Eyes on prize in visi

The seatch for tiny genetic changes promises big benefits for glaucoma patients, writ

AFTER completing a doctorate in genetics at Oxford University, Jamie Craig arrived back in Australia keen to put his hard-earned knowledge to good use. Having studied the genetics of rare complex diseases, he was eager to look at a disease that was common in Australia and apply what he'd learned in a practical way. Like most bright-eyed graduates, Craig also wanted a challenge.

As luck had it, he saw an ad for a position in Tasmania, researching glaucoma, that seemed to tick all the boxes. That was a dozen years ago and Craig, now an associate professor, has been searching for answers to this puzzling disease since.

He had no idea back then just how close to home the research would hit; his mother and aunt have since been diagnosed with the disease, which affects 500,000 Australians.

Glaucoma sneaked up on them slowly, as it does with most people; so slowly that half of all people who have it don't have a clue their vision is being stolen. The disease usually attacks their peripheral vision first, in patches, leaving the central vision alone in the early stages, so people may not notice anything has changed until they start bumping into things.

Bit by bit the fibres that connect the optic nerve to the brain are destroyed; once they die, there's no resurrection. The trick is to get in early and keep those fibres alive.

Two years ago Craig and a team of researchers at Adelaide's Flinders University set up the Australian and New Zealand Registry of Advanced Glaucoma, a five-year project that aims to use sophisticated genetic testing to predict the people likeliest to develop the most severe form of the condition.

"We can do that for a small percentage of cases now," Craig says. "But we would like to be able to more accurately predict which patients will develop glaucoma and, in particular, which patients are most at risk of going blind from it."

About 10 years ago American researchers discovered that people with mutations in a gene called myocilin were almost certain to develop a severe form of glaucoma associated with high eye pressure.

Once a patient is discovered to have high eye pressure, treatments are quite effective at controlling it and preventing further vision loss. Still, because many patients are unaware of any symptoms, they may not notice until almost all their vision is gone.

According to Craig, mutations in the myocilin gene account for only about 4 per cent of all glaucoma cases and about the same percentage of the most severe instances. Still, if a parent has the mutation in the myocilin gene, there's a 50 per cent likelihood their child will inherit that change. If they do, they're almost guaranteed to develop the disease if they live long enough.

Genetic search: Ophthalmologist and glaucoma researcher Jamie Craig

Family history, then, is a risk factor for glaucoma. A person with a close relative — a parent, brother or sister — with the most common form of glaucoma has an eight times greater risk of developing the disease than someone without such a family member. During a lifetime that equates to about a 20 per cent risk.

When the Flinders team identifies a myocilin mutation in project participants, they offer relatives counselling and subsequent testing so they can be monitored and treated if they have inherited the glaucoma gene.

But glaucoma comes in several incarnations. Although it's often associated with high pressure inside the eye, at least 20 per cent of patients have pressures within the normal range and still develop glaucoma.

Those patients can benefit from treatments to lower pressure, but not always to the same degree as those whose disease was caused by high pressure.

For that reason, patients with normal eye pressure tend to be over-represented in the group with advanced glaucoma.

"This may be partly due to the fact, in the past, such patients without high eye pressure may not have been identified until later in the disease process, as earlier screening efforts may have relied too heavily on eye pressure alone rather than examining the optic nerve appearance and peripheral vision testing," Craig says.

Experts agree that genes are probably at the root of the problem, but narrowing down precisely which genes are causing the disease has been a harrowing task.

Apart from myocilin, two other genes have been identified. But together they account for less than 1 per cent of all cases. Craig and his

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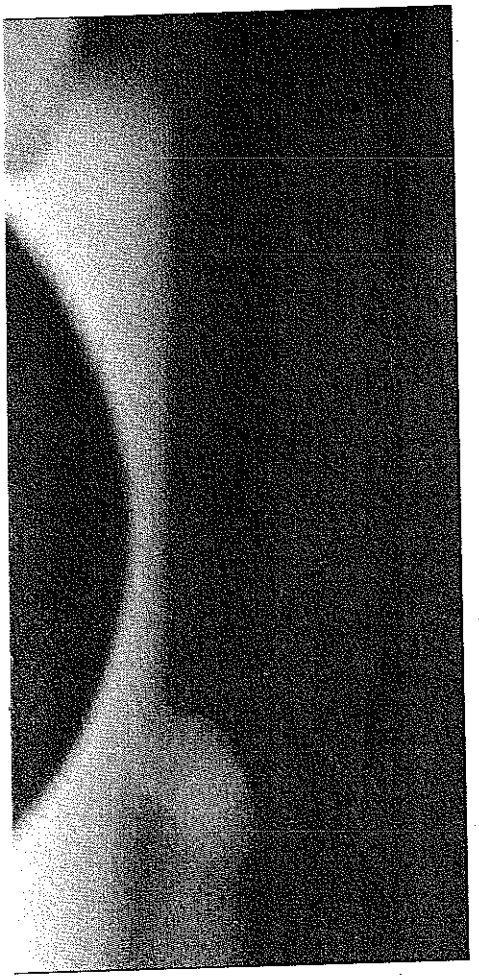

Picture: Kelly Barnes

colleagues are looking at common sequences and variations across the full complement of human genes, the genome, and comparing them against genomes of normal individuals to spot differences.

If enough genes are identified, blood or gene-based tests could be developed to determine who was at high risk, tagging them for appropriate monitoring.

"It is not cost effective to screen every person every year but if you are at high risk it can be cost effective for preventing blindness," Craig says.

"It would also allow us to restrict the most intense treatments to patients with highest risk for bad outcomes. This would help us best direct resources."

The problem is there's no way to know whether a person with the risk factor will go on to develop the disease and, if so, how severe it's likely to be. So some patients who may never develop glaucoma receive treatment just in case.

"At the moment many patients have borderline signs, but we don't always know what is the optimum time to put such a patient on treatment because once you start it's a lifetime of treatment," Craig says.

A 2004 Access Economics report predicted that the direct costs of Glaucoma would increase from $144 million that year to $289m in 2020 as the population aged. Indirect costs — such as lost productivity, blind pensions and support for those unable to care for themselves — are much higher. According to advocacy group Glaucoma Australia, the total annual cost of glaucoma in 2005 was $1.9 billion and that figure is expected to rise to $4.3bn by 2025, with one in 10 people losing sight in both eyes and one in six losing sight in one.

About 10 per cent of blindness in Australia is caused by glaucoma. In fact it's the second leading cause after age-related macular degeneration. The risk increases with age: one in 200 40-year-olds has glaucoma, while one in 10 80-year-olds has it, says University of Sydney clinical associate professor Ivan Goldberg, an ophthalmologist specialising in glaucoma. Although age and family history are the most important risk factors, others include diabetes, migraines, short-sightedness, high blood pressure, poor circulation, steroids and eye injury.

"It's a progressive disease and the damage is irreversible so the earlier we can catch it the better," Goldberg says.

Glaucoma may be picked up when eye pressure is measured or when an abnormality of the optic nerve is found during a routine check-up by an optometrist or ophthalmologist. Screening is recommended every two years after age 40, yet many people aren't screened adequately.

Along with earlier diagnosis, Goldberg and Craig say increased scientific knowledge could dramatically improve treatments. At present there are three types of treatments available: eye drops, laser treatment and surgery.

All three work by lowering pressure in the eye. All three have risks and side effects. For example, eye drops can worsen asthma, slow heart rate, darken eye colour and cause allergic reactions, including red, stinging eyes.

If researchers can identify which genes and gene products are going wrong in people prone to optic nerve damage, they may be able to design drugs that block the process early. Although that may be too late to help existing patients such as Craig's mother and aunt, future patients could benefit significantly.