs largely in context of cardiovascular disease, for association with DR.[33] Two DR phenotypes, classified as Early Treatment Diabetic Retinopathy Study (ETDRS) grade ≥14 and ≥30, were assessed using the 2,691 participants with type 2 diabetes and available fundus photography. While this was among the largest candidate gene studies for DR, there was no correlation to genes previously associated with DR, type 2 diabetes, or vascular diseases nor was there any statistically significant association among the genes tested.

Genome Wide Association Study (GWAS)

The GWAS assesses for genetic variants, generally SNPs, that may be associated with a disease of interest across the entire genome.[34, 35] In comparison to candidate gene analysis, GWAS is an unbiased approach that covers the whole genome and may identify

SNPs that have small effect sizes particularly in multifactorial disease such as DR. The threshold for genome-wide significance has traditionally been set as $P = 5.0 \times 10^{-8}$ to reflect the number of independent tests among common variants in the human genome, however recent studies have suggested altering this boundary for the population of interest (with people of African descent having twice as much genetic variation as other groups due to their population history) and the allele frequency spectrum of the genetic variants under evaluation (with more variants in the low and rare frequency range).[36, 37]

A review of four previous GWAS for DR [11] concluded that none of the four GWAS for DR published up to that point had resulted in consistent, validated loci.[11] Issues included 1) failure to reach the 5.0×10^{-8} significance threshold due to underpowered sample sizes relative to the modest genetic effects likely to be exhibited in DR 2) inconsistent criteria for the definition of DR and controls and 3) lack of accounting for important environmental causes, particularly the onset of diabetes. Since that review, five additional GWAS studies on DR have been published, the findings of which are summarized in Table 1. No polymorphisms of genome-wide significance identified during the discovery phase remained significant after replication cohorts.

Awata et al. examined a Japanese population using a three-stage analysis with 837 cases (participants with type 2 diabetes and DR of any type) and 1149 controls (participants with diabetes but without DR) which identified a variant in the intron of RP1-90L14.1 showing borderline genome-wide significance ($Pmet = 1.4 \times 10^{-7}$)[38, 39] In a white Australian cohort, 336 cases (with “sight threatening” retinopathy defined as NPDR, PDR, or clinically significant macular edema) and 508 controls (participants with diabetes without DR for at least 5 years) did not identify a SNP that reached genome-wide significance. However, meta-analysis combining the discovery as well as replication cohorts (type 1 and type 2 diabetes cohort from London, type 2 diabetes cohort from India) identified a variant on chromosome 17q25.1 which reached genome-wide significance ($P = 4.15 \times 10^{-8}$).[39]

In a Scottish type 2 diabetes cohort as part of the In Genetics of Diabetes Audit and Research (GoDARTS) project, 560 cases with severe background retinopathy or PDR and 4106 controls with no DR or mild background retinopathy (duration of diabetes not considered) identified variants in the *NOX4* gene and two nearby SNPs that reached genome-wide significance. However, neither reached that threshold in metanalysis of Caucasian replication cohorts. [40]

In 2018, Graham et al. conducted a GWAS by re-analyzing and re-framing the data gathered in the 2015 Burdon et al. study.[41] Two separate case-control relationships were used: the first with 270 cases of DME vs. 435 controls no retinopathy, and the second with 176 cases of PDR vs. 435 cases with no retinopathy. The authors’ rationale for this change was that DME and DR may have separate genetic factors. This study resulted in notably different outcomes than the previous. Although no polymorphism was found to reach genome-wide significance, the chromosomes on which the most notable SNPs were found differed. In this study, the most significant SNPs were found near *MRPL19* and *LOC285626* on chromosomes 2 and 5. For comparison, in 2015 it was an SNP near *PTK7* on chromosome 6.

The fifth and most recent GWAS conducted by Pollack et al. utilized the largest sample sizes to date for a DR study composed of 15 discovery cohorts with a total of 3,246 subjects of European descent and 2,611 of African-American descent with a large replication cohort of 18,545 Europeans, 16,453 Asians, and 2,710 Hispanics. [42] This study utilized a more stringent level of significance, setting genome-wide significance at $P<3.75\times10^{-9}$ for African-American or multiethnic cohorts and $P<6.25\times10^{-9}$ for European-descent cohorts. These levels were set in accordance to findings by Kanai et al. based upon the 1000 Genomes project.[37] In addition, covariates such as duration of diabetes, glycemic control, and race were accounted for. Metanalysis of 1990 cases (all presentations of DR and compared to 2911 controls (no DR) did not discover any significant polymorphisms in either the European or African American descent cohorts. In addition, there were three secondary-case control studies that utilized subsets of DR. These were (1) comparisons of PDR to no PDR, (2) NPDR or worse to no DR, and (3) PDR to no DR. Among these, one SNP in the discovery meta-analysis for the extremities of DR group (PDR to no DR) for subjects of European descent met genome-wide significance: rs142293996 found in the intronic region of the *NVL* gene (P-value of 2.1×10^{-9}). Subsequent replication studies demonstrated that this polymorphism still had the same direction of effect, but no longer attained the genome-wide significance threshold. The top finding among the African American discovery cohorts in the PDR vs no PDR cohort was rs115523882 near the *GOLIM4* gene, but it narrowly missed the threshold for significance ($P=4.1\times10^{-6}$). Replication studies would also fail to achieve significance. The authors also report that they were unable to replicate the findings of the other GWAS previously described in this review. Given the combination of large sample sizes, coverage of multiple ethnicities, clearly defined cases and controls, and adjustment for covariates and replication of the results of previous findings, this GWAS is the most robust to date.

In addition, Pollack et al. utilized the Disease Association Protein-Protein Link Evaluator (DAPPLE) and Meta-Analysis Gene-Set Enrichment of variaNT Associations (MAGENTA) software to determine if the polymorphisms clustered within biological networks of proteins or signaling pathways.[42] One statistically-significant network was found in the African American PDR case group which included genes involved in inflammation and protein products known to be highly expressed in ocular tissues. The authors suggest that network analysis may identify pathways involved which may not be evident when investigating individual SNPs.

There are still numerous challenges in elucidating the genetic basis of DR through GWAS. For instance, there is still difficulty obtaining sufficiently large sample sizes. Other successful GWAS have generally had several thousand cases and controls, if not more.[43] Beside the most recent by Pollack et al., the reviewed studies consisted of primary discovery case samples in the mid-hundreds. Achieving significant sample size is even more difficult with the current trend of more stringent case definitions as many patients with DR will be excluded. The validity of the categorization of patients with different grades of retinopathy continues to be a problem as well. The gold standard in the diagnosis of DR is fundus imaging and evaluation in accordance to the ETDRS criteria. While four of six studies did utilize the ETDRS criteria, only one explicitly detailed the use of fundus imaging and some utilized modified version of the criteria. Inconsistencies also extend to the covariates

used to augment the statistical analyses. Important covariates such as HbA1c are not well defined or standardized in terms of timing of collection across studies. Additionally, studies with varying ethnic populations may make replicating data to be difficult as it causes the population to become more heterogenous. These concerns can emerge during the replication phase of the same study as well: while the discovery phase of the Pollack et al. study discerned between subjects of European or African American descent, replication groups included the above ethnicities as well as those of Hispanic and Asian descent. This brings additional heterogeneity into the statistical analyses.

Whole-Exome Sequencing

While whole-genome sequencing is still cost prohibitive at a large-scale level, whole-exome sequencing (WES) is a cost-effective method which shows promise for identifying genetic mutations beyond GWAS. WES focuses on sequencing all of the protein-coding regions (exons) in the genome, which compromise only one percent of the genome but the vast majority of mutations that cause disease-related traits.[44] As mutations found in WES likely causes changes in protein sequence, one may be able to use WES to identify rare variants with significant effects on disease, which would not be identified with GWAS analysis. It should be noted that due to the tradeoff between increased effect size and lower allele frequency, large sample sizes are still typically required to detect exome-wide significant effects.

To date, two WES studies have been performed in the context of DR. The first, by Shtir et al. in 2016, used phenotypes on the extreme spectrum of diabetes: they compared 43 individuals who did not develop DR after having diabetes for a least 10 years (cases) to 64 individuals that did develop DR within 10 years (controls) in a Saudi Arabian cohort, with the goal of finding variants which are protective for DR.[45] Variants in three genes were found to be protective against the development of DR at the genome-wide significance threshold of 10^{-8} chosen by the authors: *NME3* (P=1.55×10^{-10}), *LOC728688* (P=6.23×10^{-10}), and *FASTK* (P=3.21×10^{-8}). This suggests that this “extreme phenotype” approach may be used to find variants with large effect sizes in DR with a relatively small numbers of patients, although these findings need to be replicated.

The second study by Ung et al. in 2018 utilized these extreme phenotype approach by comparing 43 patients who developed PDR requiring surgical vitrectomy (cases) and 13 patients who did not develop DR after 10 or more years (controls).[46] Subjects were drawn from the African American Proliferative Diabetic Retinopathy Study (AAPDR) as well as from the mixed ethnicity (ME) patient population of the Massachusetts Eye and Ear Infirmary and the Dean McGee Eye Institute of the University of Oklahoma. The study focused on variants found only in the case and not the control which altered protein function (e.g. missense, loss-of function) and had minor allele frequencies of less than 0.1%. Identified genes were filtered to those that occurred at least 3 times in the AAPDR cohort or at least 2 times in the ME cohort. 44 genes were identified, with 25 novel polymorphisms in 19 genes. The authors note that a number of variants were within the VEGF-B and ApoB, genes which have known functions in angiogenesis and low-density lipoprotein (LDL) cholesterol respectively and thought to be associated with the development of PDR.

Importantly, the three genes implicated by Shtir et al. were not found by Ung et al; however these were two different ethnic cohorts which may have contributed to identifying different genes, or they could represent false positive findings.

While the use of WES to investigate DR is still relatively limited, the two studies show the potential for future studies. Both studies reported variants which were novel or found in very low frequencies in databases such as the 1000 Genomes Project or previous candidate gene and GWAS studies, illustrating the strength of WES in identifying rare changes that have potentially significant impacts on phenotype.[45, 46] Additional studies with larger sample sizes using this extreme phenotype approach may yield new insights which may not have been detected with GWAS analysis.

Pharmacogenetics

Pharmacogenomics is the study of genetic variants which may influence the patient's response to treatment. This topic is one of the key components of precision medicine, where one tailors the treatment according to inherent risk factors, genetic biomarkers, and the predicted phenotype following therapy. In ophthalmology, initial studies have focused on pharmacogenetics for age-related macular degeneration, but few have addressed this issue in DR.

Pivotal clinical trials for anti-angiogenic treatment, such as RISE/RIDE, BOLT, and DA VINCI, have demonstrated a wide variation in response to steroids and anti-VEGF drugs in terms of significant visual improvement, suggesting that genetic factors may be responsible for variations in response.[47] The search for genetic variants that affect response to treatment in DR is still in its infancy, with few studies in the current literature. One Egyptian study identified the VEGF C-634G (rs2010963), found in the 5' untranslated region of VEGF to be associated with a positive treatment response with bevacizumab for DME.[48] Interestingly, this SNP was associated with DME in this population compared to controls, ,and has also been associated with DR and DME in Japanese populations.[49, 50] However, a Turkish investigation detected no association of five VEGF-A SNPs, including the rs2010963 mentioned above, in the response to ranibizumab therapy.[51] Thus, while no genetic variants have been convincingly implicated in regulating response to anti-VEGF treatment, this is a promising area of research that with larger patient cohorts, may lead to a more personalized treatment approach to DME and DR.

Future Directions

Despite intensive study over the past decade, the genetic determinants of DR remain elusive. A number of changes can be made to improve research in the future. First, the creation of large-scale consortia in order to create larger datasets can help address the issue of underpowered studies seen across various study designs. For instance, Sobrin et al. generated one of the largest candidate gene studies for DR utilizing only a fraction of the 40,000 individuals available in the CARe database for cardiovascular disease. Second, classification of DR diagnosis and staging through standardized methods such as fundus photography can reduce the heterogeneity seen in cases and controls. While many studies use fundus examination by ETDRS grading system, few utilize the gold standard of fundus

photography in their evaluation. Third, standardization of environmental covariates such as duration of disease and glycemic control can improve precision in a similar manner as the previous case. Indeed, only one study among those reviewed set a threshold for duration of diabetes to be included in the control group. Finally, focusing on specific ethnic populations in study design may be advantageous given the small effect that contributory genes may have. Solid association studies should be then followed by the analysis of molecular contribution of the selected variants to understand their role in pathogenesis of the disease. Diabetic retinopathy is one of the leading causes of vision loss worldwide; continued efforts to unravel the role of genetic determinants of DR may lead to novel insights and treatments for this blinding disease.

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Table 1:

Summary of GWAS and whole exome sequencing findings since 2014

	Study; Platform	Determination of DR	DM	Covariates	Case; Population	Control; Population	Diabetes Duration[a]	Significant findings (Gene; P-value)
GWAS	Awata T et al. *PLoS One* 2014[38] Affymetrix GeneChip 6.0	Fundus exam and international clinical diabetic retinopathy or macular edema disease severity scale	2	Sex, diabetes duration, HbA1c	DR; Japanese: 837	DM2 w/o DR; Japanese: 1,149	Case: 12.4±7.7 Control: 7.2±6.5	*RP1–90L14.1*; 1.4×10^{-7}
	Burdon KP et al. *Diabetologia* 2015[39]; Illumina Human OmniExpress	Fundus exam and modified ETDRS criteria	2	Age, sex, diabetes duration, HbA1c, hypertension, nephropathy	Sight-threatening DR[b]; White Australian: 336	DM2 w/o DR or minimal DR[c]; White Australian: 508	Case: 19.0±8.8 Control: 13.2±7.6	Near *PTK7*; 2.66×10^{-7}
	Graham PS et al. *BMC Med Genet* 2018[41]; Illumina Human OmniExpress	Fundus exam and EDTRS criteria	2	Age, sex, diabetes duration, HbA1c hypertension, nephropathy	**1** DME; White Australian: 270 **2** PDR; White Australian: 176	**1** No DR[c] **2** No DR[c]	Case: **1** 19.2±8.8 **2** 19.1±8.9 Control: 12.6±7.1	**1** *MRPL19*; 4.10×10^{-6} **2** Near *LOC285626*; 6.94×10^{-6}
	Meng W et al. *Acta Ophthalmol* 2018.[40] Affymetrix SNP 6.0, Illumina Human OmniExpress	Fundus exam and Scottish Diabetic Retinopathy Scheme or EDTRS or history of laser treatment	2	Age, sex, diabetes duration, HbA1c	Severe/proliferative DR[d]; Scottish: 560	DM2 with normal or mild background retinopathy; Scottish: 4106	Case: 23.83±7.99 Control: 14.1±4.8	*NOX4*; 4.05×10^{-9}
	Pollack S et al. *Diabetes* 2019[42]; Affymetrix SNP 6.0 Illumina 2.5M, 370, 670, Omni Quad, OmniExpress	Fundus exam and ETDRS score	2	Diabetes duration, glycemic control measure, race	Primary:[f] Any DR (≥14) / AA: 911, EUR: 1,079 Secondary **1** PDR (≥60); AA: 1,097, EUR: 398 **2** NPDR or worse (≥14); AA: 768, EUR: 644 **3** PDR (≥60); AA: 1,097, EUR: 398	Primary: DM2 w/o DR (<14); AA: 941, EUR: 1,970 Secondary: **1** No PDR (<60); AA: 1,097, EUR 398 **2** No DR (<14); AA: 941, EUR: 1,970 **3** No DR (<14);	See study Supplementary Table 1	Primary: none Secondary: **1** Near *GOLIM4* for AA; 9.42×10^{-9} Near *NOS2/LYRM9* for EUR; 7.26×10^{-9} **2** None **3** Near *NVL* for EUR; 2.10×10^{-9}

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	Study; Platform	Determination of DR	DM	Covariates	Case; Population	Control; Population	Diabetes Duration[a]	Significant findings (Gene; P-value)
						AA: 941, EUR: 1,970		
WES	Shtir C. et al. *Hum Genet.* 2016[45] / Ion AmpliSeq Exome	Fundus examination; EDTRS criteria	1, 2	Not specified	DM w/o DR after 10 years; Saudi: 43	DR; Saudi: 64	Not specified	*NME3*; 1.55×10^{-10} *LOC728699/ PDE3A*; 6.23×10^{-10} FASTK; 3.21×10^{-8}
	Ung et al. *Vision Res.* 2017[46]/ Aligent SureSelect Human All Exon	Fundus photography with modified ETDRS criteria	1, 2	Not specified	PDR; **1** AA: 31 **2** ME: 26	No DR 10+ years after DM diagnosis; AA: 13	Case: **1** AA: 6.4 **2** ME: 10.4 Control: 23.9	Not applicable

a: during discovery phase, in years

b: severe NPDR, PDR, clinically significant macular edema

c: all participants including controls received treatment for DM2 for at least 5 years

d: R3 and R4 on Scottish Retinopathy Scheme

e: R0 and R1 on Scottish Retinopathy Scheme

f: values given are based on EDTRS scale

AA: African American

EUR: of European descent

ME: mixed ethnicity