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Determinants and Heritability of Intraocular Pressure and Cup-to-Disc Ratio in a Defined Older Population

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Abstract

Purpose—To investigate the heritability of intraocular pressure (IOP) and cup-to-disc ratio (CDR) in an older well-defined population.

Design—Family-based cohort study.

Participants—Through the population-based Salisbury Eye Evaluation study, we recruited 726 siblings (mean age, 74.7 years) in 284 sibships.

Methods—Intraocular pressure and CDR were measured bilaterally for all participants. The presence or absence of glaucoma was determined by a glacuoma specialist for all probands on the basis of visual field, optic nerve appearance, and history. The heritability of IOP was calculated as twice the residual between-sibling correlation of IOP using linear regression and generalized estimating equations after adjusting for age, gender, mean arterial pressure, race, self-reported diabetes status, and history of systemic steroid use. The heritability of CDR was calculated using the same model and adjustments as above, while also adjusting for IOP.

Main Outcome Measures—Heritability and determinants of IOP and CDR, and impact of siblings' glaucoma status on IOP and CDR.

Results—We estimated the heritability to be 0.29 (95% confidence interval [CI], 0.12–0.46) for IOP and 0.56 (95% CI, 0.35–0.76) for CDR in this population. Mean IOP in siblings of glaucomatous probands was statistically significantly higher than in siblings of normal probands (mean difference, 1.02 mmHg; $P = 0.017$). The mean CDR in siblings of glaucomatous probands was 0.07 (or 19%) larger than in siblings of glaucoma suspect referrals ($P = 0.045$) and siblings of normal probands ($P = 0.004$).

Conclusions—In this elderly population, we found CDR to be highly heritable and IOP to be moderately heritable. On average, siblings of glaucoma patients had higher IOPs and larger CDRs than siblings of nonglaucomatous probands.

Primary open-angle glaucoma (POAG) is the second most common cause of blindness in the world[1] and affects approximately 2.2 million Americans.[2] Although the diagnosis of POAG centers on the characteristic excavation and atrophy of the optic nerve head and functional deficit measured by visual field (VF) change,[3] the heritability of intraocular pressure (IOP) and cup-to-disc ratio (CDR) have not been studied extensively thus far, despite the well-established role of heredity in POAG.

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Family aggregation of glaucoma was first recognized in 1869 by von Graefe,[4] followed by Duke-Elder's description of an autosomal dominantly inherited type of glaucoma.[5] Since then, several modes of glaucoma inheritance have been proposed by epidemiologists, including sex-linked recessive,[6] autosomal recessive,[7,8] autosomal dominant,[9,10] and multifactorial.[11,12] In 1987, Teikari estimated the heritability of chronic open-angle glaucoma to be 13%, based on the Finnish Twin Cohort Study,[13] which supports a polygenic and/or multifactorial mode of transmission. To date, 6 different chromosomal loci have been identified for POAG,[14–19] including the myocilin (*MYOC*)[20] and optineurin (*OPTN*)[21] genes.

Although no longer part of the definition of POAG in most studies,[3] increased IOP remains an important risk factor for the disease.[22] Data are limited regarding the heritability of IOP, with only 2 studies published to date. In 1970, Levene et al reported the first estimate of heritability of IOP, between 0.40 and 0.50.[23] More recently, Klein et al reported a heritability estimate of 0.36, based on correlations in sibling pairs, parent– child pairs, and cousin pairs.[24]

A genetic study of CDR among first-degree relatives first reported correlations highly suggestive of polygenic multi-factorial inheritance in 1967.[25] A 1975 twin study provided the first assessment of heritability of CDR, which was estimated to be between 0.60 and 0.80.[26] However, the study graded horizontal CDR rather than vertical CDR, which carries higher diagnostic value for early detection of glaucomatous optic nerve damage.[27] Most recently, Klein et al estimated heritability of vertical CDR to be 0.48, based on measurements by stereoscopic fundus photography.[24] With the exception of the Klein et al study, little recent attention has been given to the potentially important area of CDR heritability, and mechanisms have been largely unexplored.

In this study, we estimate the heritability of IOP and CDR from a cohort of sibships recruited through the Salisbury Eye Evaluation study. In addition, we also report the distribution of IOP and CDR among siblings of glaucomatous probands versus siblings of normal probands.

Materials and Methods

Subjects and General Design

Between 1993 and 1995, a random sample of potential participants (ages 65 to 84 years) was chosen from the Health Care Financing Administration Medicare database and recruited from Salisbury, located on the Eastern Shore of Maryland, to engage in the population-based Salisbury Eye Evaluation study.[28] The cohort was invited for a follow-up examination including VF testing, optic nerve head imaging, and IOP measurement. All subjects with abnormal screening examination results (see below) were referred to a fellowship-trained glaucoma specialist (DSF) for a definitive examination. In addition, locally resident siblings (residing ≤100 miles from Salisbury or Baltimore, Maryland) were invited to a central site for measurement of IOP and CDR (see below). All participants completed questionnaires regarding medical history, including use of systemic steroids and the presence of diabetes, and seated systolic and diastolic blood pressures (BPs) were measured for all subjects. Informed consent was obtained from all participants before administration of any tests. All protocols of the study adhere to the tenets of the Declaration of Helsinki and were reviewed and approved by the Johns Hopkins Medical Institutions Review Board. The study was carried out in compliance with the requirements of the Health Insurance Portability and Accountability Act.

Examination Techniques and Definitions

Screening Examination—For all participants, an optometrist assessed the vertical CDR in a masked fashion (with no knowledge of the participants' glaucoma status) using a 90-diopter (D) lens (Volk, Mentor, OH) during biomicroscopy (Topcon Slit Lamp, model SL 7E, Topcon Europe B.V., Capelle aan den Ijssel, The Netherlands). The optometrist also measured the IOP using a Tonopen (Mentor Tonometer, TonoPen XL, Bio-Rad Inc., Santa Ana, CA) fitted with a disposable rubber cover after administration of 1 drop of proparacaine hydrochloride (0.5%) in each eye for anesthesia. Two IOP readings with a coefficient of variation of <5% (as estimated by the Tonopen) were taken for each eye. If the 2 readings differed by <5 mmHg, then the mean of the 2 values was calculated; if they differed by >5 mmHg, a third reading (with a coefficient of variation of <5%) was taken and the median recorded. The Tonopen was calibrated before each day of use as per the instruction manual.

Probands were referred for a definitive examination by a glaucoma specialist if they met any one of the following criteria (siblings were not referred for a definitive examination):

1. Previously diagnosed with glaucoma or a history of glaucoma drug therapy or surgery.
2. Cup-to-disc ratio of ≥0.7 in one eye or differing by ≥0.2 between eyes (based on a screening image of the optic nerve obtained with a Discam video imaging device [Marcher Enterprises Ltd., Hereford, United Kingdom]).
3. Intraocular pressure of ≥22 mmHg.
4. Abnormal Swedish interactive testing algorithm Fast VFs on a Humphrey Field Analyzer II machine (Zeiss-Humphrey Systems, Dublin, CA) that remain abnormal upon repeated VF testing. A VF was considered abnormal if the glaucoma hemifield test was outside normal limits, borderline, or had abnormally high sensitivity or generalized reduction of sensitivity, or if the pattern standard deviation (SD) was abnormal at the $P<0.05$ level or worse.

Definitive Examination—The referred patients underwent a definitive examination by a glaucoma specialist (DSF), including Swedish interactive testing algorithm Standard VFs on a Humphrey Field Analyzer II, gonioscopy, and clinical examination of the optic nerve.

The glaucoma specialist reassessed IOP using Goldmann applanation tonometry in a masked fashion, using a random start setting and a second observer to read and reset the tonometer. Two measurements were performed for each eye, with a third reading taken and the median recorded if the 2 readings differed by >1 mmHg. The CDR was reassessed by using both the 90-D lens during biomicroscopy (same make and model as above) and stereoscopic fundus photography (Topcon America Corp., Paramus, NJ). Stereopsis was achieved by standard decentration of the camera angle. A comprehensive review of all available ocular records was performed by the glaucoma specialist.

Study Definitions—For the purpose of the present analysis, subjects were defined as having glaucoma if glaucomatous optic nerve damage was present in association with compatible VF loss, or if severe optic nerve damage was present without a reliable reproducible VF and glaucoma was determined to be the underlying mechanism based on review of records. All probands referred for definitive examination (see criteria above) but not found to have glaucoma were defined as glaucoma suspect referrals.

Intraocular Pressure Adjustment

To approximate the pretreatment value of IOP in eyes with current use of pressure-lowering medications or history of glaucoma surgery, we adjusted the reported IOP values for these subjects by an amount representative of the effect of standard pressure-lowering treatments. Based on data from the Collaborative Initial Glaucoma Treatment Study,[29] Ocular Hypertension Treatment Study,[22] and Early Manifest Glaucoma Trial,[30] we chose a 25% reduction in IOP as representative. Thus, we increased the reported IOP in eyes with a history of pressure-lowering treatment by 33% to approximate the pretreated IOP values.

Statistical Methods

For full siblings, the heritability of a quantitative trait can be estimated as twice the residual between-sibling correlation, after adjusting for the possible confounding effects of common environmental or biological factors. We performed linear regression analysis of IOP and CDR using extended generalized estimating equations[31] and calculated heritabilities using an exchangeable correlation structure. Heritability estimates for IOP were adjusted for age, gender, race, and mean arterial pressure (calculated as 2/3 × diastolic BP + 1/3 × systolic BP); we performed the analysis using IOP values both with and without adjustment for pressure-lowering medication/surgery (see above). Cup-to-disc ratio heritability analyses included variables for IOP, age, gender, and race. All analyses were performed using R-project statistical software[32,33] and the *geepack* (generalized estimating equation package) library. We also compared differences of adjusted IOP and CDR between the siblings of glaucomatous probands, glaucoma suspect referrals, and normal probands by including 2 group variables in our linear regression models. One participant was removed from regression analyses because of an extreme outlying IOP measurement of 41.5 mmHg that was 8 SDs above the overall mean IOP of 15.3 mmHg.

For comparing IOP readings using the Tonopen with those obtained using the Goldmann applanation tonometer, we used differences of 3 mmHg as the cutoffs to calculate percentage agreement. We also calculated the intraclass correlation between the IOP readings, as described elsewhere.[34] When performing weighted κ coefficient analyses for CDR, as described by Tielsch et al,[35] for comparisons between the study optometrist and study ophthalmologist, we assigned quadratic weights of 1, 0.9, 0.5, and 0 to subjects for whom the examiners differed by 0, >0 to 0.1, >0.1 to 0.2, and >0.2, respectively. Weighted κ coefficient analysis for IOP was performed in a similar fashion, with quadratic weights of 1, 0.937, 0.75, 0.437, and 0 for differences of 0, >0 to 1 mmHg, >1 to 2 mmHg, >2 to 3 mmHg, and >3 mmHg, respectively.

Results

We report heritability estimates based on 284 sibships including 726 subjects, with a mean age of 74.7±7.0 years. Among these, 26.9% of participants were black, and 40.8% were male (Table 1). Characteristics of the subjects with regards to IOP, CDR, BP, diabetes, and history of systemic steroid use are also given in Table 1.

We calculated the heritability of IOP (adjusted for surgery/medication) to be 0.29 (95% confidence interval [CI], 0.12– 0.46), which was identical to the heritability calculated using unadjusted IOP values (0.29; 95% CI, 0.20 – 0.39). When analyzed separately by race, the IOP heritability estimate for blacks did not differ significantly from zero, whereas the IOP heritability for whites was calculated to be 0.35 (95% CI, 0.24 – 0.46). Higher mean arterial pressure (β = 0.04/mmHg, P = 0.0001), black race (β = 0.66, P = 0.03), and history of diabetes (β = 0.66, P = 0.01) were all statistically significantly associated with higher IOP, whereas older age (β = −0.04 per year, P = 0.04) was associated with lower IOP. Although

women had, on average, 0.4 mmHg higher IOPs than men, this difference did not attain statistical significance ($P = 0.08$). Self-reported use of systemic steroids was not associated with IOP ($P = 0.49$) and was not included in the final model. Results of linear regression analyses and the heritability estimate of IOP are reported in Table 2.

We estimated the heritability of CDR to be 0.56 (95% CI, 0.35– 0.76). When analyzed separately by race, the CDR heritability for blacks was estimated to be 0.43 (95% CI, 0.25–0.61), whereas that for whites was calculated to be 0.62 (95% CI, 0.46 – 0.78). Only gender and race were found to be statistically significantly associated with CDR. The mean age-, race-, and IOP-adjusted CDR was slightly smaller for women ($\beta = 0.03$, $P = 0.007$). Black participants had, on average, CDRs larger than those of white individuals ($\beta = 0.08$, $P<0.0001$). Increased IOP was marginally associated with larger CDR, although this finding did not attain statistical significance ($\beta = 0.03$/10 mmHg, $P = 0.06$). Neither mean arterial pressure ($P = 0.33$), diabetes ($P = 0.71$), nor the use of systemic steroids ($P = 0.99$) was associated with CDR. Results of our heritability analyses for CDR are reported in Table 3.

The study population included 257 probands whose glaucoma status (i.e., normal, glaucoma suspect referral, or glaucoma) was confirmed by a glaucoma specialist (DSF) and 431 siblings of these probands whose glaucoma status was not assessed. When the siblings were categorized based on the glaucoma status of their respective probands, there were 49 in the normal group, 331 in the glaucoma suspect referral group, and 50 in the glaucoma group, with mean ages of 73.1±7.7 years, 73.2±7.2 years, and 75.2±7.4 years, respectively.

The mean unadjusted IOPs in siblings of glaucomatous probands, glaucoma suspect referrals, and normal probands were 16.5±3.8, 15.4±3.5, and 14.7±3.06 mmHg, respectively. After adjusting for age, gender, and race, the mean IOP of siblings of glaucomatous subjects was 1.02 mmHg ($P = 0.017$) higher than that of siblings of glaucoma suspect referrals and 1.73 mmHg ($P = 0.065$) higher than that of siblings of normal participants. The IOP difference between siblings of glaucoma suspect referrals and normal probands did not differ statistically (mean difference, 0.71; $P = 0.19$).

Mean unadjusted CDRs were 0.43±0.18 for siblings of glaucomatous probands, 0.36±0.13 for siblings of glaucoma suspect referrals, and 0.37±0.14 for siblings of normal probands. When adjusting for age, gender, and race, the CDR of siblings of glaucomatous probands was, on average, 0.07 (or 19%) larger than CDRs of the other groups ($P = 0.004$ and $P = 0.045$ for the siblings of normal and glaucoma suspect referral groups, respectively).

Clinical CDRs determined by the optometrist showed "substantial"[36] agreement (weighted κ, 0.69; 95% CI, 0.60 – 0.78; $r = 0.82$; $P<0.0001$) with the clinical grades of the glaucoma specialist for left eyes and "moderate" agreement (weighted κ, 0.56; 95% CI, 0.41– 0.71; $r = 0.70$; $P<0.0001$) with Discam stereo video images of the left eye. We also compared IOPs measured with the Tonopen (used by the optometrist) and measured with Goldmann applanation tonometry (used by the glaucoma specialist), which yielded an agreement of 72.7%, an intraclass correlation of 0.68 (95% CI, 0.62– 0.73), and a weighted κ of 0.70 (95% CI, 0.57–0.83) for the left eyes, indicating substantial agreement between the 2 instruments.[36] Findings for the right eye for both IOP and CDR were similar.

Discussion

We determined the heritability of IOP in this population to be 0.29, which is in close agreement with the value of 0.36 recently reported for the Beaver Dam population.[24] Our study population consisted of 73.1% whites, whereas 99% of the Beaver Dam population was white.[37] When we calculated the heritability of IOP separately by race, we obtained an estimate of 0.35 for whites, which compares well with the Beaver Dam estimate. On the

other hand, our study population is considerably older than that of Levene et al, who reported values at 0.40 to 0.50.[23] Nearly 40% of our study subjects had medical and ocular histories that might have impacted IOP, including pressure-lowering surgery and/or medication, diabetes, steroid use, and hypertension. The advanced age of our study population may also emphasize the cumulative contribution of other, unmeasured environmental components to the total phenotypic variance, thus further lowering the estimates of IOP heritability. We cannot completely discount the possibility of inaccuracy, as our estimate was based on IOP readings taken by Tonopen, whereas both Levene et al[23] and Klein et al[24] measured IOP by Goldmann applanation tonometry. However, we found substantial agreement between the 2 modes of IOP measurement, as has been reported elsewhere.[38] This argues against systematic error due to instrumentation.

We estimated the heritability of CDR to be 0.56, which compares well with the previous reported values of 0.48 to 0.80.[24,26] It is not surprising that a simple cross-sectional measurement of CDR should show higher heritability than IOP, which exhibits substantial diurnal variation and is more sensitive to the effects of environmental influences such as drugs.

We tested several variables in our model to explore their relationship to IOP and CDR. In our analysis, age and IOP are inversely correlated, in contrast to most previous studies of this relationship.[39–44] However, other reports suggest that cardiovascular risk factors (e.g., systolic BP, age, hematocrit, erythrocyte sedimentation rate, pulse rate, serum cholesterol) largely explain the association between age and IOP.[40,45] Several Japanese studies adjusting for the effect of BP as we did here also report a negative correlation between age and IOP.[46,47] Previous studies have shown that BP has independent positive associations with both IOP and age,[48–51] which suggests that BP should be adjusted as an independent variable when investigating the relationship between age and IOP.

We found diabetes and black race to be associated with higher IOP, which is consistent with previous reports.[39,48,49,52–55] Male gender is associated with greater CDR, which is in agreement with the findings of a higher risk of POAG in the male gender reported by the Barbados Eye Study, Framingham Eye Study, and the Long Island Glaucoma Case-Control Study.[56–58] Likewise, the association between black race and greater CDR reaffirmed the reports of previous studies.[59,60]

We compared several characteristics between the siblings of probands with and without a definitive diagnosis of glaucoma, to further examine the role of inheritance in glaucoma pathogenesis. The higher IOP in siblings of glaucomatous probands compared with those of normal probands implies that at least a component of the genetic control of the glaucoma phenotype is manifested through variation in IOP.

The observed differences in mean CDR between siblings of normal versus glaucomatous probands when controlling for IOP affirm the notion that increased CDR in glaucoma may be a partially inherited trait rather than a purely acquired one. Burk et al's observation of a higher occurrence of normal-tension glaucoma in eyes with a large cup area,[61] along with Schwartz et al's findings that the size of the cup increases with age apart from the effect of pressure,[62] suggests that a disc vulnerability component exists in the genetics of POAG, rendering the optic disc more susceptible to glaucomatous changes independent of IOP. Several studies provide the molecular substrate for this hypothesis. Zeimer and Ogura have demonstrated decreased mechanical compliance of the optic nerve head as a predisposition for glaucomatous optic nerve damage,[63] whereas Quigley et al have shown alterations in the elastic elements of the lamina cribrosa in glaucomatous eyes, compromising the elastic tissue support.[64] Alternatively, Bengtsson's estimate of 0.67 for heritability of cup diameter,

with an equally high estimate for disc diameter, suggests that inheritance of CDR may be a biometric phenomenon and not solely an expression of propensity for damage.[65]

It should be noted that increased CDR was a referral criterion for definitive examination and also one of the defining criteria for glaucoma. To the extent that this fact underlies the observed difference in mean CDR between siblings of normal versus glaucomatous probands, it is further confirmation of the heritability of CDR.

The finding in this and other studies of moderate heritability of IOP may be consistent with the effect of genes such as *MYOC*, mutations in which are thought to result in obstruction of aqueous outflow[66] through a dominant negative modality.[67] Our finding of high heritability of CDR may be more consistent with the mechanism of action of genes such as *OPTN*. This gene exerts a neuroprotective effect against tumor necrosis factor α, and mutations might confer vulnerability to the optic nerve irrespective of the effect of IOP.[68]

Several potential limitations to this study should be noted. Our study incorporated subjective clinical CDR gradings rather than stereoscopic photographic measurements. Even though we have performed the appropriate agreement analysis between the 2 methods, the use of subjective clinical data can theoretically pose systematic bias. We also used the Tonopen instead of Goldmann applanation for IOP measurements. Although we found substantial agreement between the 2 instruments with means that were within 1 mmHg of each other (data not shown), this does not entirely preclude the possibility of systematic bias.

The study population has relatively high frequencies of steroid use and diabetes, which may suggest a potentially biased pool. However, 71.7% of all available siblings of the original cohort agreed to be contacted. This relatively high level of participation argues against the possibility of significant bias of ascertainment.

In summary, we estimated the heritability of IOP and CDR in an older study population to be 0.29 and 0.56, respectively. We also found significantly elevated IOP and CDR in the siblings of glaucomatous versus normal probands, further affirming the notion that there are components of POAG genetics responsible for increased IOP and CDR. The disc vulnerability component of POAG genetics seems independent of IOP in this population. Future studies will attempt to identify more completely the genes responsible for these heritable traits.

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Table 1

Characteristics of the Study Population

	N (%)	Mean±SD
Total	726 (100)	
Gender		
Male	296 (40.8)	
Female	430 (59.2)	
Race		
White	531 (73.1)	
Black	195 (26.9)	
Medical history		
Surgery/medication*	29/57 eyes (3.9)	
Diabetes	154 (21.2)	
Steroid use	97 (13.4)	
Age (yrs)		74.7±7.0
Blood pressure (mmHg)		
Systolic		134.9±20.1
Diastolic		69.1±11.9
MAP		91.6±12.7
Mean IOP (mmHg)		15.3±3.3
Mean CDR		0.37±0.15

CDR = cup-to-disc ratio; IOP = intraocular pressure; MAP = mean arterial pressure; SD = standard deviation.

* Ocular surgery and/or drug therapy performed for the purpose of reducing IOP.

Table 2

Estimated Linear Regression Coefficients (βs), Standard Errors, *P* Values, and Heritability Estimates for Intraocular Pressure (IOP)

Variable	β (mmHg)	Standard Error	*P* Value
Age	−0.040	0.019	0.04
Female gender	0.41	0.23	0.08
Black race	0.66	0.31	0.03
Mean arterial pressure	0.035	0.009	0.0001
Diabetes	0.66	0.27	0.01
Heritability of IOP*	0.29	0.08	0.0008
Blacks	0.14	0.062	0.25
Whites	0.35	0.056	0.0017

*Calculated as twice the residual between-sibling correlation after adjusting for age, gender, race, mean arterial pressure, and diabetes status.

Table 3

Estimated Linear Regression Coefficients (βs), Standard Errors, *P* Values, and Heritability Estimates for Cup-to-Disc Ratio (CDR)

Variable	β (mmHg)	Standard Error	*P* Value
Age	0.0013	0.0009	0.14
Female gender	−0.028	0.010	0.007
Black race	0.079	0.016	−0.0001
Intraocular pressure	0.003	0.002	0.058
Heritability of CDR*	0.56	0.10	−0.0001
Blacks	0.43	0.092	0.017
Whites	0.62	0.084	0.0002

*Calculated as twice the residual between-sibling correlation after adjusting for age, gender, race, and intraocular pressure.