Bivariate Modeling of Genetic Effects on AMD Progression with Intermittent Assessment Times

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Background

•**A**ge-related **M**acular **D**egeneration (AMD), the leading cause of blindness in the developed world, accounts for more than 50% of all blindness in the United States.

•It is a neurodegenerative and non-reversible disorder, progressing from early to late stages

•Multiple large-scale genetic studies had remarkable successes in identifying disease-susceptibility genes for AMD[1]. However, the genetic causes for progression to late-AMD have not been well studied yet.

Objectives

1. Evaluate effects of known AMD risk variants on disease progression.
2. Estimate joint AMD progression-free probabilities in both eyes.

Study Population

•Study Population: Caucasian patients from AREDS (Age-Related Eye Disease study)[2]

- Longitudinal records of ocular examination and fundus photography were collected.
- Participants were examined every 6-12 months for up to 12 years.
- Severity of AMD was scaled on 1-12, with ≥ 9 being considered as late AMD.
- Late AMD: GA (dry AMD) or CNV (wet AMD) or both.
- Two eyes from the same subject could progress differently and each eye was assessed with a severity score at each visit.
- Known AMD risk alleles were obtained.

Data

•2750 Caucasian AMD subjects were genotyped

•Outcome: **Bivariate** time-to-late AMD for each eye of each patient

- True event times of all eyes are censored due to intermittent assessment times.
- Each eye's interval (L,R] is determined by its severity score at assessment times.
- Three censoring types: left, right and interval censor.

•Genetic factor: Genetic Risk Score (GRS)

- A weighted average of 34 known AMD risk variants with weights derived from the recent case-control AMD Consortium study.[1]
- Larger GRS means greater AMD risk.

•Non-genetic factors: education (>high school, ≤high school), smoking status (Yes, No)

Methods

•NPMLE of the joint distribution for bivariate interval-censored data[3]:

- estimate the joint progression-free probability for each GRS group: high, medium and low.
- estimate the marginal progression-free probability in each eye for each GRS group.
- cannot infer genetic effects on progression to late-AMD.

•Semiparametric regression for bivariate interval-censored data[4]:

- implement a latent Poisson-based EM algorithm.
- estimate covariate effects on progression to late-AMD.
- a conditional approach, using random effect to account for between-observation correlation within a cluster.

Results (I)

•Estimation of marginal and joint progression-free probabilities (Figure 1-3):

- Higher GRS corresponds to lower progression-free probability.
- Proportions of observed late-AMD are larger in higher GRS groups.

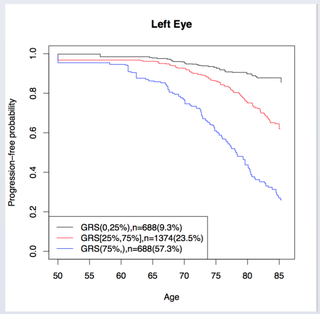

Figure 1: Marginal progression-free probability in left eye, separated by three GRS groups

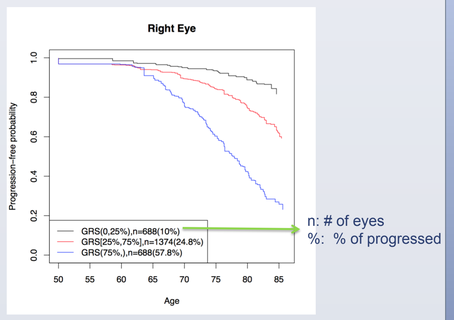

Figure 2: Marginal progression-free probability in right eyes, separated by three GRS groups

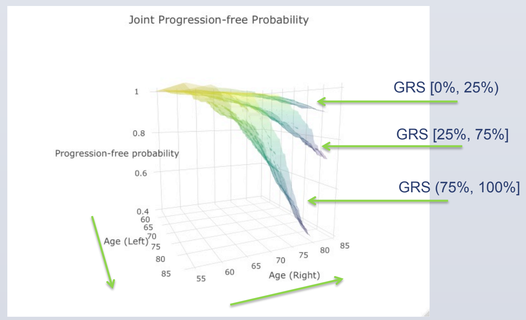

Figure 3: Joint progression-free probability in both eyes for three GRS groups

Results (II)

•Covariate effects on AMD progression (Table 1):

- Subjects with high or medium GRS are more likely to progress to late-AMD.
- Subjects who smoke are more likely to develop late-AMD.
- Subjects with higher education are less likely to progress to late-AMD.
- All estimates are interpreted on the cluster level (i.e., individual level), not on the population level.

Covariate	Hazard Ratio	95% CI	p-value
GRS (75%, 100%] vs GRS [0%, 25%)	22.20	(17.20, 28.64)	3.17×10^{-124}
GRS [25%, 75%] vs GRS [0%, 25%)	3.56	(2.87, 4.42)	1.47×10^{-28}
Smoke (Yes vs No)	1.92	(1.57, 2.33)	7.97×10^{-11}
Education (>High school vs ≤ High school)	0.51	(0.41, 0.63)	6.77×10^{-10}

Table 1: Bivariate modeling of AMD progression by covariates GRS, smoke and education

Conclusions

•Genetic risk score from multiple known AMD risk variants significantly affects the progression to late AMD.

•Higher genetic risk score corresponds with greater risk of progression to late-AMD.

Future Work

Establish a copula model for bivariate interval-censored data to:

- estimate joint progression-free probabilities of both eyes.
- evaluate the association between two eyes.
- perform GWAS to discover risk variants for AMD progression.

References

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