



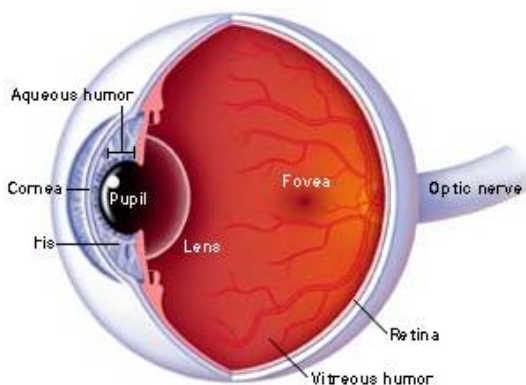
# TWINS EYE STUDY

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A collaborative project of The University of Tasmania, The University of Melbourne Department of Ophthalmology, Royal Victorian Eye and Ear Hospital, Eye Research Australia, Queensland Institute of Medical Research, St. Thomas' Hospital, London.  
Contact us: Associate Professor Dr David Mackey or Ms Lisa Kearns, Royal Victorian Eye and Ear Hospital.  
Phone: 03) 9929 8713 or 03) 6222 8553. Email: [D.mackey@utas.edu.au](mailto:D.mackey@utas.edu.au)  
Also available on internet at <http://www.eyeandear.org.au>

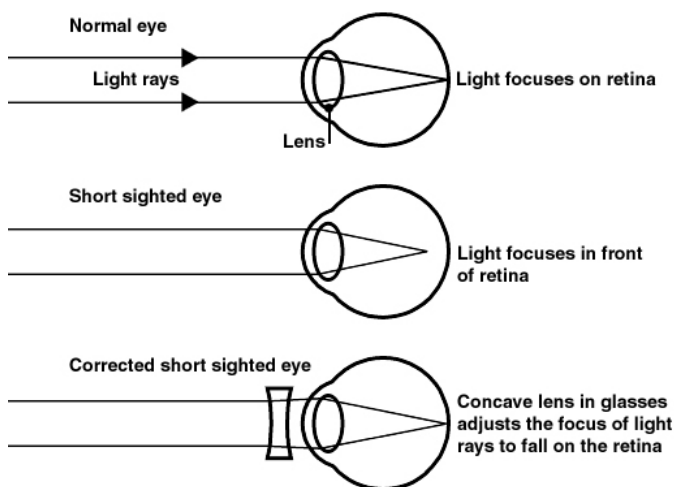
## Normal Structure of the Eye

The eye works like a camera. Light is focused by the cornea and the lens (in the front of the eye) to form an image at the back of the eye (the retina). The image signal is passed through the optic nerve to the brain, like a video cable back to the computer.

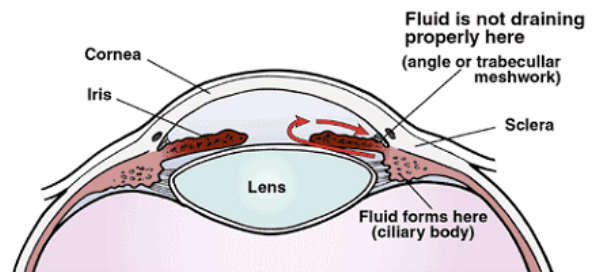


## Anatomy of the eye

If the eye is not in focus this can be corrected by glasses or contact lenses. The most common problem is myopia or shortsightedness, i.e. where people have trouble seeing things in the distance. This usually starts in teenage years. In myopia, light focuses in front of the retina (shown below).

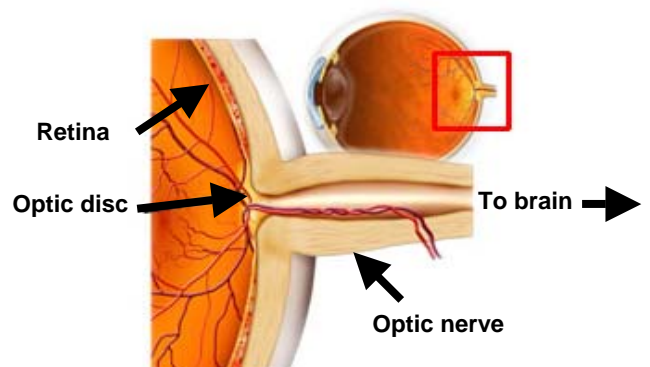


The front of the eye is nourished internally by aqueous fluid, which is produced by the ciliary body. The aqueous fluid flows around the lens, through the pupil and behind the cornea. It provides these structures with nourishment, before exiting the eye through the trabecular meshwork. This fluid also gives the eye its stability and shape and prevents it from becoming soft. If this flow is obstructed, the pressure rises and the eye can become too "hard." This can cause damage to the optic nerve at the back of the eye.



## Anatomy of the front of the internal eye

The retina is the light-sensitive inner lining of the eye. This would correspond to the actual film inside a camera. The retina consists of many different layers, among them millions of cells that convert light energy into electrical impulses. These electrical impulses are then transmitted down the optic nerve. The area where the retinal nerve fibres leave the eye, just before entering the optic nerve, is called the optic disc. This structure is important and is affected in glaucoma. The optic disc is only 1½ mm in diameter. One million nerve fibres squeeze through the optic disc and down the optic nerve towards the brain.



## Section of the back of the eye showing region of optic disc and optic nerve

The brain converts these electrical impulses into perceived images of the world around us. Further processing for colour, depth, face and shape recognition occurs in the vision centres of the brain.

### **Tests we conduct:**

Most structures, including the optic disc of the eye, can be visualised with the aid of specialised microscope called a slit-lamp. The intraocular pressure is measured with an instrument called a tonometer. This is painless and involves a special contact lens coming into gentle contact with the cornea. The thickness of the cornea influences the pressure measurement obtained (similar to a thin-walled car tyre feeling softer than a thick-walled truck tyre at the same pressure)



**Measuring pressure with a slit-lamp and tonometer (left); and measuring corneal thickness (right)**

The thickness of the cornea is measured using a small ultrasound probe called a pachymeter. Much like the sonar of a boat can measure the depth of the water beneath it, we can measure the depth (or thickness) of different structures in the eye.



**Refractive error and corneal curvature being measured with an autorefractor**

Other measurements we have been collecting include refractive error (whether you are short- or far-sighted) and corneal shape. Both these measurements are done semi-automatically with the autorefractor.

### **Glaucoma research**

Glaucoma is usually a chronic condition, which affects 1-2% of the population. It is rare before the age of 40. It is characterised by gradual damage to the back of the eye, particularly the optic nerve. If left undetected and untreated, this often leads to gradual and irreversible blindness.

Although we do not know what actually causes glaucoma, it is believed to be due to abnormal sensitivity of the optic nerve to the pressure within the eye. Most people with glaucoma have high intraocular pressures. This helps us to diagnose the disease because pressure can be measured as part of an eye examination.

Glaucoma is a difficult disease to diagnose. The three main parameters used in the diagnosis of glaucoma are: 1) raised intraocular pressure; 2) changes at the optic disc (the part of the optic nerve that can be seen and examined by the doctor; 3) loss of peripheral vision and in later stages central vision.

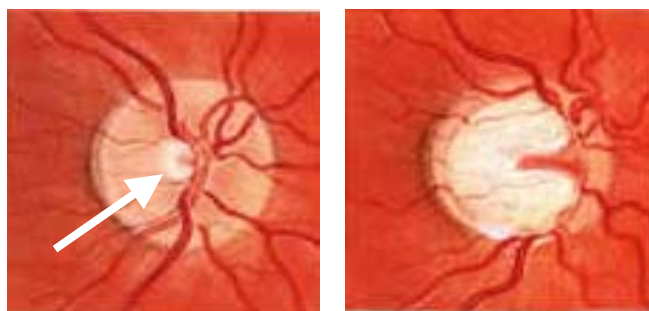
Everyone has an intraocular pressure. The normal range is from 11-21mmHg with the average being 16mmHg. Most people with a pressure over 21mmHg do not have glaucoma but a significant proportion of these individuals can develop glaucoma. The high intraocular pressure present in the majority of glaucoma sufferers seems to damage the optic nerve. The earliest signs of glaucoma often manifest at the optic nerve. This is therefore an important structure for us to learn more about.

Glaucoma damage to the optic nerve is evident from the increase in the central cup size. The cup is the central pale region of the optic disc. In glaucoma damage there is a gradual decrease in the number of nerve fibres passing through the optic nerve, resulting in a corresponding increase in this pale region of the disc.

As part of our twin research, all twin volunteers have their optic discs photographed during the examination. We then carefully analyse and measure each optic disc photograph. By comparing the correlation in size and shape of the optic disc and cup in identical or monozygotic (MZ) twins to non-identical or dizygotic (DZ) twins, we will be able to establish to what degree the optic disc and cup are genetically determined, and ultimately, what genes are responsible for this structure. These genes may be faulty or different in glaucoma patients.



A twin volunteer having her optic discs photographed



Normal optic disc

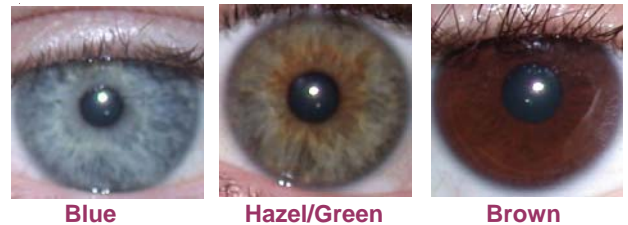
Glaucomatous optic disc

A normal optic disc appearance on the left. Note the small pale central cup (arrow). Illustration on right shows a large central cup consistent with glaucoma.

We know that glaucoma is often familial. This means that if you have a first-degree relative affected by glaucoma, you have about a 20% chance of developing the disease in your lifetime (compared to 1-2% risk in the general population). There is a strong genetic component to glaucoma. Being able to identify these genes would provide us with many benefits. Not only would doctors be able to screen and treat patients at risk (before any signs of the disease occur), but our understanding of the disease would be greatly improved. This may even one day lead to the eradication of glaucoma – the second leading cause of irreversible blindness in developed nations. However, glaucoma is a complicated genetic disease, and identifying genes have been difficult.

Twin studies allow us to explore the genetic nature of those components of the eye that are implicated in the disease. By identifying the genes involved in the normal variation of intraocular pressure, optic disc size and corneal thickness, we hope to identify genes that, with a severe mutation, may cause glaucoma.

This same strategy was employed by our collaborators at the Queensland Institute of Medical Research, led by Professor Nick Martin, looking at genes involved in the normal variation in eye colour.



Blue

Hazel/Green

Brown

They found that variation in eye colour was due to one gene (OCA2 or the P gene). A severe mutation in this gene causes total lack of pigment in the eye and skin, a condition called albinism.



Albinism

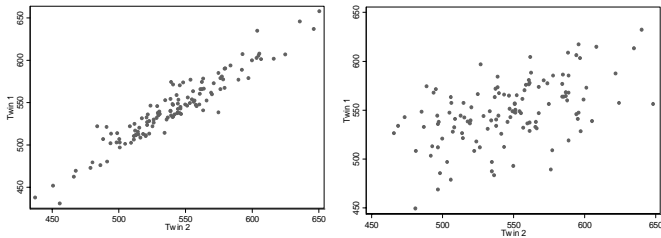
Over the next 5 years we, together with our collaborators, hope to find new glaucoma genes. This will result in new diagnostic tests and new treatment modalities based on the understanding of the genetics of the disease.

### What we have found to date?

Twin studies provide us with a unique opportunity to determine the relative genetic and environmental contributions to a particular disease or feature.

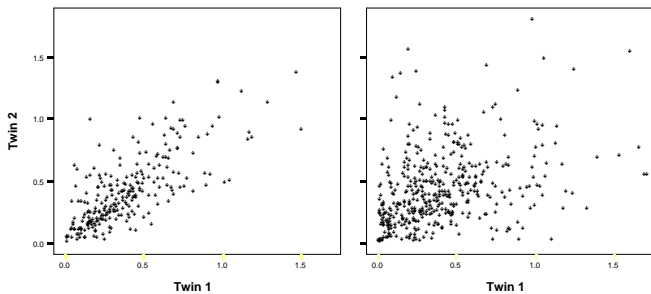
We have been particularly interested in finding the genetic factors responsible for the features involved in glaucoma (intraocular pressure, corneal thickness, and optic disc size and shape). By comparing the similarity of these structures within identical, or monozygotic (MZ) twin pairs to that within non-identical, or dizygotic (DZ) pairs, we can determine how genetic or heritable each structure is. The more genetically based the structure is, the more similar they will be in MZ twin pairs (who share all of their genes), when compared to DZ twin pairs (who only share on average half their genes).

Based on this strategy, we recently found a very high genetic component for the thickness of the cornea. As mentioned earlier, corneal thickness plays an important role in glaucoma diagnosis, management and perhaps, disease development.



**Correlation for corneal thickness.** Figure on the left shows the correlation (or similarity) of corneal thickness for MZ twin pairs. The figure on the right displays the correlation for DZ twin pairs. Note the marked increased correlation in the MZ group, indicating a strong genetic component to this structure.

After analysing and comparing the size of the optic disc in twin pairs, we concluded that this structure is also strongly heritable. This is important, as genes responsible for this structure are likely to be implicated in glaucoma.



**Correlation for optic cup size.** Figure on the left shows the correlation of optic cup area in MZ twin pairs. Figure on the right shows the correlation of optic cup area in DZ twins. The increased correlation in the MZ twin pairs indicates a significant genetic component to this structure.

An important paper on the Central Corneal Thickness is being published in the prestigious journal Investigative Ophthalmology and Visual Science.

Similar research by our collaborators in London led by Dr Chris Hammond found a similar higher correlation of identical twins for refraction (myopia). This allowed the researchers to identify several regions where genes responsible for myopia may be located. We are involved in this ongoing international collaboration

## **Where are we going with this research?**

We are well on the way to establishing the heritability of the structures and features implicated in glaucoma. The next step will be to find and identify the genes that are responsible for these structures. These genes may be glaucoma genes.

Although the structures we are researching vary between individuals and in the normal population, there will most likely be certain genes that play a major role in controlling intraocular pressure and establishing the size and thickness of the cornea, and the size and shape of the optic disc. It is the variation of these structures between the non-identical twin pairs that will become important in the search for genes.

As part of this research, all twin participants have volunteered a DNA sample. This was either in the form of a cheek swab or as a blood sample. This DNA sample was first used to establish whether twin pairs are identical or non-identical when in doubt. The DNA in the non-identical twins will be subjected to a Genome Wide Scan. This involves tagging parts of the DNA with special markers. Although similar to one another, there will be subtle differences in the DNA from one non-identical twin to another. Using sophisticated analysis techniques we will try and link the differences (and similarities) between intraocular pressure, corneal thickness, and optic disc size in DZ twins with differences (and similarities) in their entire DNA marker pattern. In this way we hope to find regions of the DNA (gene regions) that explain the variation in eye features.

As we are studying normal twins, with normal eyes, the genes we identify will be responsible for the normal structure and function within the eye. But in the same way that researchers in Queensland identified a gene that causes albinism by investigating the genes for normal eye colour, we hope to find genes for glaucoma by first studying the genes for normal function.