

# **The Heritability of Corneal Hysteresis and Ocular Pulse Amplitude: A Twin Study**

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## **Abstract**

### **Aims:**

To estimate the heritability of corneal hysteresis and ocular pulse amplitude by performing a classical twin study.

### **Methods:**

Twin pairs were recruited to participate from the Twins UK Adult Twin Registry at St. Thomas' Hospital London. Corneal hysteresis (CH) was measured using the Ocular Response Analyser (ORA-Reichert® Buffalo, NY) and Ocular Pulse Amplitude (OPA) was measured using the Dynamic Contour Tonometer (DCT-Pascal; Swiss Microtechnology AG, Port, Switzerland). The covariance of CH and OPA within monozygotic (MZ) and dizygotic (DZ) pairs was compared and genetic modeling techniques were used to determine the relative contributions of genes and environment to the variation in these two parameters seen in this population.

### **Results:**

Data for 264 twin pairs (135 MZ; 129 DZ) were analyzed. The mean CH was 10.24mmHg  $\pm$  1.54 and the mean OPA was 2.88mmHg  $\pm$  0.97. The MZ correlations were higher than DZ for both CH and OPA (correlation coefficients: 0.75:0.42 and 0.59:0.32 for MZ:DZ twins, respectively). Modeling suggested heritability of CH of 0.77 (95% CI: 0.70-0.82) with the remaining proportion of variance due to individual environmental effects of 0.23 (95% CI: 0.18-0.30). For OPA, the heritability was 0.62 (95% CI: 0.51-0.70) with the remaining proportion of variance due to individual environmental effects of 0.38 (95% CI: 0.30-0.49).

### **Conclusion:**

This study demonstrated that genetic effects are important in the determination of these two parameters in this twin population, with genetic factors explaining 77% and 62% of the variation of CH and OPA, respectively. Environmental factors account for the remainder of the variation.

## Introduction

It has been known for over 30 years that the thickness of the cornea affects the true reading of intraocular pressure (IOP)<sup>1</sup>. Glaucoma is the second leading cause of blindness worldwide<sup>2</sup> and IOP is of fundamental importance in the management and monitoring of glaucoma. It has been estimated that a measurement error of between 0.11<sup>3</sup> to 0.71mmHg<sup>4</sup> occurs per 10µm deviation from the average central corneal thickness (CCT) of 550µm. The Ocular Hypertension Study showed that CCT is an important and independent risk factor for the progression of ocular hypertension (OHT) to a first diagnosis of glaucoma<sup>5</sup>.

The Ocular Response Analyser (ORA-Reichert® Buffalo, NY) and the Dynamic Contour Tonometer (DCT- Pascal; Swiss Microtechnology AG, Port, Switzerland) are newer instruments that measure IOP more accurately, with readings less CCT-dependant. . The ORA is a non-contact tonometer that measures IOP calibrated to Goldmann and IOPcc (corneal compensated) that is less cornea dependant. It also measures other parameters, including corneal hysteresis (CH).

CH is the term given to a measure of visco-elasticity of the cornea. Hysteresis is the physical term that describes the ability of an elastic material to return to its natural shape after being deformed by an external force. It is believed that CH may play a part in glaucoma; Congdon et al demonstrated that there is an inverse correlation between CH and visual field loss<sup>6</sup>. However when axial length was included in the model, it led to a reduction in the significance of hysteresis in the model. A study involving children with congenital glaucoma showed that their CH was greatly reduced compared with normal eyes<sup>7</sup>. How the ORA functions is described in more detail elsewhere<sup>8;9</sup>.

The DCT also primarily measures the IOP, using a contact tonometer head with a convex contour radius of 10.5mm, which is therefore similar in contour to the cornea, so as to theoretically take up the shape of the cornea and not deform it. Thus the resulting IOP measurement is less affected by the thickness of the cornea. A more detailed description of the DCT can be found in the literature<sup>10</sup>. Besides measuring IOP, the DCT also gives a reading for Ocular Pulse Amplitude (OPA). This is the difference between the minimum (diastolic) and maximum (systolic) values of pulsatile IOP within the eye. OPA may be an indirect indicator of choroidal perfusion<sup>11;12</sup>. There is evidence that lower OPA is an independent risk factor for Normal Tension Glaucoma (NTG)<sup>13</sup>. CH and OPA may therefore be useful for understanding other factors affecting IOP measurement and ocular physiology and for monitoring glaucoma. The variance of a phenotype in a population is due to genetic and environmental factors. Most traits or disease occur more commonly in the families of affected individuals than in the general population. Because families share both genes and environment, it is notoriously difficult to separate out the effects of each.

Twin studies are an excellent method for studying the relative importance of genetic and environmental influences on a phenotype<sup>14</sup>. Factors such as perfect age matching and more similar environment allow twin studies to calculate a “maximal” genetic contribution to a trait. 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)<sup>15</sup>. In view of this, we carried out a classical twin study to determine the heritability of CH and OPA in a general population. Covariance of these parameters between MZ and DZ twins was compared using modern genetic modeling techniques.

## **Methods**

Two hundred and seventy-two pairs of healthy twins, mean age of 54.1 years (range 16-78 years), were recruited from the TwinsUK Adult Twin Registry, held at St. Thomas' Hospital, London. They 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 patients gave informed consent. Zygosity was determined by a standardized questionnaire<sup>6</sup> and confirmed by DNA analysis of short tandem-repeat polymorphisms in the pairs for whom there was any uncertainty about zygosity. Individuals who were unwilling to have drops inserted in their eyes (2 subjects) or for whom a reading could not be obtained due to excessive blinking (1 subject) were excluded. Because the study was a volunteer population-based study, subjects with glaucoma were included in the analysis.

A drop of proxymethacaine 0.5% with fluorescein was administered in each eye prior to any IOP measurements. Two readings per eye were taken; in the case of the ORA, first and second tests were taken on one eye then on the next and if the accuracy was poor, a third reading was taken. In the case of the DCT, two readings per eye were again taken; however, a first reading was taken on the alternate eye before taking the second reading. Only those with reliability equal to or better than three were used (mean reliability was 1.8+/-0.9). The mean CH or OPA of all four readings was used as the variable of interest in this study. We also examined correlations between CH/OPA and IOP, CCT, systolic and diastolic blood pressure (BP), age, body mass index (BMI) and spherical equivalent (SE).

## **Statistical Methods**

Data handling and preliminary analyses were undertaken using STATA (*Intercooled Stata for Windows 95, Version 5.0*, StataCorp, College Station, TX; 1997). The covariance matrices for MZ and DZ twin pairs were used in the Mx genetic modeling program<sup>17</sup>. 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. The broad-sense heritability, which estimates the extent to which variation in optic disc parameters 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 sub model with the lowest AIC is the best fitting.

## Results

Of the original 272 pairs of twins recruited, eight pairs were excluded: five pairs because one or both twin had undergone excimer laser refractive surgery and the other three pairs because one of each pair could not undergo the tests. Thus, 264 twin pairs (135 MZ, 129 DZ), were included in the analysis; all were Caucasian and 92.5% were female. The overall mean of all four CH readings for each individual was 10.24 mmHg  $\pm$  1.54. CH measurements for right and left eyes correlated significantly, (correlation coefficient 0.61 [ $p < 0.001$ ]). The mean OPA from the four readings (2 right and 2 left) for each individual was 2.88 mmHg  $\pm$  0.97. The OPA measurements in the right and left eyes also correlated significantly, with intraclass correlation of 0.89 ( $p = < 0.001$ ). The CH and OPA both showed a normal distribution (Figs. 1&2). The means of both parameters were similar for MZ and DZ twins, as shown in Table 1. Of the 264 pairs of twins examined in this study, three (1.1% of the whole cohort) had glaucoma and two (0.75%) were referred on to their general practitioner for further investigation with suspicion of glaucoma. Exclusion of these individuals did not alter the mean values or the correlations, and so they remained in further analyses.

Correlations between IOP and CH were different when using the DCT and ORA. CH was negatively correlated with IOP when measured by DCT ( $r = -0.18$   $p < 0.001$ ), but not significantly correlated when measured with the ORA ( $r = -0.02$   $p = 0.70$ ). CH was associated with higher CCT ( $r = 0.43$   $p < 0.001$ ), lower age ( $r = -0.38$   $p < 0.001$ ) and (higher or lower?) systolic BP ( $r = -0.17$ ,  $p < 0.001$ ), but not significantly associated with diastolic BP ( $p = 0.09$ ), BMI ( $p = 0.13$ ) or SE ( $p = 0.08$ ). OPA, on the other hand, was positively correlated with IOP measured by both

instruments ( $r=0.22$   $p < 0.001$  for DCT, and  $r= 0.33$   $p < 0.001$  for ORA). OPA was associated with a higher SE ( $r=0.21$   $P < 0.001$ ), a lower BMI ( $r= -0.15$   $P < 0.001$ ) and a lower diastolic BP ( $r= -0.21$   $P < 0.001$ ). There was no significant correlation between OPA and systolic BP ( $P=0.9$ ), age ( $P=0.21$ ), or CCT ( $P=0.18$ ).

Results for the MZ twin pairs were more highly correlated than the DZ pairs for both CH and OPA (Table 1). Correlations were higher for CH (MZ:DZ 0.75:0.42) than OPA (MZ:DZ 0.59:0.35). The higher correlations support a significant genetic influence on both traits. Genetic modeling suggested the best-fitting model for both parameters to be the AE model, meaning that additive genetic effects and individual environmental effects explained the variance (Table 2). The calculated heritability ( $h^2$ ) of CH was 0.77(95% CI: 0.70-0.82), with the remaining proportion of variance due to individual environmental effects of 0.23(95%CI: 0.18-0.30). The heritability of OPA was 0.62 (95% CI: 0.51-0.70), with the remaining proportion of variance due to individual environmental effects of 0.38 (95% CI: 0.30-0.49).

## Discussion

We demonstrated that both OPA and CH, which play a role in glaucoma and IOP,<sup>6;18</sup> are strongly influenced by genes..

Despite a similar distribution of CCT in the Asian population, tonometric measurement of cannulated Asian eyes revealed lower applanation IOP readings compared to Europeans<sup>6</sup>. One possible explanation is that eyes with the same CCT may differ in elastic responsiveness (CH) due to ethnic variation and this may explain the variation in tonometric values. We have shown that CH is indeed a strongly heritable phenotype and this would support the theory that other factors apart from the CCT, such as genetically determined elastic responsiveness, may affect IOP and glaucoma susceptibility.

There is evidence that the lamina cribrosa of long eyes is thinner than that of short eyes<sup>19</sup>. Although we did not find CH to be significantly correlated with SE, which is a reasonable proxy of axial length, properties such as the visco-elasticity of the cornea (CH) may reflect the structure of the eye and its susceptibility to glaucoma. CH may become an important parameter to measure in the future for long-term monitoring of glaucoma and other disease processes of the cornea in which IOP is important<sup>9</sup>. CH has been shown to provide further information about the biomechanics of the cornea, beyond that of CCT<sup>20</sup>. Two recent separate works have shown that following LASIK surgery, CH was significantly reduced, which may reflect changes in the visco-elastic properties of the cornea caused by the surgery<sup>21;22</sup>. Clear corneal cataract surgery has been shown to cause an increase in CCT, but diminished CH<sup>23</sup>. Hager believes this to be due to the postoperative corneal oedema, which leads to a change in visco-elasticity of the cornea. CH has already been shown to be higher in normal than in keratoconic eyes<sup>24</sup>. All these findings strengthen the idea that CH is actually a measure of the

elasticity of the cornea and that this is an important physical property of the eye. It may therefore be used in the future to monitor changes in the physical properties of the cornea in individuals with corneal disorders,.

One recent study looked at whether OPA could characterize different types of glaucoma. The researchers found that OPA was significantly higher in OHT than in controls and NTG patients and that after trabeculectomy, the OPA was significantly lower than in the normal eyes<sup>25</sup>. Another study also found OPA to be reduced in NTG sufferers and elevated in OHT<sup>26</sup>. These results show that OPA may be a useful parameter to monitor when managing different forms of glaucoma.

It is interesting to note that we found CH to be negatively correlated with IOP when using the DCT, but not significantly correlated with IOP when using the ORA measurements. An inverse relationship was found between the two parameters when using the DCT. Laiquzzaman et al. also found no significant correlation between IOP and CH using the ORA<sup>27</sup>. In addition they found no significant relationship between the variation of CH and IOP with time of day. Other work by Hager, when using GAT, ORA and noncontact tonometry, found that the only IOP related to CH was IOPcc; that is the value of IOP that is adjusted by measurement of the visco-elasticity of the cornea<sup>20</sup>. This also coincides with our findings, where there was no correlation between CH and IOP when measured by the ORA or Goldmann. The difference between the two instruments' correlation between IOP reading and CH may be due to the fact that they measure IOP by different methods; the DCT is a contact tonometer whereas the ORA is not. However we found that CH was also not significantly correlated with IOP when measured by Goldmann ( $p=0.09$ ). This would weaken the argument that the difference in correlation is due to the contact properties of the ORA and DCT. CH showed a positive correlation with CCT, a negative correlation with systolic BP and age and no correlation with diastolic BP. Kirwan et al. also found a moderately significant positive correlation with CCT, but they found no significant correlation with age in an adult study<sup>28</sup>, although their mean CH in a previous study on children was higher<sup>7</sup>. They suggest CH may decline with age, and our negative correlation supports this. Lam also found a positive correlation between CH and CCT<sup>29</sup>. In the case of OPA, we found it to be positively correlated with IOP when using both IOP measurements, similar to previous literature<sup>18;30</sup>. We found OPA to be negatively correlated with diastolic BP and not correlated with age, systolic BP and CCT. One study looking at four groups of people with Primary Open Angle Glaucoma, NTG and OHT and normal individuals found no correlation between OPA and age, diastolic or systolic BP<sup>13</sup>.

Although this study was based on a volunteer twin population, the previously diagnosed prevalence of glaucoma of 1.1% is similar to population-based studies.<sup>31-33</sup> The normal distribution of both CH and OPA, and their similar mean measures (CH mean of 10.2 mmHg +/-1.5, compared to other studies with means of 10.7mmHg +/- 2 and 10.6mmHg +/- 2.3<sup>20;24</sup>, and mean OPA 2.9 mmHg

+/-0.97 compared to 3.1mmHg +/-0.9<sup>34</sup> and 2.8mmHg +/-0.3<sup>35</sup>) suggest no significant biases. Generally, twin data are generalisable to the singleton population, as twins have similar morbidity and mortality to the rest of the population<sup>36</sup>. Heritability is a population-specific factor and our study applies to this population of British women, which could be different to other populations with different gene pools or environmental circumstances.

In conclusion this study has demonstrated that genetic effects are important in determination of both these parameters in this twin population, with genetic factors explaining 77% and 62% of the variation of CH and OPA, respectively. The findings may help to identify genes involved in the control of these parameters, which may help to better understand their role in glaucoma and in the normal physiology of the eye. In the longer term it may also help to develop specific tests and disease-modifying agents that could be used in the management of susceptible individuals. To our knowledge, this research is the first to look at the influence of genes on these two parameters.

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Table 1: Demographic details of twin pairs included in this study

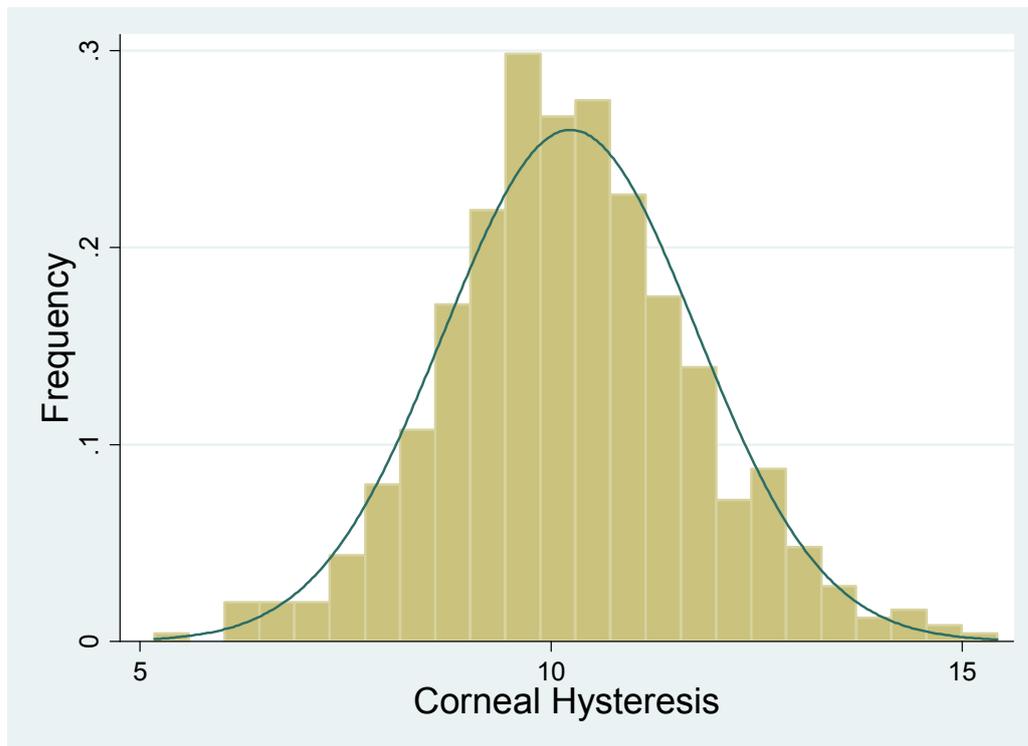
|  | <u>MZ</u>    | <u>DZ</u>    |
|--|--------------|--------------|
| Number of twin pairs                   | 135          | 129          |
| Mean age (SD) in years                 | 54.3 (14.6)  | 53.1 (13.8)  |
| Corneal Hysteresis (mmHg)              | 10.28 (1.43) | 10.21 (1.61) |
| Corneal Hysteresis correlation (r)     | 0.75         | 0.42         |
| Ocular Pulse Amplitude (mmHg)          | 2.86 (0.93)  | 2.89 (1.00)  |
| Ocular Pulse Amplitude correlation (r) | 0.59         | 0.32         |

*Abbreviations:* MZ monozygotic, DZ dizygotic, SD standard deviation

Table 2: Model fitting results for Univariate Analysis of Optic Disc, Cup and Rim area.

|            | Model     | $X^2$        | Df       | P            | AIC           |
|------------|-----------|--------------|----------|--------------|---------------|
| <b>CH</b>  | ACE       | 5.577        | 3        | 0.134        | -0.423        |
|            | ADE       | 5.667        | 3        | 0.129        | -0.333        |
|            | <b>AE</b> | <b>5.667</b> | <b>4</b> | <b>0.225</b> | <b>-2.333</b> |
|            | CE        | 35.381       | 4        | 0            | 27.381        |
|            | E         | 141.937      | 5        | 0            | 131.397       |
| <b>OPA</b> | ACE       | 6.966        | 3        | 0.073        | 0.966         |
|            | ADE       | 7.073        | 3        | 0.070        | 1.073         |
|            | <b>AE</b> | <b>7.073</b> | <b>4</b> | <b>0.132</b> | <b>-0.927</b> |
|            | CE        | 17.987       | 4        | 0.001        | 9.987         |
|            | E         | 81.071       | 5        | 0            | 71.071        |

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



**Fig 1:** Frequency Distribution of Corneal Hysteresis, showing normal distribution.

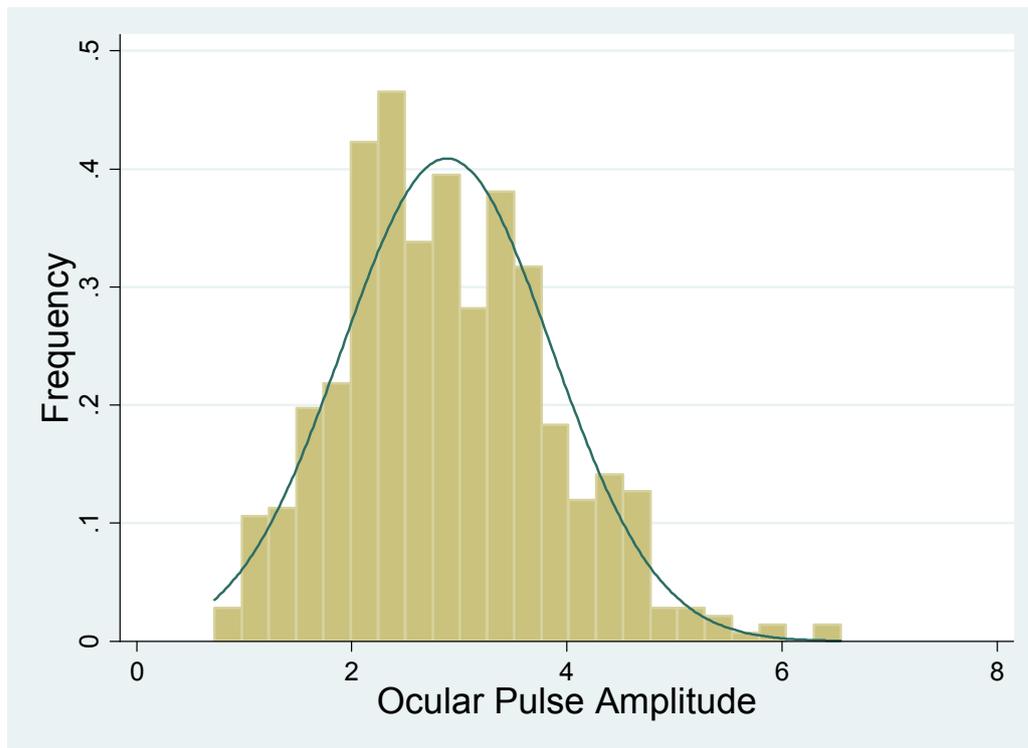


Fig 2. Frequency distribution for Ocular Pulse Amplitude, showing normal distribution