Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Cohort descriptions

The RS cohort I started in 1990 and included 7983 participants aged 55 years and older. Cohort II started in 2000, included 3011 participants aged 55 years and older, and cohort III was examined in 2006 and included 3932 participants aged 45 years and older. In RS I mean follow-up was 10.4 years, RS II 11.3 years and RS III 5.7 years. All three studies were performed in the same district in Rotterdam, The Netherlands. The entire Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG).

The study methods were kept similar over time, although additions were possible, and color fundus photography changed from analogue to digital at the third follow-up examination. For the first examinations, fundus photographs were taken with the Topcon TRV-50VT camera (Topcon Optical Company, Tokyo, Japan), the last three examinations with a Topcon TRC 50EX and a Sony DXC-950P digital camera (0.44 megapixel). All photos were taken stereoscopic. Optical coherence tomography (OCT) was added to the protocol from 2007 onwards; the SD-OCT 1000 spectral-domain scanner (Topcon Corp., Tokyo, Japan) from 2007 to 2008, SD-OCT 1000 Mark-II spectral-domain scanner (Topcon Corp., Tokyo, Japan) from 2008 to 2011, and SD-OCT 2000 spectral-domain scanner (Topcon Corp., Tokyo, Japan) from 2011 to date. Fundus auto-fluorescence and near infra-red images were captured with Heidelberg Retina Angiograph 2 (Heidelberg Engineering, Heidelberg, Germany). Genetic risk variants were ascertained in the RS by multiple platforms; whole exome sequencing, exome chip, or by imputation[1]. Best corrected visual acuity (BCVA) was measured using the Lighthouse Distance Visual Acuity Test, a modified ETDRS chart. Smoking status was obtained by questionnaire.

The BMES recruited 3654 participants aged ≥49 years living in two postcode regions west of Sydney between 1992 and 1994 [2]. Examinations were approved by the University of Sydney and the Sydney West Area Health Service Human Research Ethics Committees. Zeiss fundus cameras (Carl Zeiss, Oberkochen, Germany) were used in the first three visits of the BMES. A CanonCF-60 DSi with DS Mark II body (Canon, Tokyo, Japan) was used in the last visit. Genetic risk variants were obtained by the Illumina Human670-Quad v1 custom array imputed with HapMap CEU data (release #22) or 1000 Genomes version 1. Best corrected visual acuity (BCVA) was measured using a logarithm of the minimum angle of resolution (logMAR) chart and transformed using the formula; decimal visual acuity = antilog(-LogMAR) = $10^{-\text{LogMAR}}$ [3]. Smoking habits were assessed by questionnaire.

In both cohorts no financial compensation was offered for participation, however patients received referral on clinically relevant incidental findings.

eMethods 2. Grading of geographic atrophy, classification of visual impairment, software used for calculations, and genetic risk score

Exclusion criteria were ungradable GA due to poor image quality, incomplete coverage of the ETDRS grid on CFP. Choroidal neovascularization or treatment for neovascularization prior to GA was not considered GA, nor was RPE atrophy without the presence of any other AMD lesion. GA was delineated on screen on digital images by four experienced graders from EyeNED Reading Center. All images available (CFP, OCT, near infra-red and auto fluorescence) from the same eye were linked by identification of reference points such as vessel bifurcations, in order to obtain a common reference system for each coordinate in the image[4,5]. GA was delineated by hand drawing the border of GA on color fundus photos (see Supplement Figure 1) while simultaneously delineating the lesion on all other images available. Adjustments were made when necessary based on the other imaging modalities. Peri-papillary atrophy (PPA) appearing in the ETDRS grid was graded as part of GA when the atrophy was connected to the macular atrophy. In five eyes the GA connected with the PPA during the follow-up of the study, when it attached the PPA within the ETDRS grid was calculated as GA.

GA area was measured by converting pixels to millimeters (mm) based on the radius of the ETDRS-grid, which was fixed at 3mm. Final calculations of the GA area were based on the consensus of four graders. Inter-observer agreement was assessed by dice coefficients, defined as twice the intersection of two areas divided by the sum of the individual areas. A dice score of one is perfect agreement, a score of zero is no agreement. Bland-Altman plots are shown in Supplement Figure 2 for different pairs of graders.

Features of AMD such as presence of PPA, soft drusen and hyperpigmentations within the ETDRS grid were graded according to the three continent consortium classification (3CC)[6], a modified version of Wisconsin age-related maculopathy grading system (WARMGS).

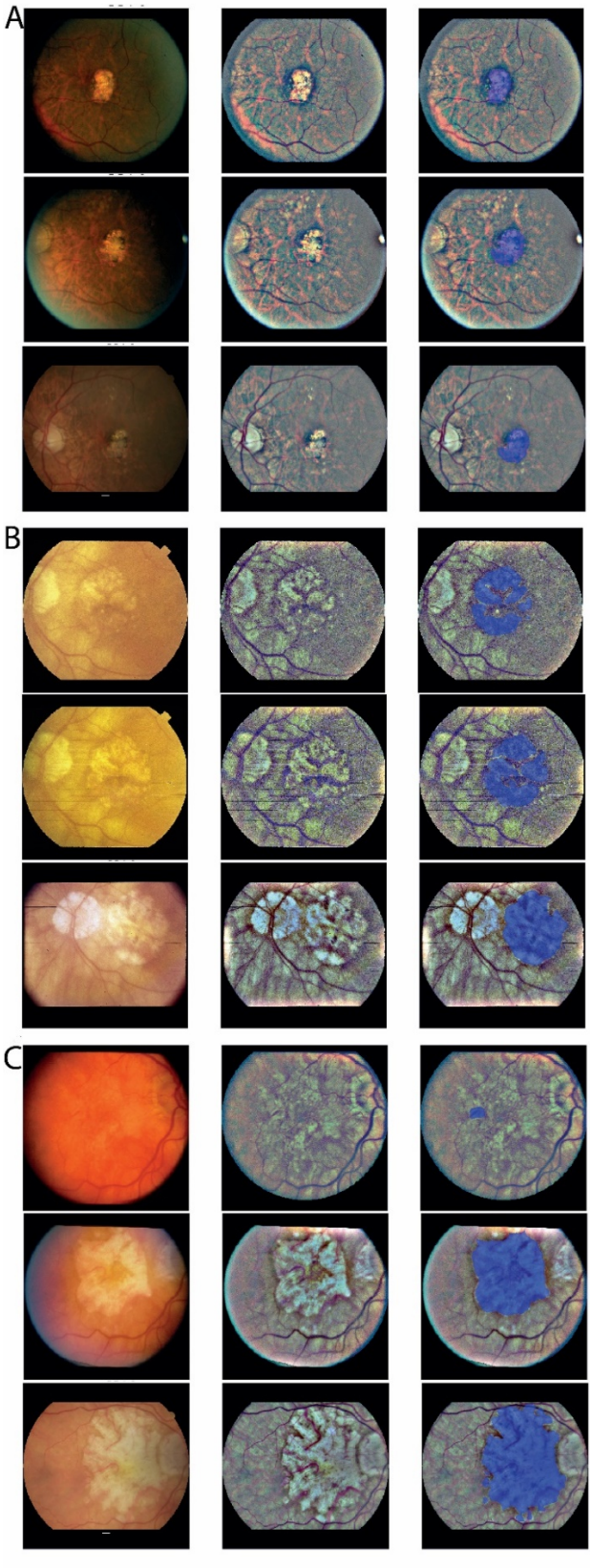
Visual impairment was classified into four categories in accordance with the World Health Organization International Classification of diseases ICD-11, see eMethods. : blindness <0.05 (<20/400 Snellen (ft)); severe visual impairment <0.1 (<20/200 Snellen (ft)); moderate visual impairment <0.33 (<20/63 Snellen (ft)); and mild visual impairment <0.5 (<20/40 Snellen (ft)).

Calculations were made using SPSS (IBM Corp. Released 2012 IBM SPSS Statistics for Windows, Version 25.0 Amonk, NY: IBM Corp). Graphical outputs were constructed with GraphPad Prism 7 (GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com").

Genetic risk score

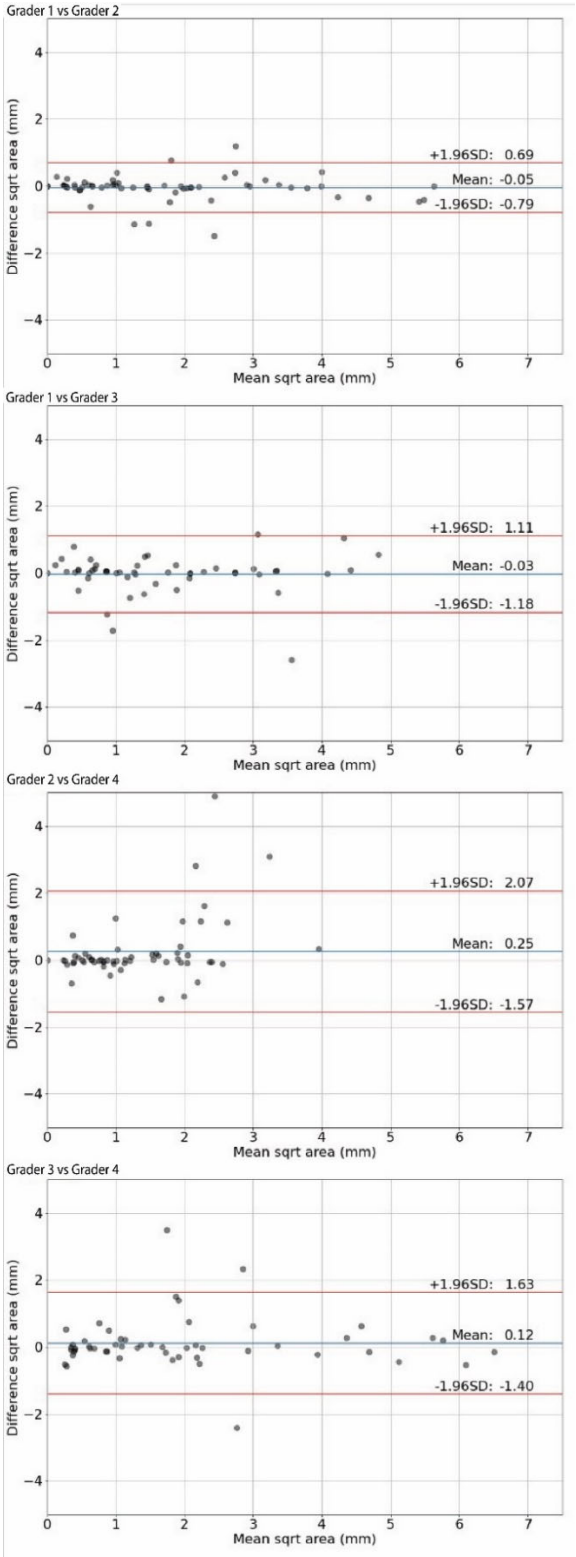
To calculate the genetic risk for each person we used the beta's of the major risk SNPs from the Fritsche *et al*. 2016 paper[7]. When SNPs were not available a proxy was used; *CHF* rs1061170 as proxy for rs10922109 (beta -0.6733) and rs1329424 for rs570618 (beta 0.5539). We used *ARMS2* SNP rs10490924 as a proxy for rs3750846 (beta 1.0750), for *C3* rs2230199 (beta 0.3853) no proxy was needed. Beta's were multiplied by the dosage and subsequently summed for each individual.

Supplement Figure 1. Grading of geographic atrophy



Grading of geographic atrophy. Left column shows the fundus photo, middle column shows the enhanced photo, right column shows the delineated atrophic area. Figure A shows slow enlagerment over a follow up time of 11 years. Figure B shows medium enlargement over a follow-up time of 11 years. Figure C shows fast enlargement over a follow-up time of 12 years.

Supplement Figure 2. Bland-Altman plot



Bland-Altman plot showing the difference square root area in mm and mean square root area in mm for different pairs of graders.

References

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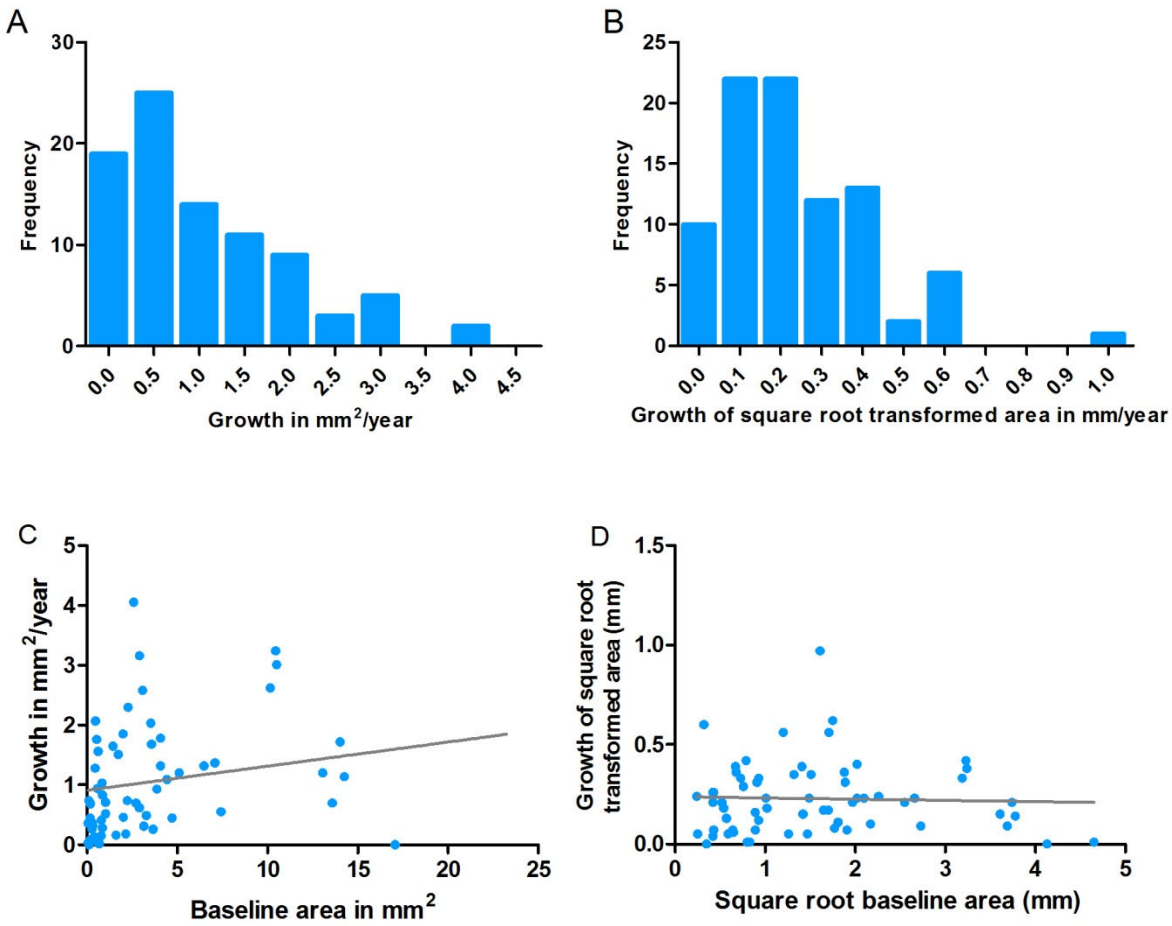
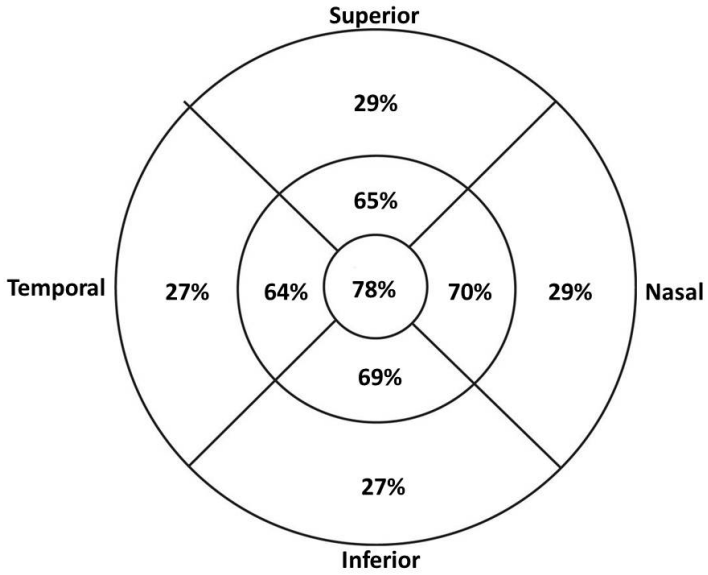
eFigure 1. Distribution of geographic atrophy enlargement



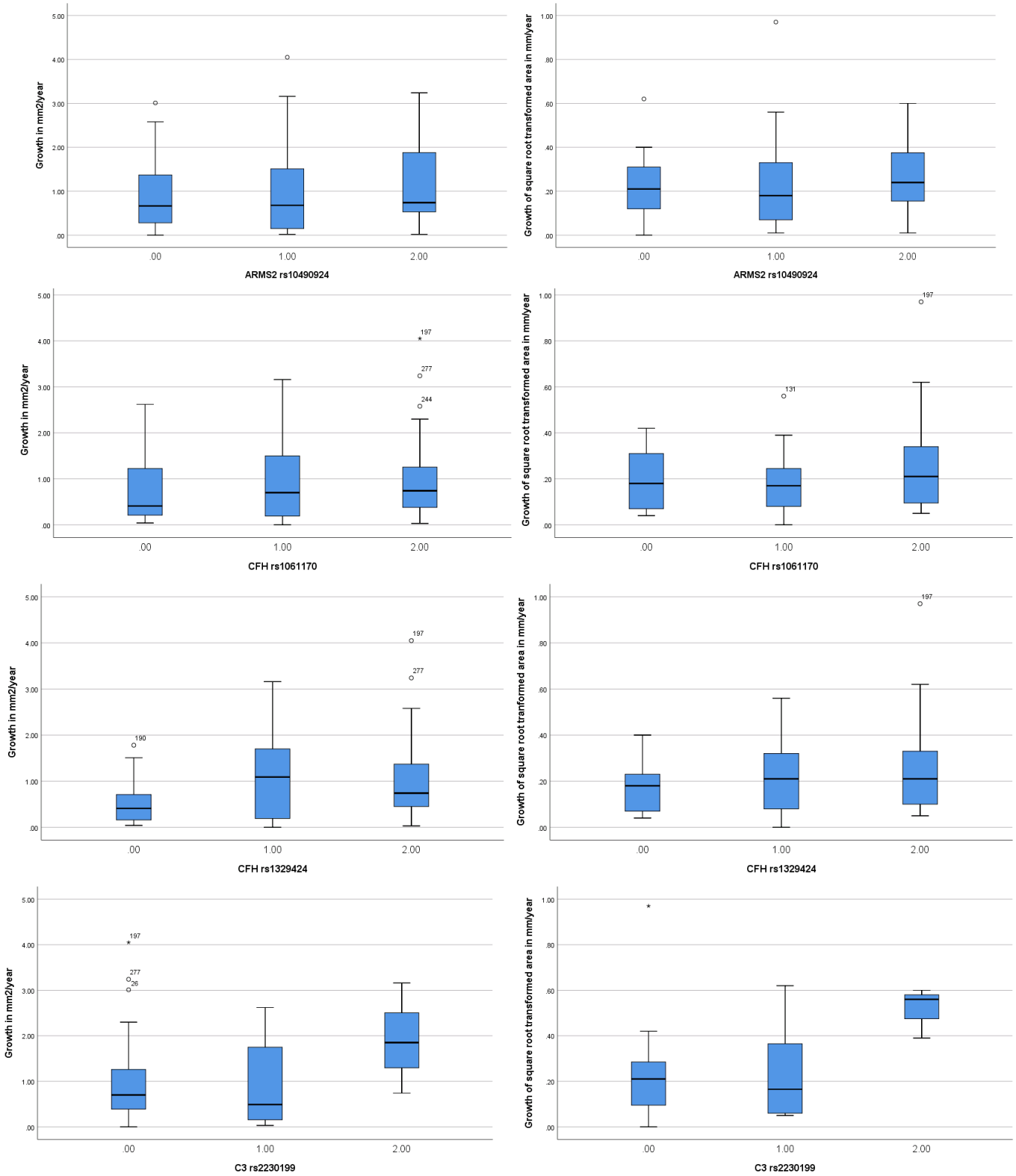
Distribution of GA enlargent in mm^2/year and mm/year (Figure a and b). Enlargement related to start area before and after square root transformation (Figure c and d).

eFigure 2. Geographic atrophy in ETDRS grid



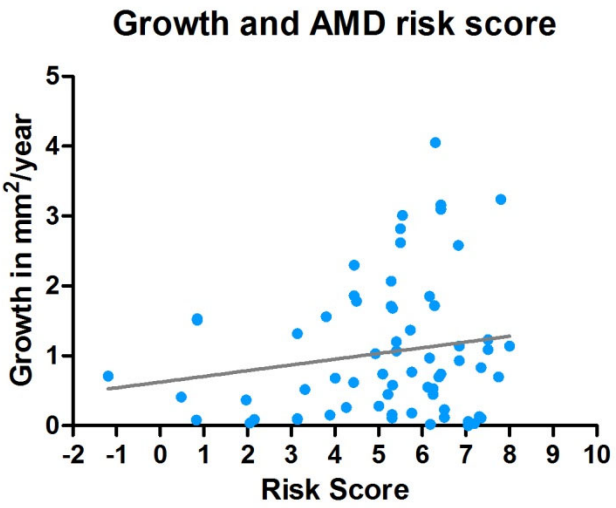
Areas involved of the ETDRS grid involved in incident GA.

eFigure 3. Geographic atrophy enlargement related to single-nucleotide polymorphisms



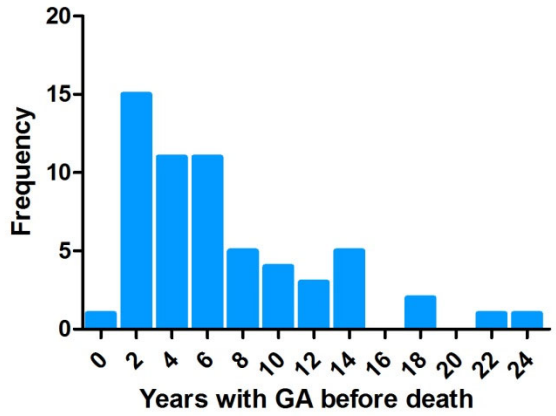
Enlargement and enlargement of square root transformed area as a function of ARMS2 SNP (rs10490924), CFH SNPs (rs1061170 and rs1329424) and C3 SNP (rs2230199)

eFigure 4. Geographic atrophy enlargement and age-related macular degeneration risk score



The correlation of enlargement with the AMD risk score including genetic, environmental and phenotypic factors.

eFigure 5. Years with geographic atrophy before death



Frequency histogram of years with GA before death.