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Heritability of intraocular pressure: a classical twin study

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ABSTRACT

Aims: To estimate the heritability of intraocular pressure (IOP) by performing a classical twin study and to determine whether the use of different instruments influences calculation of eye IOP heritability.

Methods: Twin pairs were recruited to participate from the TwinsUK Adult Twin Registry at St. Thomas' Hospital London. IOP was measured using Goldmann applanation tonometry (GAT). A subset of twins also had their IOP measured using the Ocular Response Analyser (ORA; Reichert, Buffalo, NY) and the Dynamic Contour Tonometer (DCT, Pascal; Swiss Microtechnology AG, Port, Switzerland). We compared the covariance of IOP within monozygotic (MZ) and dizygotic (DZ) pairs using genetic modelling techniques to determine the relative contribution of genes and environment to the variation in IOP seen in this population.

Results: Data for 422 twin pairs (211 MZ; 211 DZ) were analysed. The mean IOP for GAT was 15.4 (SD 2.7) mm Hg (range: 8.7–26.2 mm Hg). The MZ correlations were significantly higher than DZ for IOP measured by GAT, DCT and ORA (correlation coefficients: GAT: 0.57:0.39, DCT: 0.62:0.36, Goldmann-correlated ORA (IOPg) 0.73:0.47, for MZ:DZ twins, respectively). Modelling suggested heritability for GAT IOP of 0.62, with individual environmental factors accounting for 0.38 of the variation.

Conclusion: This study demonstrated that genetic effects are important in determining IOP in this twin population. IOP readings differed depending upon the instrument used, and this resulted in different heritability values; genetic factors explained 62%, 63% and 74% of the variation in IOP using GAT, DCT and ORA IOPg, respectively. Environmental factors determined the remainder of the variation.

Elevated intraocular pressure (IOP) is the principal modifiable risk factor for the development and progression of open angle glaucoma.¹ Glaucoma is the second leading cause of blindness, affecting an estimated 70 million people worldwide.² IOP remains an important risk factor for glaucoma, although it no longer forms part of the definition of the disease.^{3–5} It has been shown that changing aqueous humour production alters the IOP,⁶ and most glaucoma drugs act by reducing aqueous production or increasing its outflow. Experimental elevation of IOP can indeed induce glaucomatous optic neuropathy.⁷ Segregation analyses in the Beaver Dam Eye Study suggested a polygenic component with environmental influence for IOP.⁸ In previous work, the researchers estimated 36% heritability for IOP after adjusting for covariates.⁹ A commingling analysis from the Australian Blue Mountains Eye Study suggested the presence of a major gene contributing to 18%

of the variance of IOP.¹⁰ Novel genetic loci for IOP have been identified,^{8 11–15} but not yet replicated. The complexity of the phenotypic definition of glaucoma has contributed to the difficulties in identifying genes involved in this disease.¹⁴

Twin studies are an excellent method for studying the relative importance of genetic and environmental influences on a phenotype.¹⁵ The variance of a phenotype in a population is due to genetic and environmental factors. Because families share both genes and environment, it is difficult to separate out the effects of each. Because identical or monozygotic (MZ) twin pairs share the same genes, and non-identical or dizygotic (DZ) twins share on average half of their segregating genes, any greater concordance or correlation between MZ twins can be attributed to this additional genetic sharing. Twin models assume that both MZ and DZ twins share the same common family environment (the equal environment assumption).¹⁶ Factors such as perfect age matching and more similar environment allow twin studies to calculate a “maximal” genetic contribution to a trait. The heritability is the estimate of variance explained by genetic factors. We conducted a classical twin study to determine the heritability of IOP in an unselected sample of healthy twin volunteers by using modern genetic modelling techniques to compare the covariance of IOP between MZ and DZ twins.

To our knowledge, the only previous twin report on IOP heritability is from an elderly cohort Finnish twin study.¹⁷ The heritability estimate was 0.64. We set out to determine the heritability using the clinical standard of Goldmann applanation tonometry (GAT) and compared this with our heritability calculated from two newer methods of measuring IOP: the Ocular Response Analyser (ORA-Reichert, Buffalo, NY) and the Dynamic Contour Tonometer (DCT, Pascal; Swiss Microtechnology AG, Port, Switzerland). These instruments may allow an IOP measurement, which is less dependent on central corneal thickness (CCT), and also allow calculation of other potential variables of interest such as corneal hysteresis and pulse amplitude. The ORA is a non-contact tonometer that measures a Goldmann-equivalent IOP (IOPg), as well as a corneal-compensated IOP (IOPcc).^{18 19} The DCT, a contact tonometer, measures IOP with a concave tonometer head to reduce corneal deformation.²⁰

METHODS

Twins were recruited to participate in the TwinsUK Adult Twin Registry, held at St. Thomas' Hospital London, and were unaware of

any hypotheses or proposals for specific studies; only later were they invited to have an eye examination. Our institutional ethics committee approved the study, and all the subjects gave informed consent. Zygosity was determined by a standardised questionnaire²¹ and confirmed by DNA analysis of short tandem-repeat polymorphisms in those for whom there was any uncertainty about zygosity. As the study was a volunteer population-based study, subjects with glaucoma were not excluded. Because corneal refractive surgery alters corneal thickness, and this alters IOP measurement, subjects were excluded if they had undergone refractive surgery. Subjects were not excluded from the analyses if they underwent any other form of ocular surgery.

All IOP measurements for both twins of a pair were performed on the same day, at the same time of day, and by the same investigator (FC) to eliminate any potential biases. Each eye was tested twice, and the mean of all four IOP readings was used for subsequent analysis; where only one reading per eye was available, the mean of the two readings was used. For GAT, a drop of proxymethacaine 0.5% with fluorescein was instilled in each eye prior to testing the pressures. The tonometer dial was set first at 0 mm Hg, and increased until the end point was reached, for each eye. This was repeated by setting the tonometer at 40 mm Hg and reducing appplanation until the end point was determined.

A subset of the twins had data available from IOP measurements taken with the ORA tonometer and the DCT tonometer. When these two instruments were used, the order of testing was: ORA first, followed by the DCT and GAT. The reason for adopting this order was to deform the cornea as little as possible by selecting the instruments in order of least corneal deformability. In the case of the DCT, only measurements with a quality of 3 or higher were used, and the mean quality for DCT readings was 1.8. Other covariates collected at the time of examination included height (m) and weight (kg) to calculate the body-mass index (BMI), and blood pressure (systolic and diastolic).

Data handling and preliminary analyses were undertaken using STATA (Intercooled Stata for Windows 95, Version 5.0, 1997, StataCorp, College Station, TX). The covariance matrices for MZ and DZ twin pairs were used in the Mx genetic modelling program.²² This method is based on comparing the covariances of a measured trait between MZ and DZ twins. The observed phenotypic variance can be divided into additive genetic (A), dominant genetic (D), common environmental (C) and unique environmental (E) components. The common environmental component estimates the contribution of family environment, whereas the unique environmental component estimates the effects that apply only to each individual, including measurement error. The broad-sense heritability, which estimates the extent to which variation in IOP in a population can be explained by genetic variation, can be defined as the ratio of genetic variance (A+D) to total phenotypic variance (A+D+C+E). The best-fitting model is calculated by the

use of the Akaike Information Criterion (AIC). The AIC describes the model with best goodness of fit combined with parsimony (fewest latent variables) and is calculated as $2 \times$ the degrees of freedom—the model fit chi-square. The submodel with the lowest AIC is the best fitting.

RESULTS

A total of 864 Caucasian twin volunteers (432 twin pairs) were examined, of whom 91% were female. Historically, TwinsUK was set up to investigate predominantly female disorders, such as osteoporosis. Since then, the number of males recruited has increased, but the majority of twins who volunteer is still largely female. Only one reading per eye was available for six right eyes and 13 left; in all others, there were two readings per eye, and these were averaged. Ten pairs of twins were excluded from further analysis because of previous excimer laser refractive surgery; in nine cases, one of the pair had this performed, and in one pair, both twins had undergone this procedure. Data were available for 422 pairs of twins: 211 MZ pairs (mean age 50.9 years, SD 15.4, range 16–81) and 211 DZ pairs (mean age 55.9 years, SD 12.1, range 17–77). Seven subjects were previously diagnosed as having glaucoma (0.8% of the cohort), and a further five subjects were referred to local ophthalmology services (0.6%) for further investigation for glaucoma based on examination findings from this study. Exclusion of these subjects did not alter mean values and twin-pair correlations, and they were therefore included in the analysis. Data using the ORA were available for 343 pairs of twins (MZ: 169; DZ: 174). The DCT was used to collect data on 273 twin pairs (MZ: 141; DZ: 132).

The mean GAT IOP was 15.4 (SD 2.7) mm Hg (range: 8.7–26.2 mm Hg). Right and left eyes correlated significantly, with a GAT interocular correlation of 0.79 ($p < 0.001$). The interocular correlations for DCT and ORA respectively, were 0.81 ($p < 0.001$) and 0.78 ($p < 0.001$). The mean IOPs for DCT and ORA are shown in table 1. As can be seen in table 1, the values for MZ and DZ twins were similar and were normally distributed (not shown). The MZ and DZ intrapair correlation coefficients are also detailed in table 1 and show that the MZ twin pairs were more highly correlated than the DZ pairs for all four IOP measurements, which supports a genetic influence on IOP.

Genetic modelling suggested the best-fitting model for all four IOPs to be the AE model, meaning that additive genetic effects and individual environmental effects explained the variance (table 2). The calculated heritability (h^2) for GAT IOP was 0.62 (95% CI 0.54 to 0.69) with the remaining 0.38 proportion of variance due to individual environmental effects (95% CI 0.31 to 0.46). The h^2 for DCT was 0.63 (95% CI 0.58 to 0.71), for IOPg 0.74 (95% CI 0.67 to 0.76) and for IOPcc 0.71 (95% CI 0.63 to 0.77). The remaining proportion of variance due to individual environmental effects, for these IOP measures, is shown in table 3. After adjusting for age, BP, BMI, SE and CCT, the h^2 for GAT did not alter significantly: 0.64 (95% CI 0.55 to 0.71).

Table 1 Comparison of mean IOPs and correlations, using GAT, DCT and ORA

	No. of twins	Mean age (SD)	MZ	DZ	IOP/mm Hg (SD)	rMZ	rDZ
GAT	422	53.2 (14)	211	211	15.4 (2.7)	0.57	0.39
DCT	273	54.4 (14.1)	141	132	16.5 (2.7)	0.62	0.36
ORA (IOPg)	343	52.8 (14.4)	169	174	15.6 (3.1)	0.73	0.47
ORA (IOPcc)	343	52.8 (14.4)	169	174	16.2 (3.2)	0.67	0.46

DCT, dynamic contour tonometer; DZ, dizygotic; GAT, Goldmann applanation tonometry; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-equivalent intraocular pressure; MZ, monozygotic; ORA, ocular response analyser.

Table 2 Model fitting results for univariate analysis of intraocular pressure (IOP) using Goldmann applanation tonometry (GAT)

	Model	χ^2	Df	p	AIC
GAT IOP	ACE	6.814	3	0.078	0.814
	ADE	7.945	3	0.047	1.945
	AE	7.945	4	0.094	-0.055
	CE	20.263	4	0	12.263
	E	126.527	5	0	116.527

Best-fit models are highlighted in bold.

A, additive genetic; AIC, Akaike Information Criterion; C, common environment; D, dominant genetic; df, change in degrees of freedom between submodel and full model; E, unique environmental effects; χ^2 , chi-square goodness-of-fit statistic. p, probability that $\Delta\chi^2$ (change in χ^2 comparing submodel with full ADE or ACE and age model) is zero.

The correlation between IOP and age was weakly, but significantly, positive (correlation coefficient $r=0.093$, $p=0.006$). BMI was also found to have a weak positive correlation with IOP ($r=0.06$ $p=0.05$). Both the systolic and diastolic blood pressures (BP) were found to have a highly significant positive correlation with IOP: systolic BP ($r=0.14$ $p<0.001$), diastolic BP ($r=0.14$ $p<0.001$). CCT was also significantly correlated with IOP ($r=0.16$ $p<0.001$).

DISCUSSION

We have shown that, depending on the measurement technique used, the heritability of IOP in this twin study was over 60%. The heritability of 0.62 (95% CI 0.54 to 0.69) using GAT and 0.74 (95% CI 0.67 to 0.79) with ORA (IOPg) is similar to the Finnish Twin Study of Aging estimation of 0.64 (95% CI 0.53 to 0.71), which measured non-contact tonometry in a smaller number of twins with average age 10 years older than those in this study.¹⁷ Other heritability estimates of IOP from family and sibling-based studies have been much lower, ranging from 0.29 to 0.50.^{3 17 23-26} Twin studies tend to show a higher heritability, in part due to the shared common environment that twins have, such as same age, intrauterine environment and family background.

Heritabilities were estimated when using the different IOP measurement techniques. The point estimate of the ORA IOP was highest at 0.74, compared with 0.62 for GAT. This might suggest that use of the ORA measure might allow the greatest power when performing future genetic analyses. Although this might be the case, it is important to note that the 95% CIs overlapped, and so the actual heritabilities lie within the same range. One possible reason for the ORA reading giving the higher heritability is that this is the tonometer with the least human involvement and therefore, possibly, less human measurement error. It is known that measurement error reduces the heritability estimate. MacGregor examined the difference in heritability of height when using questionnaires compared with actual clinical measurement. They showed that when the trait in question is measured poorly, the variance due to environment increases, leading to deflated estimates of the heritability.²⁷ If measurement error can be reduced, this will decrease the residual variance, increasing the power to detect linkage or association in a genome scan. The reason for the GAT and DCT heritabilities being more alike than the ORA could be the fact that they are both contact tonometers, while the ORA is not. Another factor causing this difference in heritability could be the fact that for each tonometer, a different subset of twins was used; however, the ORA twins were a subset of the GAT twins, and the DCT a further subset of both GAT and ORA twins, making some sort of selection of twins having ORA unlikely.

Table 3 Heritability results using GAT, DCT and ORA

	No of twin pairs	h^2 (95% CI)	Environment (95% CI)
GAT	422	0.62 (0.54 to 0.69)	0.38 (0.31 to 0.46)
DCT	273	0.63 (0.53 to 0.71)	0.37 (0.29 to 0.47)
IOPg	343	0.74 (0.67 to 0.76)	0.26 (0.21 to 0.33)
IOPcc	343	0.71 (0.63 to 0.77)	0.29 (0.23 to 0.37)

DCT, Dynamic Contour Tonometer IOP; GAT, Goldmann intraocular pressure; h^2 , heritability; IOPcc, ORA corneal compensated intraocular pressure; IOPg, ORA Goldmann correlated intraocular pressure.

The prevalence of known (and suspected) glaucoma cases in the sample was similar to that in population-based studies,²⁸⁻³⁰ and inclusion or exclusion of these subjects did not significantly alter results. The normal distribution of IOPs and mean values was comparable with large population-based studies (15.4 (2.7) mm Hg compared with similarly aged females from the Beaver Dam Eye Study of 15.1 (3) mm Hg³¹ and 15.8 (2.5) mm Hg in the Blue Mountain Eye Study¹), and interocular correlations were similar (0.79 vs 0.81¹⁷). We feel, therefore, that there was little evidence of any ascertainment or other biases.

Heritability is a population-specific factor, and our study applies to this population of British women, which could be different for other populations. A possible limitation of twin studies may be the "equal environment" assumption that MZ and DZ twins share the same common family environment in which they are brought up; however, the assumption generally holds up to testing.¹⁶ Recruitment bias was minimised by the fact that the twins had volunteered for reasons other than eye studies, and were subsequently invited for an eye examination, without initially specifying glaucoma to be an outcome of interest.

The strength of family-based IOP collection such as in this twin cohort study, allows for the potential of genome-wide linkage scans, to try to identify genetic loci which may be underlying the normal trait of IOP. Identification of novel genes involved in IOP regulation may provide future drug targets, as well as a greater understanding of mechanisms involved in IOP and glaucoma. Phenotyping of large samples of unrelated subjects may allow genome-wide association scanning to identify glaucoma or IOP associations with single nucleotide polymorphisms; tests of combined linkage and association will be possible with twin samples. Genome-wide linkage scans have already been performed for IOP: weak potential linkage loci on chromosomes 6 and 13 were identified in a pilot study based on sibling pairs from the Beaver Dam Eye Study.⁸ Interestingly, these results were not replicated by the same group in a larger family-based sample from the same cohort; however seven regions of interest with the strongest evidence of linkage on chromosome 19p were found.¹¹ Another study found a significant linkage to chromosome 10q22 for maximum IOP, in an extended Australian pedigree.¹³ The genome-wide significance level of this result ($p=0.0165$) strongly suggests that this region contains a gene that contributes to the variance of IOP. Linkage to this region has also been found for systemic hypertension in a Japanese population.³² The association between blood pressure and IOP has been well documented in the literature.³³⁻³⁵ Mutations in the myocilin gene (MIM 601652, chromosome 1q) are associated with glaucoma risk and cause early-onset significantly raised IOP—and may be responsible for glaucoma in 2% to 4% of glaucoma patients.³⁶ In a recent study by Monemi *et al*, a new locus for POAG (GLC1G) and the disease-causing gene WDR36 have been identified.³⁷ WDR36 is

considered to be a modifier gene for glaucoma.^{38–41} Its role is still controversial; the main single nucleotide polymorphism (SNP), originally identified in Monemi's study, was later identified as a neutral variant in an Australian population.³⁹ The findings in two German studies indicated that WDR36 variants may be only a rare cause of normal tension glaucoma or no causal association with POAG.^{42–43} In a recent Japanese study, WDR36 SNPs were identified as a genetic susceptibility allele for high-pressure glaucoma.⁴⁴

In conclusion, this study has demonstrated that genetic effects are important in the determination of IOP in this twin population, with genetic factors explaining 62% of the variation in GAT. The point estimate of heritability using the ORA non-contact tonometer was higher at 0.74, which may suggest that this might be more powerful a measure to use in genetic studies. These results may lead to the search for genes involved in the control of the IOP using linkage and association studies, and to further elucidate our understanding of the mechanisms of glaucoma and the susceptibility of individuals to high IOPs. Greater understanding of mechanisms may also help to identify disease-modifying agents or environmental interventions to reduce disease in susceptible individuals.

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Ethics approval: The institutional ethics committee approved the study.

Patient consent: Obtained

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