ONLINE FIRST

Effect of the Y402H Variant in the Complement Factor H Gene on the Incidence and Progression of Age-Related Macular Degeneration

Results From Multistate Models Applied to the Beaver Dam Eye Study

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Objectives: To investigate the effect of age, sex, and the Y402H variant in the complement factor H (*CFH*) gene on the incidence, progression, and regression of age-related macular degeneration (AMD) as well as the effect of these factors and AMD on mortality, using multistate models.

Methods: Analyses included 4379 persons aged 43 to 84 years at the time of the census. The status of AMD on a 5-level severity scale was graded from retinal photographs taken at up to 5 study visits between 1988 and 2010. Multistate models in continuous time were used to model the effects of age, sex, and *CFH* genotype on the incidence, progression, and regression of AMD and mortality.

Results: The *CFH* Y402H genotype CC was associated, relative to genotype TT (reported as hazard ratio; 95% CI), with increased incidence of AMD (no to minimally severe early AMD, 1.98; 1.57-2.49), progression of AMD (minimally severe early to moderately severe early AMD, 1.73; 1.29-2.33; moderately severe early to severe early AMD, 1.30; 0.86-1.94; and severe early to late AMD, 1.72; 1.01-2.91) but not with regression of AMD or mortality. Late AMD was associated with increased mortality (1.37; 1.15-1.62) relative to no AMD, but earlier stages of AMD were not.

Conclusions: Using the multistate models, we show that the Y402H risk variant is associated with lifetime incidence of early AMD and progression of early to late AMD and that late AMD is associated with mortality risk.

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INFORMATION REGARDING THE development and progression of age-related macular degeneration (AMD) has emerged from clinical and epidemiologic studies.[1-11] This has resulted in the development of severity scales ranging from no lesions through the most severe lesions (neovascular AMD and/or geographic atrophy).[6,12-14] Most scales use size, type, and area of drusen and retinal pigment epithelium pigmentary abnormalities to define intermediate severity levels.

Most epidemiologic studies have investigated the incidence and progression of AMD; few have examined regression and the associated protective factors.[2,5,9,11] In the Chesapeake Bay Waterman Study,[2] large soft drusen disappeared in 34% of the eyes during a 5-year follow-up period. In the Melton Mowbray study,[9] 20% of soft drusen regressed during a 7-year period. It is unclear what factors are associated with regression or how AMD transitions through various stages.

Previous studies[15-18] have shown that the Y402H polymorphism in the complement factor H (*CFH*) gene (OMIM *134370) on chromosome 1q is strongly associated with AMD, suggesting a role for innate immunity and inflammation in AMD pathogenesis. Most studies have examined relationships of the Y402H polymorphism with the incidence of early or progression to late AMD, but few have considered progression through various stages of AMD or regression of AMD.[19-22]

Multistate models (MSMs) can be used to gain greater insight into this relationship. We use MSMs to model transitions from the state at a study visit to the state at a subsequent visit.[23-27] In practice, disease states are observed at intermittent study visits and exact transition times are

Table 1. The 5-Level Beaver Dam Eye Study AMD Severity Scale

Level	Label	Description
1	No AMD	Hard drusen or small soft drusen (<125 μ in diameter only, regardless of area of involvement) and no pigmentary abnormality (increased retinal pigment or RPE depigmentation) present
2	Minimally severe early AMD	Hard drusen or small soft drusen (<125 μ in diameter, regardless of area of involvement), with any pigmentary abnormality (increased retinal pigment present and/or RPE depigmentation present) OR soft drusen (≥125 μ in diameter) with drusen area <196 350 μ^2 (equivalent to a circle with a diameter of 500 μ) and no pigmentary abnormalities
3	Moderately severe early AMD	Soft drusen (≥125 μ in diameter) with drusen area <196 350 μ^2 (equivalent to a circle with a diameter of 500 μ) and with any pigmentary abnormality (increased retinal pigment present and/or RPE depigmentation present) OR soft drusen (≥125 μ in diameter) with drusen area ≥196 350 μ^2 (equivalent to a circle with a diameter of 500 μ) with or without increased retinal pigment but no RPE depigmentation
4	Severe early AMD	Soft drusen (≥125 μ in diameter) with drusen area ≥196 350 μ^2 (equivalent to a circle with a diameter of 500 μ) and RPE depigmentation present, with or without increased retinal pigment
5	Late AMD	Pure geographic atrophy in the absence of exudative macular degeneration OR exudative macular degeneration with or without geographic atrophy present

Abbreviations: AMD, age-related macular degeneration; RPE, retinal pigment epithelium.

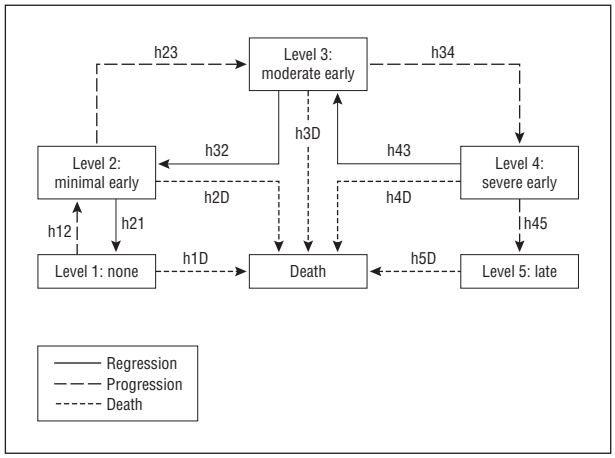

Figure 1. Transition diagram for 5-level age-related macular degeneration scale. Arrows indicate possible instantaneous transitions between states. hXY indicates hazard for instantaneous transition from state X (1, 2, 3, 4, or 5) to state Y (1, 2, 3, 4, 5, or D [death]).

not observed; even when the date of death is known, the AMD state at death is unknown.[28-31] Additionally, observations are frequently censored. For example, at the end of follow-up, participants are known to be alive, but their AMD state at that time is unknown. In this study, we used MSMs to examine the effects of age, sex, and the Y402H variant in the *CFH* gene on the incidence, progression, and regression of AMD as well as mortality in the population-based Beaver Dam Eye Study (BDES).

METHODS

POPULATION

Methods used to identify the population have been described.[32-36] A private census of Beaver Dam, Wisconsin, was performed from fall 1987 to spring 1988.[32] Of the 5924 persons aged 43 to 84 years, 4926 participated in the baseline examination,[33] 3722 participated in the 5-year follow-up,[34] 2962 participated in the 10-year follow-up,[35] 2375 participated in the 15-year follow-up,[36] and 1913 participated in the 20-year follow-up. Characteristics of the population at each examination and reasons for nonparticipation appear elsewhere.[33-36]

PROCEDURES AND DEFINITIONS

Similar procedures were used at all examinations.[3,5,37-41] Data were collected with institutional review board approval from the University of Wisconsin–Madison, informed consent was obtained from each participant at each examination, and the study adhered to the tenets of the Declaration of Helsinki. Pertinent parts of the examination consisted of taking stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye.

Grading procedures have been described.[39-41] In brief, after placing a circular grid on 1 photographic slide of the stereoscopic pair, a preliminary masked grading was done followed by a detailed grading using the Wisconsin Age-Related Maculopathy Grading System; each was performed independently of the fellow eye and the gradings of other observers.[39,40] Next, edits and reviews were performed. Finally, graders made side-by-side comparisons of 15- and 20-year follow-up photographs that showed change in AMD lesions. The senior grader and the principal investigator (R.K.) performed a final unmasked review of all 5 visits for progression and regression. Information on gradability has been published.[3,5,11,41] The status of AMD in each eye was classified using the 5-step BDES AMD severity scale (**Table 1**). Severity was classified on the basis of the worse eye of each participant.

Information on the Y402H polymorphism for *CFH*, classified as absence (genotype TT), presence of 1 high-risk allele (genotype CT), and presence of 2 high-risk alleles (genotype CC), was available for 4479 participants. Distributions of other characteristics for these individuals did not differ significantly from those of the rest of the population (data not shown).

Vital status was monitored by reading the obituaries in local newspapers and by making annual telephone contact. Persons not known to have died but could not be contacted had their survival time entered as their last contact date. We ascertained mortality starting after the 1988-1990 baseline examination to the end of the 20-year examination.

STATISTICAL ANALYSIS

The incidence, progression, and regression of AMD and mortality were modeled, using MSM in continuous time. We identified mutually exclusive and exhaustive states representing the current status of each participant at a given age. Herein, individuals were classified as being in 1 of the 5 levels on the BDES AMD severity scale, or death. **Figure 1** illustrates the underlying MSM.

Table 2. Characteristics of the Cohort by Current AMD Status (Worse Eye) at the Beginning of the BDES Follow-up Intervals

Characteristic	No. (%)[a]				
	No AMD, L1 (n = 8474)	Minimal Early AMD, L2 (n = 1524)	Moderate Early AMD, L3 (n = 833)	Severe Early AMD, L4 (n = 250)	Late AMD, L5 (n = 294)
Age, mean (SD), y	63 (10)	67 (10)	73 (10)	76 (9)	80 (8)
Male sex	3644 (43.0)	736 (48.3)	357 (42.9)	82 (32.8)	106 (36.1)
Participated in examination					
BDES 1	3151 (37.0)	530 (35.0)	247 (30.0)	47 (19.0)	75 (26.0)
BDES 2	2185 (26.0)	444 (29.0)	239 (29.0)	64 (26.0)	67 (23.0)
BDES 3	1724 (20.0)	316 (21.0)	197 (24.0)	70 (28.0)	70 (24.0)
BDES 4	1414 (17.0)	234 (15.0)	150 (18.0)	69 (28.0)	82 (28.0)
CFH Y402H genotype					
TT	3482 (41.0)	594 (39.0)	287 (34.0)	66 (26.0)	43 (15.0)
CT	3903 (46.0)	743 (49.0)	404 (48.0)	138 (55.0)	180 (61.0)
CC	1089 (13.0)	187 (12.0)	142 (17.0)	46 (18.0)	71 (24.0)

Abbreviations: AMD, age-related macular degeneration; BDES, Beaver Dam Eye Study; *CFH*, complement factor H; L, level.
[a]No. (%) of participant follow-up intervals.

Transitions are governed by 12 intensities, 1 for each possible instantaneous transition between states (represented by arrows in Figure 1), which represent the hazard of moving between states. Dependence of transition intensities on age, sex, and *CFH* Y402H genotype was specified using log-linear regression models. Age was entered as a linear term and updated annually. Sex and *CFH* Y402H genotype were entered using indicator variables. Covariate effects on transitions within the AMD scale were unconstrained. Covariate effects on transitions to death were constrained to be equal, but intercepts were allowed to vary. Nonlinear effects of age and 2-way interactions between age, sex, and *CFH* Y402H were evaluated.

The MSM incorporates all available information on the history of disease progression into likelihood calculations. Current AMD state is observed at intermittent study follow-up visits; transition times and numbers of intermediate transitions are not observed. Death times are available, but AMD state at death is unknown. If participants are alive at the end of follow-up, the final AMD state is unknown. At study visits, the AMD state may be unknown. For example, if the right eye has moderately severe early AMD (level 3) and the left eye is ungradable, the AMD state could be level 3, 4, or 5. The timing of follow-up visits is assumed to be uninformative. A sensitivity analysis for which observations from visits outside the scheduled visit window (±6 months of the anniversary of the baseline visit) were censored was conducted. Results of analyses of the complete data and of this subset were virtually identical, validating the assumption of uninformative visit times (data not shown).

Analyses were conducted in R[42] using the msm package.[43] Covariate effects on transition intensities are summarized as hazard ratios. Using matrix exponentiation, we obtain annual transition matrices for each initial state, age, sex, and *CFH* Y402H genotype. From these transition matrices, we calculate estimated transition probabilities to each AMD state (and death) after 5 years and estimated the cumulative incidence of each AMD state (and death) for specified subgroups. Cumulative incidence calculations use annual assessments of AMD status; participants are assigned to the most severe state observed at or prior to the current age. Confidence intervals for these nonlinear functions of the transition intensity parameters are obtained from a parametric bootstrap.[44]

RESULTS

Of the 4973 individuals seen at any study visit, 134 were excluded for ungradable AMD status at all visits and 460 were excluded for missing *CFH* Y402H genotype; 4379 participants contributed data from 12 640 BDES follow-up intervals (up to 4 per person). **Table 2** displays the characteristics of the participants at the start of each interval by AMD level. Those with more severe AMD were older and more likely to be female, to have *CFH* Y402H genotype CT or CC, and to be seen at later visits. Similar relationships were seen among participants with partial AMD severity information (data not shown).

Table 3 shows the transitions between consecutive BDES visits. The first column presents transitions for the 8474 BDES visits at which participants had no AMD (level 1). At their next BDES visit, 71.4% (n=6050) were still free of AMD, 4.6% (n=386) progressed to minimally severe early AMD (level 2), 2.1% (n=181) progressed to level 3, 0.2% (n=13) progressed to level 4, 0.1% (n=8) progressed to late AMD, and 12.0% (n=1015) died. The remaining individuals (n=821) had missing/partial information. Altogether, 5.8% (n=493) were seen with no information (levels 1-5), 0.2% (n=17) had minimal early AMD or worse (levels 2-5), 0.1% (n=10) had moderate early AMD or worse (levels 3-5), 0.02% (n=2) had severe early AMD or worse (levels 4 and 5), and 3.5% (n=299) were not seen.

The plurality of participants maintained the same AMD state at the next visit, but the absolute proportions declined with increasing severity (71.4%, 44.4%, 35.3%, 30.0%, and 53.4% for levels 1-5, respectively). Progression was more common than regression (17.3% vs 9.8% for level 2, 21.0% vs 8.9% for level 3, and 22.8% vs 6.4% for level 4). Mortality increased with severity (12.0%, 18.2%, 24.4%, 31.2%, and 43.2% for levels 1-5, respectively). Few participants were not seen at the next scheduled visit, and the proportion not seen did not vary with AMD severity. Similar relationships were seen for those with partial information (data not shown).

Table 3. Observed State Transitions During Consecutive Visit Intervals

AMD Level, End of Interval	AMD Level, Beginning of Interval, No. (%)[a]				
	No AMD, L1 (n = 8474)	Minimal Early AMD, L2 (n = 1524)	Moderate Early AMD, L3 (n = 833)	Severe Early AMD, L4 (n = 250)	Late AMD, L5 (n = 294)
1	6050 (71.4)	149 (9.8)	7 (0.8)	0	. . .
2	386 (4.6)	677 (44.4)	67 (8.0)	7 (2.8)	. . .
3	181 (2.1)	211 (13.8)	294 (35.3)	9 (3.6)	. . .
4	13 (0.2)	39 (2.6)	115 (13.8)	75 (30.0)	. . .
5	8 (0.1)	13 (0.9)	60 (7.2)	57 (22.8)	157 (53.4)
1-5	493 (5.8)	60 (3.9)	26 (3.1)	7 (2.8)	. . .
2-5	17 (0.2)	28 (1.8)	9 (1.1)	0	. . .
3-5	10 (0.1)	16 (1.0)	21 (2.5)	6 (2.4)	. . .
4-5	2 (0.02)	1 (0.1)	4 (0.5)	3 (1.2)	. . .
Dead	1015 (12.0)	277 (18.2)	203 (24.4)	78 (31.2)	127 (43.2)
Not seen	299 (3.5)	53 (3.5)	27 (3.2)	8 (3.2)	10 (3.4)

Abbreviations: AMD, age-related macular degeneration; ellipses, structurally missing values; L, level.
[a] No. (%) of participant follow-up intervals.

Table 4. Estimated Covariate Effects on Transition Intensities or Hazards

Covariate	HR (95% CI)							
	Incidence or Progression				Regression			Mortality
	L1 to L2	L2 to L3	L3 to L4	L4 to L5	L2 to L1	L3 to L2	L4 to L3	Any AMD to Death
Age, per 5 y	1.43 (1.37-1.49)	1.31 (1.24-1.39)	1.24 (1.14-1.34)	1.27 (1.14-1.41)	1.04 (0.95-1.13)	0.91 (0.81-1.03)	0.91 (0.68-1.21)	1.66 (1.61-1.70)
Sex, male	0.96 (0.82-1.13)	0.88 (0.72-1.08)	0.69 (0.52-0.91)	1.17 (0.82-1.68)	0.83 (0.60-1.14)	1.30 (0.83-2.04)	0.46 (0.14-1.50)	1.55 (1.42-1.69)
CFH Y402H genotype								
TT	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
CT	1.35 (1.13-1.60)	1.09 (0.87-1.36)	1.44 (1.04-1.98)	1.60 (1.03-2.48)	0.87 (0.62-1.22)	0.49 (0.23-1.04)	0.49 (0.16-1.48)	0.94 (0.85-1.01)
CC	1.98 (1.57-2.49)	1.73 (1.29-2.33)	1.30 (0.86-1.94)	1.72 (1.01-2.91)	0.92 (0.54-1.56)	0.60 (0.37-0.97)	0.41 (0.09-1.83)	0.98 (0.86-1.12)
AMD severity[a]								
Level 1								1 [Reference]
Level 2								1.04 (0.82-1.32)
Level 3								1.01 (0.79-1.30)
Level 4								1.05 (0.71-1.55)
Level 5								1.37 (1.15-1.62)

Abbreviations: AMD, age-related macular degeneration; *CFH*, complement factor H; HR, hazard ratio; L, level.
[a] Level 1 indicates no AMD; L2, minimally severe early AMD; L3, moderately severe early AMD; L4, severe early AMD; and L5, late AMD.

COVARIATE EFFECTS ON TRANSITION INTENSITIES

Covariate effects from the MSMs are presented in **Table 4**. There was no evidence of nonlinear age effects ($P = .54$ for quadratic terms) or interactions (age and sex, $P = .54$; age and *CFH* Y402H genotype, $P = .84$; or sex and *CFH* Y402H genotype, $P = .87$).

Older age was associated with increased AMD incidence and progression and mortality but not with AMD regression (Table 4). Being male was associated with increased mortality but not with AMD incidence, progression, or regression. The *CFH* Y402H genotypes CC and CT were associated, relative to genotype TT, with increased AMD incidence and progression but not with regression or mortality. Late AMD was associated with increased mortality relative to no AMD, but earlier stages of AMD showed no association.

FIVE-YEAR TRANSITION PROBABILITIES BY AGE, SEX, AND *CFH* Y402H GENOTYPE

Five-year transition probabilities by age and *CFH* Y402H genotype are displayed for women (**Figure 2**A) and for men (Figure 2B). One can assess relative transitions between states (1) by *CFH* Y402H genotype for initial AMD state and age and (2) by age.

Effects of the *CFH* Y402H risk genotype CC on progression of AMD are clear. Relative to individuals with genotype TT, for those free of AMD at age 50 years, the rate of progression to level 2 at age 55 for those with genotype CC was higher (women, 4.2% vs 2.2%; men, 4.1% vs 2.1%). A similar effect of genotype was seen for those free of AMD at age 70 whose severity progressed to level 2 at age 75 (women, 11.3% vs 7.1%; men, 11.0% vs 6.7%). At age 90 years, progression to level 2 at age 95 was similar regardless of genotype (women, 8.4% vs 8.2%; men, 6.1% vs 5.7%), but rates of progression to level 3, level 4, and late AMD were higher for those with genotype CC (women, 12.1% vs 5.9%, 4.2% vs 1.6%, and 2.0% vs 0.4%, respectively; men, 8.3% vs 3.6%, 1.8% vs 0.6%, and 1.0% vs 0.2%, respectively).

For individuals with AMD at level 2 at age 50 years, regression to no AMD by age 55 was common (11.7%-16.0%) but did not vary with *CFH* genotype; progression to level 3 and level 4 was more common for CC individuals than for TT individuals (women, 18.9% vs 10.6% and 1.9% vs 0.8%,

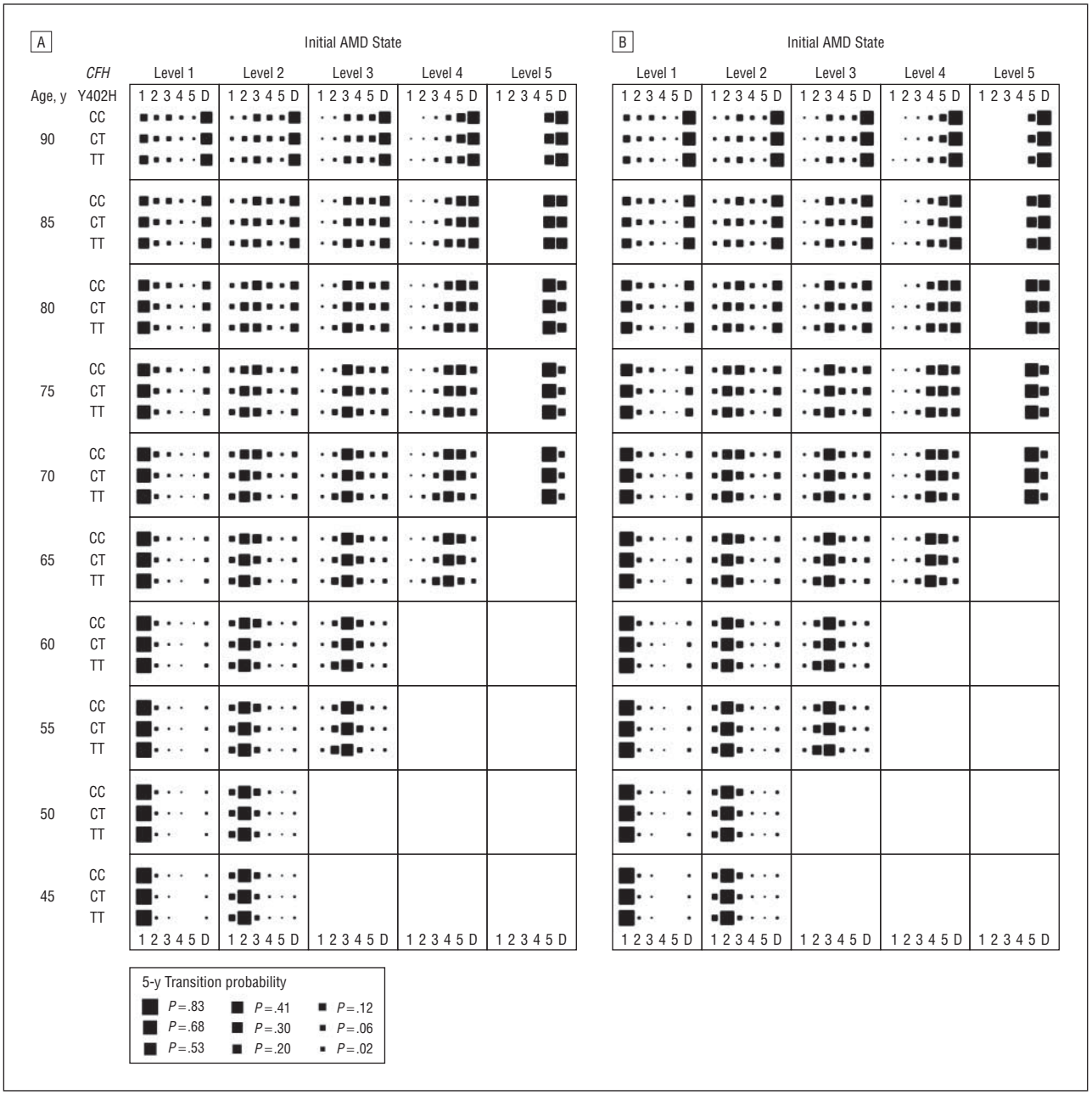

Figure 2. Five-year transition probabilities to age-related macular degeneration (AMD) states (1, 2, 3, 4, or 5) and death (D) for the specified initial AMD state (level 1, level 2, level 3, level 4, or level 5), age, and complement factor H (*CFH*) Y402H genotype for women (A) and for men (B). The size of the squares represents the 5-year transition probability, as given in the figure key.

respectively; men, 17.0% vs 9.1% and 1.2% vs 0.5%, respectively). At age 70 years, regression was less frequent and progression was more frequent; CC individuals remained at greater risk of progression. At age 90 years, regression was infrequent and progression declined because of the competing risk of death; CC individuals remain at greater risk of progression. Similar observations can be made for individuals with level 3 and level 4 AMD (Figure 2).

Effects of age on the 5-year transition probabilities are clear. Mortality increases substantially with age. For example, in TT women with no AMD, 5-year mortality rates increased from 0.8% at age 45 to 72.9% at age 95. The progression of AMD generally increased with age until at least age 80 years; regression declined with increasing age. For example, in TT women, 5-year rates of progression from level 3 to level 4 and late AMD increased from 9.9% and 1.0% at age 55 years to peaks of 18.8% and 7.7% at ages 80 and 90 and then declined to 8.2% and 5.9%, respectively, at age 95; 5-year rates of regression from level 3 to level 2 or no AMD declined from 26.5% and 3.2% to 1.2% and 0.2%.

CUMULATIVE INCIDENCE OF AMD FOR INDIVIDUALS WITH NO AMD AT AGE 45 YEARS

Figure 3 shows the cumulative incidence of level 2 or higher, level 3 or higher, level 4 or higher, and late AMD through age 100 years based on annual assessments of

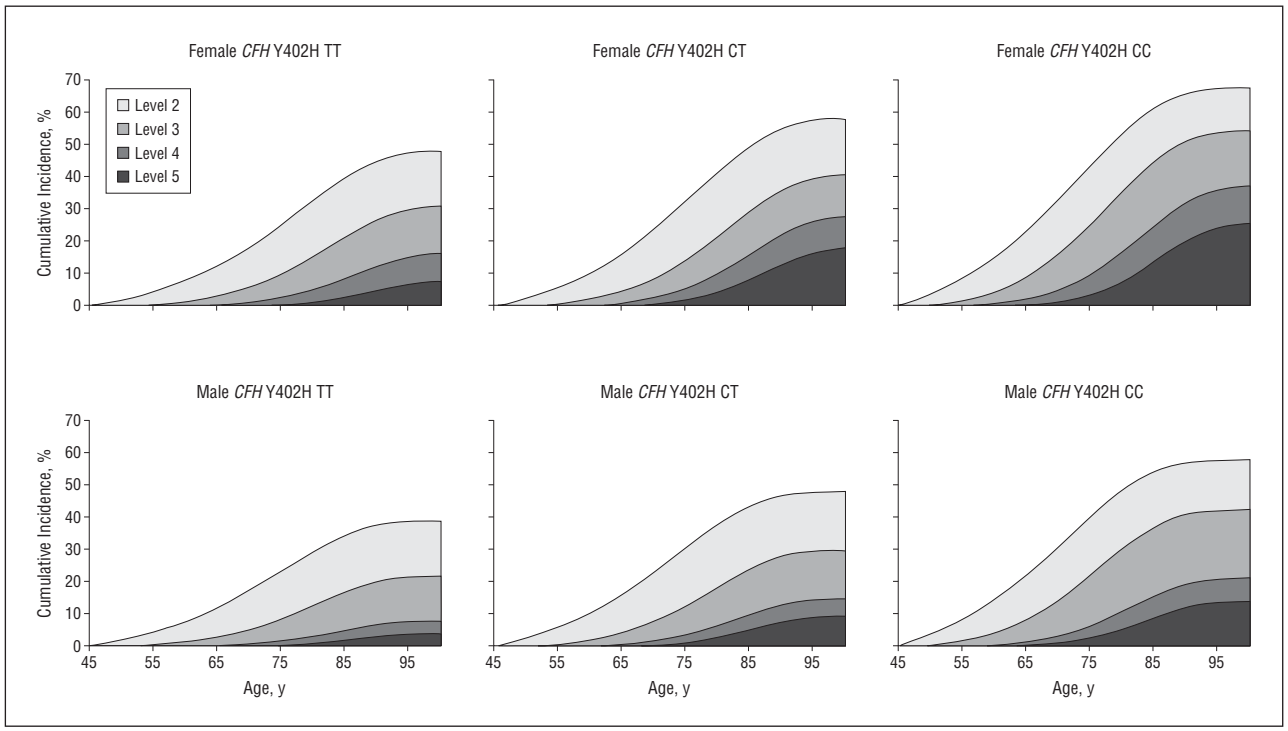

Figure 3. Cumulative incidence of minimally severe early age-related macular degeneration (AMD) (level 2) or higher (top curve), moderately severe early AMD (level 3) or higher, severe early AMD (level 4) or higher, and late AMD (level 5; bottom curve) through age 100 years for individuals with no AMD (level 1) at age 45 years by sex and complement factor H (*CFH*) Y402H genotype (TT, CT, CC). Estimates are based on annual assessments of AMD status.

AMD state for persons free of AMD at age 45. For TT women, the cumulative incidence of late AMD increased to 7.8%, the cumulative incidence of level 4 or higher increased to 16.5%, the cumulative incidence of level 3 or higher increased to 31.1%, and the cumulative incidence of level 2 or higher increased to 48.3%.

Cumulative incidence of level 2 or higher was greater for women and for CC individuals than for men and for TT individuals. For example, cumulative incidence of level 2 by age 65 years was 23.0% (95% CI, 19.0%-27.6%) for CC women vs 12.4% (10.7%-14.6%) for TT women and 21.8% (18.0%-27.2%) for CC men vs 11.7% (9.5%-14.4%) for TT men. By age 80 years, cumulative incidence of level 2 was 61.2% (54.5%-67.1%) vs 39.6% (36.1%-43.8%) for women and 54.1% (48.2%-61.0%) vs 34.1% (29.5%-39.6%) for men. By age 100 years, it was 67.7% (61.2%-72.9%) vs 48.3% (44.4%-53.1%) for women and 57.8% (52.1%-64.4%) vs 38.6% (33.2%-44.1%) for men. Cumulative incidence of late AMD was similarly greater for women and for CC individuals than for men and for TT individuals at all ages.

COMMENT

In a cohort followed for 20 years, we showed that, after adjusting for age and sex, the Y402H variant in the *CFH* gene is associated with the incidence of early AMD and progression along the AMD severity scale, up to and including progression to late AMD. We also identified an association between late AMD and mortality. Although other studies have shown associations between incidence of late AMD (and sometimes early AMD) and the *CFH* Y402H risk allele, our models demonstrated that the effect is monotonic and detectable at all stages of the disease. This provides further evidence of the effects of this risk allele across the continuum of AMD.

The MSM used here is advantageous for modeling staged disease progression in studies like the BDES. The model incorporates all facets of the natural history of AMD as well as death into a single, biologically plausible model rather than modeling aspects of the disease process in isolation. It accommodates the different observation times (including longer times resulting from missing examinations) that are independent of the participants' current state. We use a biologically meaningful time scale (participant age) rather than an artificial time scale (time of study). The model also incorporates time-varying covariates by updating covariate values at observation times. Disadvantages of the MSM are the large computation burden involved in model fitting and the sparseness of information regarding some transitions.

Our findings show the profound effect of the competing risk of death on the incidence and progression of AMD in persons aged 85 years or older (Figure 2). In our study, late AMD was associated with a 37% increase in overall mortality; earlier stages of AMD and the *CFH* variant were not associated with increased mortality. This is consistent with some earlier studies[45-49] that examined associations of AMD and survival. Our findings are consistent with those of the Age-Related Eye Disease Study,[46] which showed increased mortality risk in persons with advanced-stage macular degeneration, and with the Copenhagen City Eye Study,[47] which showed increased mortality risk in women with late AMD. However, AMD was not associated with

mortality in the Rotterdam Study,[48] the Blue Mountains Eye Study,[49] or the Beijing Eye Study.[50] The relationships of AMD and other ocular conditions with mortality, adjusting for smoking, hypertension, and other potential confounders, will be examined in future work. Better understanding of the role of AMD as an indicator of increased mortality may be especially important for persons with exudative AMD undergoing treatment with intravitreal anti–vascular endothelial growth factor agents.[51]

Ten percent of eyes at level 2, 9% of eyes at level 3, and 7% of eyes at level 4 regressed between visits (Table 3). Soft drusen and pigmentary abnormalities may regress and disappear, accounting for these findings.[15,16,18,26] Our findings suggest that regression from levels 3 and 4 to levels 2 and 3, respectively, are diminished by 40% and 59% in the presence of the high-risk *CFH* Y402H CC genotype, although only the former change was statistically significant. While masked side-by-side comparisons of photographs minimized the effect of media opacity, photographic artifacts, and grader error, it is possible that these factors may explain some apparent regression. Factors leading to disappearance or regression of these lesions remain to be studied.

In conclusion, we demonstrated the advantages of MSMs in assessing the relationships of *CFH* Y402H, age, and sex with the incidence, progression, and regression of AMD. This modeling approach should similarly provide greater insight regarding roles of other candidate genes as well as environmental and host factors in AMD.

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