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Natural History of Drusenoid Pigment Epithelial Detachment Associated with Age-Related Macular Degeneration: Age-Related Eye Disease Study 2 Report No. 17

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Abstract

Purpose: To investigate the natural history and genetic associations of drusenoid pigment epithelial detachment (DPED) associated with age-related macular degeneration (AMD).

Design: Retrospective analysis of a prospective cohort study.

Participants: Of the 4203 Age-Related Eye Disease Study 2 (AREDS2) participants, 391 eyes (325 participants) were identified as having DPED without late AMD at the time of DPED detection. Genetic analyses included 120 white AREDS2 participants and 145 AREDS participants with DPED.

Methods: Baseline and annual stereoscopic fundus photographs were graded according to a standardized protocol to detect DPED, a well-defined yellow elevated mound of confluent drusen, measuring 433 μ m in diameter, and to evaluate progression rates to late AMD: geographic

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Conflicts of Interest:

Jeannette Yu, Elvira Agrón, Amitha Domalpally, Traci Clemons, Freekje van Asten, Tiarnan Keenan, Catherine Cukras, Emily Chew: None.

Online Supplemental Materials:

This article contains additional online-only material. The following should appear online-only: Supplementary tables 1 to 8 and figures 1 to 8.

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atrophy (GA) and neovascular (NV) AMD. Five single nucleotide polymorphisms (*CFH* [rs10611670], *C3* [rs2230199], *CFI* [rs10033900], *C2/CFB* [rs114254831], *ARMS2* [rs10490924]) and genetic risk score (GRS) group were investigated for association with DPED development. Kaplan-Meier analyses and multivariable proportional hazard regressions were performed.

Main Outcome Measures: Progression rates to late AMD and decrease of three lines in visual acuity (VA) from time of DPED detection; association of rate of DPED development with genotype.

Results: Mean (SD) follow-up time from DPED detection was 4.7 (0.9) years. Presence of DPED was associated with increased risk of progression to late AMD (hazard ratio [HR]=2.36, 95% confidence interval [CI]=1.98–2.82, $p<0.001$); 67% of eyes progressed to late AMD five years after DPED detection. DPED was associated with increased risk of three lines of VA loss (HR=3.08, CI=2.41–3.93, $p<0.001$) with 46% of eyes experiencing vision loss at five years (with or without progression to late AMD). *ARMS2* risk alleles (1 vs. 0: HR=2.72, CI=1.58–4.70, $p<0.001$; 2 vs. 0: HR=3.16, CI=1.60–6.21, $p<0.001$) and increasing GRS group (4 vs. 1) (HR=12.17, CI=3.66–40.45, $p<0.001$) were significantly associated with DPED development in AREDS. There were no significant genetic results in the AREDS2 analyses.

Conclusions: This study replicates the results of previous natural history studies of eyes with DPED including the high rates of progression to late AMD and vision loss (regardless of progression to late AMD). The genetic associations are consistent with genes associated with AMD progression.

Précis:

Drusenoid pigment epithelial detachment (DPED) is associated with high rates of progression to late age-related macular degeneration and visual acuity loss. No genetic risk allele was found to be associated with the development of DPED.

Introduction

Macular drusen and retinal pigmentary changes are the hallmark lesions of age-related macular degeneration (AMD),¹ the most common cause of vision loss among the elderly in industrialized countries.^{2,3} Drusenoid pigment epithelial detachment (DPED),⁴ first described by Casswell⁵ in 1985 as part of the clinical spectrum of AMD, is distinguished from other subtypes of pigment epithelial detachment (PED) such as serous or vascularized PEDs; these have different anatomical features and are often associated with different visual prognosis than DPED.⁶

A study of the natural history of geographic atrophy (GA) in participants enrolled in the Age-Related Eye Disease Study (AREDS) demonstrated that DPEDs are formed by confluence of large drusen but usually undergo subsequent drusen regression, often leading to processes of hyperpigmentation, hypopigmentation, and finally GA, with evidence of refractile drusen in some cases.⁷ Indeed, DPED was identified as an independent risk factor for the development of late AMD, with progression to GA occurring more often than progression to neovascular AMD (NV-AMD).⁴ More recent studies using spectral domain

optical coherence tomography (SD-OCT) to evaluate DPED have revealed that overlying hyperreflective foci, as well as DPED height, volume, and diameter, are risk factors associated with DPED regression and progression to GA.^{8, 9}

The discovery of biomarkers associated with higher risk of progression to late AMD may help in the refinement of existing risk models for predicting progression of disease and aid in stratifying recruitment into future clinical trials, as well as provide additional insight into AMD pathogenesis. In the context of much progress in the elucidation of AMD genetic associations,^{10–12} the International AMD Genomics Consortium recently demonstrated the use of the AMD genetic risk score (GRS) as a potential factor for predicting progression to late AMD.¹³ Furthermore, recent analyses of genotype-phenotype correlations in AMD, using AREDS and AREDS2 data, demonstrated that drusen area and presence of refractile drusen are strongly linked to genetic risk at the complement factor H (*CFH*) locus.¹⁴ There is great interest in whether the DPED phenotype may also have a specific correlation with *CFH* risk variants or simply represents a clinical feature of increased disease severity in general, irrespective of AMD genotype.

The AREDS2 study population provides another opportunity to evaluate the natural history of DPED and additionally to assess whether genetic variants known to be correlated with late AMD are also associated with the development of DPED. Clinical data from AREDS participants with DPED and genetic information were added to further study the genetic factors associated with DPED development.

Methods

Study Population

The study design and methods of AREDS2 have been previously described.¹⁵ Briefly, AREDS2 (2006 – 2012) was a multicenter, randomized, controlled, clinical trial designed to study the safety and efficacy of supplementation with lutein and zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids on progression to late AMD. Eighty-two retinal specialty clinics in the United States enrolled 4203 participants aged 50 to 85 years. Inclusion criteria for these participants were the presence of bilateral large drusen or unilateral late AMD (defined as GA (GA) or NV-AMD) with large drusen in the fellow eye. The institutional review board at each institution approved the protocol and written informed consent was obtained from all study participants. The research was conducted under the Declaration of Helsinki.

Standardized baseline and annual study visits were performed with comprehensive ocular exams that included best-corrected visual acuity (VA) measurements. Stereoscopic fundus photographs were taken at each visit and graded by trained, masked graders at the AREDS2 Reading Center at the University of Wisconsin. The standardized imaging and evaluation protocol has been previously described.¹⁶ Detailed questionnaires were also administered at baseline to collect information on demographics, medical and social history, medication use, and nutrition.

AREDS2 eyes with DPED (as defined below) detected at any time during AREDS2 and without evidence of late AMD at the time of DPED detection were included in the present natural history study. Eyes that had DPED detected at the baseline visit were considered the “prevalent” group, and eyes that developed DPED during the study follow-up were categorized as the “incident” group. The comparison group comprised AREDS2 eyes that did not have DPED at any time during AREDS2 follow-up and did not have late AMD at the baseline study visit.

For the genetic analyses, white AREDS2 participants with available genetic data were included if they had DPED in either eye at any time in the study and did not have late AMD in either eye at baseline or at the time of DPED detection. The comparison group consisted of white AREDS2 participants with genetic data, no late AMD at the baseline study visit, and no DPED detected at any time during AREDS2 follow-up. The genetic analyses were replicated in a cohort of similar AREDS participants with DPED to assess for heterogeneity. The design of AREDS has been previously described.^{17, 18} Briefly, this randomized clinical trial (1992 to 2001) enrolled 4757 participants in 11 clinical centers to evaluate the efficacy and safety of antioxidant vitamins and zinc supplements on late AMD, with annual standardized, graded stereoscopic fundus photographs. We included white AREDS participants with genetic data if they met these criteria: AREDS AMD category 3 (at least one large druse, extensive intermediate-sized drusen, or non-central GA) or category 4 (late AMD in one eye)¹⁹ at baseline, at least five years of follow-up, DPED detected in either eye at any time, and no late AMD in the same eye at the time of DPED detection. The comparison group consisted of AREDS participants with the same criteria but no DPED detected at any time during study follow-up. This allowed the AREDS and AREDS2 study populations to be more comparable for the genetic analysis.

Genotype Procedures

Genotyping was performed in 1826 AREDS2 participants and in 2889 AREDS participants by custom Illumina HumanCoreExome array, as described previously.¹³ Because of past work highlighting the importance of the complement system in drusen formation and ARMS2 in progression to late AMD, we chose to evaluate the lead genetic variant at four genes encoding complement pathway factors and regulators, as well as at *ARMS2*: rs1061170 at *CFH*, rs2230199 at *C3*, rs10033900 at *CFI*, rs114254831 at *C2/CFB*, and rs10490924 at *ARMS2*.

The AMD GRS was calculated for each participant, according to methods described in Fritsche et al., 2016.¹³ Briefly, the GRS is a weighted risk score based on 52 independent variants at 34 loci identified in a large genome-wide association study as having significant associations with late AMD risk. The GRS for each participant was centered using the mean GRS of a control population defined in Fritsche et al.,¹³ such that persons with GRS equal to the control mean had a centered GRS of 0. The GRS group for each participant was then determined as such: persons with centered GRS = 0 were in GRS group 0 (range -3.66 – 0). Persons with centered GRS > 0 were divided into quartiles and placed in the corresponding GRS quartile group. For instance, a person in GRS group 3 had a GRS in the third quartile of all GRS scores in the cohort above the control mean. Quartile ranges were calculated

using the combined AREDS and AREDS2 genetic cohorts. The centered GRS range of each quartile was: group 1 (0 – 0.79), group 2 (0.79 – 1.51), group 3 (1.51 – 2.30), and group 4 (2.30 – 6.38). We included the GRS in order to assess not only the associations of the five SNPs individually, but also the significance of a person's overall genetic predisposition to late AMD.

Natural History Outcomes

We evaluated study eyes for two primary outcomes: (1) progression to late AMD, i.e. GA and/or NV-AMD, and (2) decline in VA of 3 lines (15 ETDRS letters) from the time of DPED detection.

DPED was viewed on stereoscopic color fundus photographs as an elevated mound with one or more large soft confluent indistinct drusen with a diameter of 433 microns (AREDS circle I-2).¹⁶ Deposits of pigment may be visible on the surface of the DPED. The presence of DPED along with area and proximity to center of the macula were documented.

Progression to late AMD was defined on stereoscopic fundus photographs as the presence of any GA or NV-AMD. Of note, any GA, regardless of foveal involvement, along with NV-AMD have been reclassified as late AMD.¹ GA was defined as a lesion with diameter 433 μ m (AREDS circle I-2), with at least two of the following features: loss of RPE pigment, circular shape, and sharp margins. NV-AMD was defined as a positive history of treatment or the presence of at least two of the five following photographic features: serous RPE detachment, subretinal or intraretinal hemorrhage, intraretinal lipid exudates, subretinal fibrosis, and fibrovascular RPE detachment.¹⁶

Statistical Analysis

Age- and sex-adjusted Cox proportional hazard models and Kaplan-Meier analyses were performed for assessment of progression to late AMD and to vision loss, accommodating for the variable follow-up time in the AREDS2 cohort, particularly for eyes with incident DPED. Differences in genotype distributions between participants with and without DPED were analyzed by the chi-square test. The effect of the number of risk alleles and the GRS group on the development of DPED was assessed using Cox proportional hazards models adjusted for age and sex. Bonferroni corrections were applied to an alpha value of 0.05. All analyses were performed using the SAS System (Version 9.4, SAS Inc, Cary, NC).

Results

Natural History

Of the 4203 participants enrolled in AREDS2, 391 eyes of 325 participants had DPED without late AMD at the time of DPED detection. Of these, 121 eyes (30.9%) had DPED at study baseline (prevalent cohort), whereas 270 eyes (69.1%) developed DPED during the study (incident cohort). Median follow-up time in AREDS2 was five years.

Baseline Characteristics—Demographic characteristics of the AREDS2 participants included in the analyses are displayed in Table 1. Of the 325 participants with DPED, 138 (42.5%) were male, and mean age at DPED detection was 71.6 ± 7.0 years (range 50.3 –

86.1 years) (Table 1). On average, participants had 4.7 ± 0.9 years of follow-up (range 0 – 5.9 years). Compared with AREDS2 participants without DPED, participants with DPED were significantly younger at baseline ($p < 0.001$) and had significantly longer follow-up time ($p < 0.001$).

The fundus features and VA of DPED study eyes (at first detection of DPED) and for the comparison group (at study baseline) are displayed in Table 2. Data are also presented separately for DPED study eyes that progressed and did not progress to late AMD during the study. Overall, eyes with DPED had significantly larger drusen area, higher frequency of hyperpigmentary changes, lower frequency of hypopigmentary changes, and worse VA than eyes without DPED, although the majority of eyes with DPED had VA in the 20/20–20/40 range. Notably, eyes with DPED that progressed to late AMD during the study had significantly greater DPED area (at time of DPED detection) than eyes with DPED that did not progress to late AMD ($p < 0.001$). In all but 18 (4.6%) eyes with DPED, the DPEDs were located within 500 μ m of the fovea.

Progression to Late AMD—Kaplan-Meier curves are displayed in Figure 1, demonstrating rates of progression to late AMD (by subtype) in all eyes with DPED starting at the time of DPED detection. By five years, the estimated rate of progression to late AMD was 67%, with estimated rates of progression to GA, CGA, and NV-AMD being 54%, 50%, and 34%, respectively. These are estimated rates and for the actual data, the proportions that did not develop late AMD, or progressed to CGA, or CNV were approximately 44.2%, 27.4% and 28.4%, respectively at 5 years (supplementary table 1 [available at <http://www.aaojournal.org>]).

Age- and sex-adjusted Cox proportional hazard regressions were performed in order to assess the effect of DPED presence on the risk of progression to late AMD (and to GA, CGA, and NV-AMD, analyzed separately); the results are shown in Table 3. The presence of DPED imparted significantly increased risk for progression to all late AMD outcomes, with reference to the comparison group. Notably, the hazard ratio for progression to CGA was highest.

Time-to-event calculations were performed to determine the mean length of time between development of DPED and subsequent development of late AMD. These calculations were performed on the incident DPED group only because time of DPED appearance was unknown in the prevalent DPED group (where DPED was already present at the study baseline). On average, study eyes developed CGA at 2.2 ± 1.1 years after DPED incidence, NV-AMD at 2.0 ± 1.2 years, and any form of late AMD at 2.1 ± 1.1 years. An outcome of either GA or NV-AMD seemed to occur approximately two years, on average, after the development of DPED.

Fundus Features in Eyes Not Progressing to Late AMD—Eyes with DPED that did not progress to late AMD were assessed for fundus features such as hyperpigmentation, hypopigmentation, and refractile drusen at each follow-up year (Figure 2). Details of the number of eyes that were analyzed are found in the supplementary table 2 for Figure 2 (available at <http://www.aaojournal.org>). At the time of DPED detection, most eyes had

hyperpigmentation while few eyes had hypopigmentation or refractile drusen. Over time, analyses with age and sex-adjusted repeated measures logistic regression demonstrated the rates of hyperpigmentation (odds ratio (OR): 0.97 95% confidence limits (CL): 0.81 to 1.15, $p=0.73$) to remain stable while those of hypopigmentation (OR: 1.64, 95% CL: 1.44 to 1.87, $p<0.0001$) and refractile drusen (OR: 1.55, 95% CL: 1.36 to 1.76, $p<0.0001$) steadily increased.

Visual Acuity Outcomes—VA analyses were conducted excluding the 18 eyes with DPED located more than 500 μ m away from the fovea (“non-central DPED”). Figure 3 displays the VA over time in eyes with central DPED including the overall mean VA of all eyes and then by subgroup according to presence or absence of progression to late AMD. Kaplan-Meier curves for eyes with central DPED losing ≥ 15 letters in VA are displayed in Figure 4. By five years, the estimated proportions of eyes that lost ≥ 15 letters from the time of DPED detection were 46% for all eyes, and 62%, 57%, and 26% for eyes that progressed to CGA, to NV-AMD, and no progression to late AMD, respectively. For those eyes that did not progress to late AMD, the presence of hypopigmentary changes was associated with a two fold increased risk of losing ≥ 15 letters from the time of DPED detection (odds ratio of 2.22 and 95% confidence limit: 1.08, 4.56, $p=0.03$). The visual acuities of these eyes that did not progress to late AMD are also depicted in supplementary table 3 and supplementary figure 3 (available at <http://www.aaojournal.org>).

In all eyes with central DPED, age- and sex-adjusted Cox proportional hazard regression showed that DPED was associated with over three-fold increased risk (HR = 3.08; CI = 2.41 – 3.93; $p < 0.001$) of loss of ≥ 15 letters of VA from time of DPED detection compared to the comparison group (eyes in AREDS2 that did not ever have DPED).

The VA course of the 18 eyes with non-central DPED are described separately here: mean $\pm$ SD VA was 78.5 ± 8.7 letters (20/25) at DPED detection and 72.1 ± 8.3 letters (20/40) at four years after DPED detection. At DPED detection, 13/18 eyes (72.2%) had VA in the range of 20/20 – 20/40, with 2/18 (11%) eyes having $> 20/20$ VA and 3/18 (16.7%) of eyes with VA worse than 20/40. At year four, 7/10 (70%) of eyes had VA in 20/20 – 20/40 while 3/10 (30%) had VA worse than 20/40. Detailed assessments of the visual acuities by subgroups are available in supplementary Table 5 (available at <http://www.aaojournal.org>).

DPED Characteristics—Prevalence of DPED decreased substantially in the first year after DPED detection: at one year, 38.5% had remaining DPED. After the first year, DPED prevalence continued to decrease but less rapidly: at two and three years after DPED detection, 29.5% and 25.9% of eyes had DPED, respectively. Detailed results are displayed in supplementary Table 6. Additionally, in eyes with remaining DPED, average DPED area increased over time (supplementary Figure 4) and DPED generally became closer to the fovea (supplementary Figure 5).

These natural history findings were additionally evaluated separately for incident and prevalent cohorts, results of which can be found in the supplementary Tables 1 to 8 and Figures 1 to 8 (available at <http://www.aaojournal.org>).

Genetics

Genetic Analyses—Of the 4203 participants enrolled in AREDS2, 1826 participants consented to genotype analysis and 1776 were additionally white. Of these, 120 participants had DPED during the study without late AMD in the same eye at the time of DPED detection; this comprised 41 participants with DPED present at baseline and 79 participants who developed DPED during the study follow-up. The comparison group comprised 887 participants.

Of the 4757 participants enrolled in AREDS (mean follow-up time 6.3 years), 2889 participants had genotype data. Of these, 1435 were white with an AREDS AMD category of 3 or 4 at baseline. In this group, there were 145 participants with DPED in at least one eye, without late AMD at time of DPED detection, who had at least five years of follow-up; this comprised 67 participants with DPED at baseline and 78 who developed DPED during the study. The comparison group consisted of 801 AREDS participants.

Mean $\pm$ SD age of the AREDS and AREDS2 cohorts was 69.2 ± 5.0 and 71.3 ± 6.8 years, respectively ($p = 0.004$). Sex distribution was similar between the two groups (39.3% male in AREDS cohort, 45.0% male in AREDS2 cohort, $p = 0.35$). Additionally, mean $\pm$ SD centered GRS was 1.70 ± 1.20 for the AREDS study group and 1.62 ± 1.18 for the AREDS2 study group ($p = 0.62$); GRS group distribution was also similar between the two cohorts ($p = 0.26$).

Table 4 compares the genotype distribution of the study and comparison participants in the AREDS2 and AREDS cohorts. In the AREDS cohort, the *ARMS2* risk allele was significantly more prevalent and the centered GRS was significantly higher in study participants compared to the comparison group. No significant differences in genotype distribution were observed between study and comparison participants in the AREDS2 cohort.

Proportional hazards regressions for the development of DPED based on SNP and GRS group were performed, using only incident DPED participants ($n = 79$ for AREDS2; $n = 78$ for AREDS) and adjusting for age and sex. The results are displayed in Table 5. In the AREDS cohort, participants with 1 or 2 versus 0 risk alleles at *ARMS2* had significantly higher risk of DPED ($p < 0.001$ for both comparisons), with a higher hazard ratio for 2 risk alleles compared to 1. Additionally, participants in GRS groups 2, 3 or 4 had a significantly increased risk of developing DPED, compared with those in GRS group 0 ($p < 0.001$ for each comparison); in general, hazard ratios tended to be numerically higher with increasing GRS. No results in the AREDS2 cohort, and no other results in AREDS analyses were significant after Bonferroni correction.

Discussion

In this analysis, we replicated the natural history study of DPED that was originally performed in the AREDS⁴ using longitudinal analysis of eyes with DPED and intermediate AMD in the AREDS2. Our findings demonstrate that: (1) DPED is associated with a significantly increased risk of progression to late AMD, particularly to CGA; (2) while VA

at the time of DPED detection was relatively high, the presence of DPED imparted a significantly increased risk of losing 15 letters from the time of DPED detection, regardless of progression to late AMD; (3) eyes with DPED that did not progress to late AMD experienced increased rates of hypopigmentation and refractile drusen, with rates of hyperpigmentation remaining stable.

Pigment epithelial detachments are defined as the anatomic separation of the RPE from the underlying Bruch's membrane.²⁰ As a subtype of PED, flattening of DPED was noted by Casswell et al.⁵ in 1985 to be associated with atrophy of the RPE and lead to subsequent vision loss. While previous studies have evaluated the natural history of DPED,^{4, 21, 22} this study in the context of the AREDS2 population investigates DPED in a cohort with more severe AMD.

A study of precursor lesions at the site of future GA in AREDS participants demonstrated that lesions preceding GA included large drusen (including DPED), retinal pigmentary changes, and refractile drusen.⁷ The evolutionary sequence from DPED to GA begins with the development of large, soft drusen and DPED with hyperpigmentary changes, followed by the collapse of large drusen and DPED, the development of hypopigmentary changes and refractile drusen, and finally, progression to GA (Figures 5 and 6). Our analyses strongly support this sequence, with the finding that DPED collapse is often accompanied by an increase in hypopigmentation and refractile drusen before the development of late AMD, usually in the form of GA. Hypopigmentary changes are thought to represent degeneration and disorganization of the RPE, while refractile drusen may be related to end-products of regressed drusen and apoptotic RPE cells.²³ That these findings are generally preceded by DPED suggests that DPED represents dysfunctional RPE, thus instigating a sequence of events that eventually lead to GA. Specifically, it has been proposed that the long-term separation of the RPE from the underlying Bruch's membrane/choriocapillaris complex causes a decline in RPE function and the death of photoreceptors over time.²⁰ Additionally, it is thought that as drusen enlarge, the material within them disintegrates and becomes finer in nature, predisposing to more rapid drusen collapse and the development of GA.²⁴ Perhaps even before the overt development of GA, DPED may predispose to dysfunctional photoreceptors and subsequent outer retinal atrophy. This hypothesis may explain the substantial rates of losing 15 letters of VA (26%) even in eyes with DPED that did not progress to late AMD during the study. This is also reflected by the doubling of the risk of visual loss in those eyes that developed hypopigmentation.

DPED has been established as an independent risk factor for CGA, although progression to NV-AMD (Figure 7) and persistence of the DPED itself are also common.^{4, 21} In particular, Cukras and colleagues,⁴ in a study of DPED in eyes in AREDS participants, found increasing risk of progression to CGA over time that eventually exceeds the rate of development of NV-AMD. We confirm this finding in AREDS2 eyes, suggested by a longer time from DPED detection to appearance of CGA (mean 2.6 years) than appearance of NV-AMD (mean 2.0 years), with 50% and 34% estimated to progress to CGA and NV-AMD, respectively, at five years. Additionally, we report that while DPED imparts increased risk of progression to all forms of late AMD, the hazard ratio is consistently highest for progression to CGA. Consistent with this, our finding that DPED imparts significantly increased risk of

vision loss confirms similar findings in previous studies.^{4, 5, 21} These findings support the hypothesis that DPED is one of the first steps in a multistep evolution from drusen to late AMD, in which CGA represents the end stage.

Genetics of DPED:

Our main genetic findings demonstrated that in the AREDS cohort, *ARMS2* risk variants and increasing GRS group were significantly associated with increased risk of DPED development. In the AREDS2 cohort, however, none of the five SNPs, considered in isolation, nor the GRS group, were significantly associated with development of DPED compared to other cases with intermediate AMD. Although we were not able to identify any consistent genetic associations with DPED, thus precluding us from reaching any solid conclusions, we speculate why these seemingly large differences in genetic effects between AREDS and AREDS2 exist.

A recent study analyzing 34 genetic risk variants for AMD along with a subsequently derived GRS showed that the effect of the GRS on the progression to late AMD was much higher in AREDS than in AREDS2.²⁵ In this study, AREDS participants tended to have younger age, lower drusen load, and less severe disease than AREDS2 participants, who were selected for having bilateral large drusen or unilateral late AMD. After subsetting the AREDS data to only include those with intermediate AMD, the effect of the GRS was substantially attenuated, although it remained somewhat stronger in AREDS compared to AREDS2. This study also showed that the strongest predictor of progression was baseline AMD severity and addition of the GRS only marginally improved prediction of progression. To be comparable to AREDS2, we included only those AREDS participants with AMD category 3 or 4. Although now on average age, AMD category and GRS score were similar between the two cohorts, there nevertheless remained a wider range of AMD severity in the AREDS cohort than in AREDS2 as AREDS2 participants had bilateral large drusen per definition. Thus, due to selection for eyes with DPED, the AREDS DPED population likely had greater disease severity than the no-DPED group. The *ARMS2* locus has been consistently associated with progression to late AMD^{26–28}, suggesting that the significance of the *ARMS2* risk alleles in DPED development in AREDS may reflect the role of this locus in driving progression to late AMD. Hoffman et al.²⁹ reported that a GRS composed of 19 common genetic risk variants was associated with baseline drusen load, but not with subsequent drusen progression, suggesting that while a deleterious genetic profile may drive the development of drusen, subsequent drusen advancement and progression to late AMD may be driven less by genetics. Perhaps the increased disease severity in AREDS2 overpowers the effect of genetics in development of this lesion. All in all, while it is possible that the discrepant results observed in the AREDS and AREDS2 genetic analyses may be partially explained by cohort differences, we cannot draw definitive conclusions regarding the genetics of DPED. Additional research and replication are necessary to better understand this topic.

Strengths

In this analysis, the AREDS2 dataset provided baseline and annual best-corrected VA data and standardized stereoscopic color fundus photographs graded centrally in a large cohort of

patients with DPED followed longitudinally for a long period of time. The rates of loss to follow-up in AREDS2 were less than 3%. Statistical analyses took into account the variable follow-up occurring after the initial detection of DPED. Furthermore, these findings corroborate those from the AREDS cohort⁴ that had similar types of data collection.

Study Limitations:

The main limitation of this study lies in its retrospective nature, as well as our reliance on one imaging modality (color fundus photographs). The use of additional imaging modalities such as SD-OCT, fluorescein angiography, or fundus autofluorescence imaging would provide more detailed and accurate information regarding DPED and its associated fundus features. A subset of AREDS2 participants had both fundus autofluorescence and optical tomography performed. These data will provide opportunities for future analyses.

Another limitation is the shorter follow-up period in AREDS2 compared with follow-up period of the AREDS cohort. The genetic analyses involve relatively small sample sizes with limited power to detect genetic associations with the development of DPED. Finally, our investigation was restricted to only five SNPs and excluded some risk alleles, perhaps contained within the GRS. Future studies may examine additional SNPs or a different genetic profile altogether.

Conclusion:

In conclusion, we have validated the natural history of DPED in a cohort with intermediate AMD, demonstrating high rates of progression to late AMD and vision loss. Additionally, we have studied the genetic associations of DPED. Increased genetic risk score and the *ARMS2* locus may be associated with the development of DPED, a late form of AMD. Further investigation is required to elucidate the genetic association of this lesion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ferris FL, III, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology* 2013;120(4):844–51. [PubMed: 23332590]

2. Bunce C, Wormald R. Causes of blind certifications in England and Wales: April 1999–March 2000. *Eye* 2008;22(7):905. [PubMed: 17332762]
3. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122(4):477–85. [PubMed: 15078664]
4. Cukras C, Agrón E, Klein ML, et al. Natural history of drusenoid pigment epithelial detachment in age-related macular degeneration: Age-Related Eye Disease Study Report No. 28. *Ophthalmology* 2010;117(3):489–99. [PubMed: 20079925]
5. Casswell AG, Kohen D, Bird AC. Retinal pigment epithelial detachments in the elderly: classification and outcome. *British Journal of Ophthalmology* 1985;69(6):397–403. [PubMed: 2408659]
6. Hartnett ME, Weiter JJ, Garsd A, Jalkh AE. Classification of retinal pigment epithelial detachments associated with drusen. *Graefes Arch Clin Exp Ophthalmol* 1992;230(1):11–9. [PubMed: 1547961]
7. Klein ML, Ferris FL, Armstrong J, et al. Retinal precursors and the development of geographic atrophy in age-related macular degeneration. *Ophthalmology* 2008;115(6):1026–31. [PubMed: 17981333]
8. Ouyang Y, Heussen FM, Hariri A, et al. Optical coherence tomography based observation of natural history of drusenoid lesion in eyes with dry age-related macular degeneration. *Ophthalmology* 2013;120(12):2656–65. [PubMed: 23830761]
9. Balaratnasingam C, Yannuzzi LA, Curcio CA, et al. Associations between retinal pigment epithelium and drusen volume changes during the lifecycle of large drusenoid pigment epithelial detachments. *Investigative Ophthalmology & Visual Science* 2016;57(13):5479–89. [PubMed: 27760262]
10. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science* 2005;308(5720):385–9. [PubMed: 15761122]
11. Maller J, George S, Purcell S, et al. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nature Genetics* 2006;38(9):1055–9. [PubMed: 16936732]
12. Micklisch S, Lin Y, Jacob S, et al. Age-related macular degeneration associated polymorphism rs10490924 in ARMS2 results in deficiency of a complement activator. *Journal of Neuroinflammation* 2017;14:4. [PubMed: 28086806]
13. Fritsche LG, Igl W, Bailey JN. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. 2016;48(2):134–43.
14. van Asten F, Simmons M, Singhal A, et al. A deep phenotype association study reveals specific phenotype associations with genetic variants in age-related macular degeneration: Age-Related Eye Disease Study 2 (AREDS2) report no. 14. *Ophthalmology* 2018;125(4):559–68. [PubMed: 29096998]
15. Chew EY, Clemons T, SanGiovanni JP, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology* 2012;119(11):2282–9. [PubMed: 22840421]
16. Danis RP, Domalpally A, Chew EY, et al. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 report number 2). *Investigative Ophthalmology & Visual Science* 2013;54(7):4548–54. [PubMed: 23620429]
17. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clin Trials* 1999;20(6):573–600. [PubMed: 10588299]
18. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. *Am J Ophthalmol* 2001;132(5):668–81. [PubMed: 11704028]
19. Group A-REDSR. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss (AREDS Report No. 8). *Archives of Ophthalmology* 2001;119(10):1417–36. [PubMed: 11594942]
20. Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. *Retina* 2013;33(9):1735–62. [PubMed: 23873168]

21. Roquet W, Roudot-Thoraval F, Coscas G, Soubrane G. Clinical features of drusenoid pigment epithelial detachment in age related macular degeneration. *British Journal of Ophthalmology* 2004;88(5):638–42. [PubMed: 15090415]
22. Filho CAdAG, Yehoshua Z, Gregori G, et al. Spectral-domain optical coherence tomography imaging of drusenoid pigment epithelial detachments. *Retina* 2013;33(8):1558–66. [PubMed: 23584692]
23. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. *Eye* 1988;2(5):552–77. [PubMed: 2476333]
24. Sarks JP, Sarks SH, Killingsworth MC. Evolution of soft drusen in age-related macular degeneration. *Eye* 1994;8(3):269–83. [PubMed: 7525362]
25. Ding Y, Liu Y, Yan Q, et al. Bivariate analysis of age-related macular degeneration progression using genetic risk scores. *Genetics* 2017;206(1):119–33. [PubMed: 28341650]
26. Fritsche LG, Loenhardt T, Janssen A, et al. Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. *Nature Genetics* 2008;40(7):892–6. [PubMed: 18511946]
27. Kanda A, Chen W, Othman M, et al. A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* 2007;104(41):16227–32. [PubMed: 17884985]
28. Sarli A, Skalidakis I, Velissari A, et al. Investigation of associations of ARMS2, CD14, and TLR4 gene polymorphisms with wet age-related macular degeneration in a Greek population. *Clinical Ophthalmology (Auckland, NZ)* 2017;11:1347–58.
29. Hoffman JD, van Grinsven MJJP, Li C, et al. Genetic association analysis of drusen progression. *Investigative Ophthalmology & Visual Science* 2016;57(4):2225–31. [PubMed: 27116550]

Figure 1:
Kaplan-Meier curves for progression to late age-related macular degeneration by year after drusenoid pigment epithelial detachment (DPED) detection

Figure 2:
Prevalence of fundus features in eyes with drusenoid pigment epithelial detachment (DPED) that did not progress to late age-related macular degeneration by year

Figure 3:

Average visual acuity score plotted over time for eyes with central DPED Footnotes: DPED = drusenoid pigment epithelial detachment; CGA = central geographic atrophy; NV-AMD = neovascular age-related macular degeneration; AMD = age-related macular degeneration. Eighty letters of visual acuity translates to Snellen visual acuity of 20/25. Analyses exclude the 18 eyes with DPED located greater than 500 μ m away from the fovea.

Figure 4:

Kaplan-Meier curves for percentage of eyes losing 15 letters from time of DPED detection for eyes with central DPED

Footnotes: DPED = drusenoid pigment epithelial detachment; CGA = central geographic atrophy; NV-AMD = neovascular age-related macular degeneration; AMD = age-related macular degeneration.

Analyses exclude the 18 eyes with DPED located greater than 500 μ m away from the fovea.

Figure 5:

These fundus photographs demonstrate the natural course of bilateral drusenoid pigment epithelial detachments of an AREDS2 participant who was a 61 year old white female. Baseline fundus photographs of both eyes (Figures 5A [right eye] and B [left eye]) showed presence of bilateral, confluent large drusen. Visual acuities were 20/16 and 20/25, right and left eyes respectively. At one year follow-up, bilateral DPEDs were detected and the fundus photographs demonstrated elevated mounds of confluent drusen (Figures 5C and D) and retinal pigment epithelial hyperpigmentary changes (Figure 5C). The visual acuities were

20/25 and 20/30, right and left eyes respectively. Both DPEDs began to regress one year later (Figures 5E and F), giving way to geographic atrophy in the right eye (Figure 5E) and the development of retinal pigmentary changes in the left eye (Figure 5F). Further changes of geographic atrophy are seen in both eyes through the next 2 years of follow-up (Figures 5G, H, I and J). Visual acuities remained 20/25 and 20/30, right and left eyes, respectively throughout the entire follow-up as the fovea was preserved in both eyes.

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Figure 6:

This 65 year old man developed drusenoid pigment epithelial detachment in his left eye in year 2 of his follow up with visual acuity of 20/40. The DPED resulted in central geographic atrophy 1 years later, with visual acuity of 20/250.

Figure 7:

This 81 year white female had baseline large drusen (Figure 7A) which increased in area (Figure 7B) over the next year. Drusenoid pigment epithelial detachment (DPED) was detected in year 4 of the study (Figure 7C) and the regression of the DPED was accompanied by the progression to neovascular AMD 2 years later (Figure 7D). Anti-vascular endothelial growth factor therapy was administered. Visual acuity remained, on the average, around 20/30 throughout the course of the study.

Table 1.

Demographics and medical history of participants with DPED and comparison participants

	Participants with DPED ¹ (n = 325)	Participants without DPED ² (Comparison group) (n = 3669)	P value
	mean (SD)		
Age, years	71.6 (7.0)	73.1 (7.8)	< 0.001
Follow-up, years	4.7 (0.9)	4.3 (1.3)	< 0.001
	N (%)		
Male sex	138 (42.5%)	1600 (43.6%)	0.69
White race	319 (98.2%)	3534 (96.3%)	0.09
Education			0.50
- High school or less	91 (28.0)	1158 (31.6)	
- At least some college	154 (47.4)	1681 (45.8)	
- Post-grad	70 (21.5)	766 (20.9)	
History of smoking			0.31
- Never	153 (47.1)	1588 (43.3)	
- Former	155 (47.7)	1832 (49.9)	
- Current	17 (5.2)	249 (6.8)	
History of hypertension	183 (56.3)	2140 (58.3)	0.46
History of angina	13 (4.0)	177 (4.8)	0.50
Statin use	138 (42.5)	1628 (44.4)	0.51
Aspirin use			0.82
- No	169 (52.0)	1877 (51.2)	
- < 2 per day	151 (46.5)	1748 (47.6)	
- 2 per day	5 (1.5)	44 (1.2)	
NSAID use	46 (14.2)	384 (10.5)	0.04

DPED = drusenoid pigment epithelial detachment; SD = standard deviation; NSAID = nonsteroidal anti-inflammatory drug.

¹Participants that had DPED at any time in the study without late age-related macular degeneration (AMD) at time of DPED detection²Participants that did not have DPED in either eye at any time or late AMD at baseline (comparison group).

Table 2.

Fundus features and visual acuity at the time of DPED detection or at the baseline study visit

	Eyes with DPED ¹ (n = 391)	Eyes without DPED ² (Comparison eyes) (n = 6131)	P value ³	Eyes with DPED that progressed to late AMD (n = 148)	Eyes with DPED that did not progress to late AMD (n = 243)	P value ⁴
	N (%)			N (%)		
<u>Fundus Features</u>						
Large drusen (≥ 125 μm)	391 (100)	5726 (93)	p < 0.001	148 (100)	243 (100)	
Very large drusen (≥ 250 μm)	378 (97)	2805 (46)	p < 0.001	148 (100)	238 (98)	p = 0.09
Hyperpigmentation	375 (96)	3903 (64)	p < 0.001	144 (97)	231 (95)	p = 0.28
Hypopigmentation	68 (18)	1352 (23)	p = 0.01	30 (20)	38 (16)	p = 0.19
Refractile drusen	30 (8)	392 (6)	p = 0.32	14 (9)	16 (7)	p = 0.30
Drusen area			p < 0.001			p = 0.84
- Less than area of circle 790 μ m in diameter (< O2)	3 (1)	1147 (19)		1 (1)	2 (1)	
- Greater than area of circle 790 μ m in diameter, but less than area of circle half disc in diameter (O2 to ½ DA)	8 (2)	1092 (18)		4 (3)	4 (2)	
- Greater than area of circle half disc in diameter, but less than area of circle 1 disc in diameter (½ DA to 1 DA)	44 (11)	1514 (25)		15 (10)	29 (12)	
- Greater than or equal to area of circle 1 disc in diameter (≥ 1 DA)	336 (86)	2379 (39)		128 (86)	208 (86)	
<u>DPED Features</u>						
Proximity to fovea of DPED ≥ 500 μ m	373 (95)			142 (96)	231 (95)	p = 0.69
DPED proximity to fovea, μ m (mean ± SD)	90.1 ± 231.4			91.2 ± 250.8	89.4 ± 219.3	p = 0.96
DPED area, DA (mean ± SD)	1.1 ± 0.9			1.4 ± 1.1	0.9 ± 0.7	p < 0.001
AMD severity score			p < 0.001			p = 0.05
- 1–3	0	271 (4)		0	0	
- 4–6	19 (5)	2736 (45)		5 (3)	14 (6)	
- 7–8	372 (95)	3124 (51)		143 (97)	229 (94)	
<u>Visual Acuity</u>			p < 0.001			p = 0.001
- >20/20	12 (3)	902 (15)		3 (2)	9 (4)	
- 20/20 – 20/40	310 (81)	4602 (75)		108 (73)	202 (83)	
- 20/40 – 20/200	61 (16)	566 (9)		35 (24)	26 (11)	
- < 20/200	2 (1)	49 (1)		2 (1)	0	

DPED = drusenoid pigment epithelial detachment; AMD = age-related macular degeneration; DA = disc area.

¹Eyes that had DPED without late AMD at time of DPED detection.²Eyes that did not have DPED at any time or late AMD at baseline.

³ P value for comparison of eyes with DPED and eyes without DPED (comparison group).

⁴ P value of comparison of eyes with DPED that progressed to late AMD and eyes with DPED that did not progress to late AMD during the study.

Fundus features and visual acuity were assessed at time of DPED detection for eyes with DPED and at the baseline study visit for comparison eyes (comparison group).

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Table 3.

Multivariate Cox proportional hazard regression with repeated measures for the effect of having DPED on the hazard of progression to late age-related macular degeneration

	HR	95% CI	P value
GA	2.50	1.99 – 3.15	< 0.001
CGA	4.94	3.80 – 6.43	< 0.001
NV-AMD	1.99	1.54 – 2.59	< 0.001
Late AMD	2.38	1.99 – 2.84	< 0.001

DPED = drusenoid pigment epithelial detachment; HR = hazard ratio; CI = confidence interval; GA = geographic atrophy; CGA = central geographic atrophy; NV-AMD = neovascular age-related macular degeneration; AMD = age-related macular degeneration.

Bonferroni correction: $p < 0.0125$ considered significant. Adjusted for age and sex.

Table 4.

Genotype distribution of DPED participants and comparison participants in both Age-Related Eye Disease Study (AREDS) and AREDS2.

	AREDS2			AREDS Category 3 and 4		
	Participants with DPED	Participants without DPED (Comparison group)	<i>P</i> value*	Participants with DPED	Participants without DPED (Comparison group)	<i>P</i> value†
	N (%)			N (%)		
<i>CFH</i> – rs10611670			0.36			0.07
- TT	15 (13)	157 (18)		28 (19)	206 (26)	
- TC	54 (45)	372 (42)		62 (43)	361 (45)	
- CC	51 (43)	358 (40)		55 (38)	234 (29)	
<i>ARMS2</i> – rs10490924			0.76			< 0.001
- GG	51 (43)	358 (40)		43 (30)	379 (48)	
- GT	48 (40)	386 (44)		75 (52)	321 (40)	
- TT	21 (18)	143 (16)		27 (19)	101 (13)	
<i>C3</i> – rs2230199			0.08			0.26
- CC	54 (45)	482 (54)		69 (48)	439 (55)	
- CG	51 (43)	336 (38)		67 (46)	314 (39)	
- GG	15 (13)	69 (8)		9 (6)	48 (6)	
<i>CFI</i> – rs10033900			0.28			0.30
- CC	36 (30)	208 (23)		29 (20)	196 (25)	
- CT	51 (43)	423 (48)		70 (48)	395 (49)	
- TT	33 (28)	256 (29)		46 (32)	210 (26)	
<i>C2/CFB</i> – rs114254831			0.73			0.44
- AA	57 (48)	439 (50)		75 (52)	409 (51)	
- AG	50 (42)	371 (42)		54 (37)	327 (41)	
- GG	13 (11)	77 (9)		16 (11)	65 (8)	
GRS group			0.17			< 0.001
- 0	10 (8)	128 (14)		11 (8)	221 (28)	
- 1	22 (18)	135 (15)		17 (12)	160 (20)	
- 2	23 (19)	184 (21)		30 (21)	158 (20)	
- 3	24 (20)	206 (23)		44 (30)	127 (16)	
- 4	41 (34)	234 (26)		43 (30)	135 (17)	
	mean ± SD (range)			mean ± SD (range)		
Centered GRS	1.6 ± 1.2 (1.4 – 4.1)	1.4 ± 1.3 (–3.5 – 5.3)	0.13	1.7 ± 1.2 (–1.4–4.5)	0.9 ± 1.4 (–3.1–5.3)	< 0.001

DPED = drusenoid pigment epithelial detachment; AREDS2 = age-related eye disease study 2; AREDS = age-related eye disease study; GRS = genetic risk score; SD = standard deviation.

* *P* value for comparison of participants with DPED and participants without DPED (comparison group) in AREDS2.

[†] P value of comparison of participants with DPED and participants without DPED (comparison group) in AREDS.

Subgroup 0 under GRS group includes participants with GRS at or below the predefined control mean; subgroups 1–4 under GRS group refer to quartiles above the control mean.

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Table 5.

Age- and sex-adjusted proportional hazards regression with repeated measures for development of DPED based on single nucleotide polymorphism presence and genetic risk score group

	CFH	ARMS2	C3	CFI	C2/CFB
AREDS2					
1 vs 0 alleles					
HR (95% CI)	1.35 (0.71 – 2.60)	0.77 (0.47 – 1.27)	1.53 (0.96 – 2.46)	0.64 (0.39 – 1.07)	1.20 (0.75 – 1.92)
<i>P</i> value	0.36	0.31	0.08	0.09	0.45
2 vs 0 alleles					
HR (95% CI)	1.08 (0.54 – 2.11)	1.05 (0.58 – 1.93)	1.83 (0.87 – 3.82)	0.56 (0.31 – 1.03)	1.70 (0.84 – 3.44)
<i>P</i> value	0.83	0.87	0.11	0.06	0.14
AREDS Cat. 3 and 4					
1 vs 0 alleles					
HR (95% CI)	1.36 (0.73 – 2.53)	2.72 (1.58 – 4.70)	1.38 (0.88 – 2.16)	0.82 (0.46 – 1.45)	0.91 (0.56 – 1.46)
<i>P</i> value	0.34	< 0.001	0.16	0.49	0.69
2 vs 0 alleles					
HR (95% CI)	1.81 (0.96 – 3.42)	3.16 (1.60 – 6.21)	0.50 (0.12 – 2.06)	1.26 (0.70 – 2.28)	1.35 (0.65 – 2.79)
<i>P</i> value	0.07	< 0.001	0.34	0.43	0.42

	Risk Group 1	Risk Group 2	Risk Group 3	Risk Group 4
AREDS2				
HR (95% CI)	1.69 (0.62 – 4.56)	2.07 (0.82 – 5.23)	1.90 (0.76 – 4.78)	2.18 (0.89 – 5.31)
<i>P</i> value	0.30	0.12	0.17	0.09
AREDS Cat. 3 and 4				
HR (95% CI)	2.31 (0.55 – 9.69)	8.22 (2.42 – 27.92)	14.81 (4.50 – 48.76)	12.17 (3.66 – 40.45)
<i>P</i> value	0.25	< 0.001	< 0.001	< 0.001

DPED = drusenoid pigment epithelial detachment; AREDS2 = age-related eye disease study 2; AREDS = age-related eye disease study; HR = hazard ratio; CI = confidence interval.

In genetic risk score risk group analyses, risk group 0 serves as the reference group. With Bonferroni correction, *P* value < 0.008 was considered significant.