Prediction of Age-related Macular Degeneration in the General Population

The Three Continent AMD Consortium

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Purpose: Prediction models for age-related macular degeneration (AMD) based on case-control studies have a tendency to overestimate risks. The aim of this study is to develop a prediction model for late AMD based on data from population-based studies.

Design: Three population-based studies: the Rotterdam Study (RS), the Beaver Dam Eye Study (BDES), and the Blue Mountains Eye Study (BMES) from the Three Continent AMD Consortium (3CC).

Participants: People (n = 10 106) with gradable fundus photographs, genotype data, and follow-up data without late AMD at baseline.

Methods: Features of AMD were graded on fundus photographs using the 3CC AMD severity scale. Associations with known genetic and environmental AMD risk factors were tested using Cox proportional hazard analysis. In the RS, the prediction of AMD was estimated for multivariate models by area under receiver operating characteristic curves (AUCs). The best model was validated in the BDES and BMES, and associations of variables were re-estimated in the pooled data set. Beta coefficients were used to construct a risk score, and risk of incident late AMD was calculated using Cox proportional hazard analysis. Cumulative incident risks were estimated using Kaplan–Meier product-limit analysis.

Main Outcome Measures: Incident late AMD determined per visit during a median follow-up period of 11.1 years with a total of 4 to 5 visits.

Results: Overall, 363 participants developed incident late AMD, 3378 participants developed early AMD, and 6365 participants remained free of any AMD. The highest AUC was achieved with a model including age, sex, 26 single nucleotide polymorphisms in AMD risk genes, smoking, body mass index, and baseline AMD phenotype. The AUC of this model was 0.88 in the RS, 0.85 in the BDES and BMES at validation, and 0.87 in the pooled analysis. Individuals with low-risk scores had a hazard ratio (HR) of 0.02 (95% confidence interval [CI], 0.01–0.04) to develop late AMD, and individuals with high-risk scores had an HR of 22.0 (95% CI, 15.2–31.8). Cumulative risk of incident late AMD ranged from virtually 0 to more than 65% for those with the highest risk scores.

Conclusions: Our prediction model is robust and distinguishes well between those who will develop late AMD and those who will not. Estimated risks were lower in these population-based studies than in previous case-control studies.

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Group members listed online in Appendix 1 (http://aaojournal.org).

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly of industrialized countries.[1,2] Approximately 21 million elderly individuals are affected worldwide, and this number is expected to increase dramatically with the aging population.[3,4] Age-related macular degeneration can be divided into several stages: early AMD, characterized by subcellular deposits (drusen) and pigmentary changes, and late AMD, subdivided into atrophy of the retinal pigment epithelium (dry AMD) and choroidal neovascularization (wet AMD). Despite improved treatment options, late AMD can cause irreversible blindness, whereas severe stages of early AMD are mostly

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asymptomatic but signal a high risk of progression to late AMD.[5]

Age, early AMD phenotype, and genetic and environmental factors play important roles in the pathogenesis of late AMD.[6–11] These factors may be used to predict this end stage and to identify high-risk individuals. Reasons for assessing predictive values may be risk-dependent (personalized) patient care and surveillance strategies for therapy. Future intervention research, such as randomized, controlled clinical trials, can use prediction models to select individuals with a high risk of outcome events.

Previously reported prediction models were based on selections of cases and nonaffected controls.[12–28] Most studies compared only the extreme ends of disease, excluding the majority of the population with an intermediate disease risk. This has inherent methodological concerns because the disease risk is overestimated by design. Population-based studies include a whole spectrum of risk levels, and therefore findings from these studies would be more generalizable[29] and better suited for clinical implementation.

In this study, we present a prediction model for late AMD based on population-based cohort studies from 3 continents. We optimized a prediction model in one of the cohorts and subsequently validated it in the other 2 cohorts. We included established genetic, environmental, and clinical risk factors in the model, assessed relative and cumulative risks, and provided a risk score that can be used to estimate the risk of AMD in individuals.

Methods

For this article, we followed the guidelines for genetic risk prediction studies.[30]

Study Populations

The Three Continent AMD Consortium (3CC) consists of 4 population-based studies: the European Rotterdam Study (RS), the American Beaver Dam Eye Study (BDES), the Los Angeles Latino Eye Study, and the Australian Blue Mountains Eye Study (BMES). For the purposes of this study, the Los Angeles Latino Eye Study was excluded because of the absence of genotype and follow-up data.

The RS is a prospective, population-based cohort study investigating chronic diseases in the elderly. All inhabitants aged 55 years and older living in a suburb of Rotterdam, The Netherlands, were invited to participate in the study.[31,32] Of the initial cohort of 10 275 eligible individuals, 7983 (78% of those eligible) participated in the overall study (98% were white). The ophthalmologic part began later and included 6780 participants (78% of those eligible). Baseline examinations took place from 1990 to 1993, and 4 follow-up examinations were performed in 1993–1995, 1997–1999, 2002–2004, and 2009–2011. The Erasmus Medical Center Ethics Committee approved the study, which complies with the Declaration of Helsinki. All participants gave written informed consent for participation in the study.

The BDES is a prospective cohort study investigating eye diseases among the population of Beaver Dam, Wisconsin.[33] To identify all residents in the city or township of Beaver Dam who were aged 43 to 84 years, a private census was performed from 1987 to 1988. Of the 5924 eligible individuals, 4926 (83% of those eligible) participated in the baseline examination between 1988 and 1990 (99% were white). There were follow-up examinations every 5 years: 1993–1995, 1998–2000, 2003–2005, and 2008–2010. The BDES was approved by the institutional review board from the University of Wisconsin-Madison and adhered to the tenants of the Declaration of Helsinki. All participants provided signed, informed consent for participation in the study.

The BMES is a prospective cohort study of eye diseases and other health outcomes in an urban population.[34] All residents aged 49 years or older, living in 2 postcode areas of the Blue Mountains region in West Sydney, Australia, were invited to participate in the study. In 1992–1994, baseline examinations were performed in 3654 participants (82.4% of those eligible). Reexaminations were performed after 5, 10, and 15 years (in 1997–1999, 2002–2004, and 2007–2009, respectively). All BMES examinations were approved by the human research ethics committees of the Western Sydney Area Health Service and the University of Sydney and complied with the Declaration of Helsinki. All participants provided written, informed consent for participation in the study.

Participants were eligible for the current analysis when genotype data, as well as gradable fundus photographs at baseline and at least 1 follow-up eye examination were available (Fig 1, available at http://aaojournal.org). People with late AMD at baseline were excluded. This resulted in 4753 (RS), 3542 (BDES), and 1811 (BMES) participants available for analysis, with a median follow-up of 10.7 years in RS (interquartile range [IQR], 12.8), 15.6 years in BDES (IQR, 10.4), and 11.8 years in BMES (IQR, 5.6). In total, 10 106 participants with a median follow-up of 11.1 years (IQR, 11.0) were included in the analysis. To investigate possible selection bias, we analyzed whether people excluded from this study differed in the baseline level of AMD from those who were included. The 2 groups did not differ in early AMD levels (10–40) after adjustment for age and sex ($P = 0.95$).

Diagnosis of Age-Related Macular Degeneration

All participants underwent fundus photography after pharmacologic mydriasis. Fundus transparencies of all studies were graded according to the Wisconsin Age-Related Maculopathy Grading[35,36] by trained graders under the supervision of senior retinal specialists or senior researchers (RS: P.T.V.M.dJ., J.R.V., C.C.W.K.; BDES: B.E.K.K., R.K.; BMES: P.M., J.J.W.). The graded fundus photographs were classified using a classification common to all studies: the 3CC AMD severity scale[37] (Table 1, available at http://aaojournal.org). All prevalent and incident late AMD cases from each of these 3 studies were cross-checked by investigators of the other 2 studies, with consensus obtained via discussion during multiple teleconferences. The eyes of each participant were graded and classified separately, and the eye with the more severe grade was used to classify the person.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes. All eligible study participants in the RS were genotyped with the Illumina Infinium II HumanHap550 array or Taqman assays (Applied Biosystems, Foster City, CA). HapMap CEU data (release #22) was used for imputation.

DNA from BDES participants was extracted from the buffy coats of blood obtained at baseline examinations or subsequent examinations that were stored frozen at −80°C. DNA samples arrayed in 96-well plates were submitted for genotyping via an Illumina iSelect Custom Genotyping Panel (Illumina Inc., Hayward, CA) at the Genomics Core Facility at Case Western Reserve University or via the KASP Assay at LCG Genomics (Teddington, Middlesex, UK). The data collected were analyzed using Illumina's Genome Studio or the KASP SNP Genotyping System. The