



GIST

Glaucoma Inheritance Study in Tasmania

a collaborative project of

- *The Tasmanian Ophthalmologists
- *The Centre for Eye Research Australia
- *The Royal Victorian Eye and Ear Hospital
- *The Royal Hobart Hospital
- *The University of Tasmania

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THE GIST PROJECT and YOU

This Newsletter is also available on the internet at:

<http://www.eyeandear.org.au/healthinfo/glaucoma.asp> and has associated links to other sites and references.

Thank you for your participation and support for the Glaucoma Inheritance Study in Tasmania (GIST). This newsletter aims to update participants and their families on the progress of the study over the first 8 years and how it may affect you.

1) Highlights of Findings

Please note that details of currently published scientific articles included.

Since the start of the GIST at the end of 1993, we have seen nearly 4,000 people. Over 2,000 were affected by glaucoma in Tasmania alone. In addition, we have seen many other family members in every state of Australia, from over 500 families.

In 1997, the GLC1A gene, was recognised as an important glaucoma gene. Since that time, participants have been screened for mutations in this gene. This gene was found to be abnormal in 3-5% of people who have glaucoma.

• GLC1A/Myocilin gene (formerly known as TIGR):

i) Stone EM, Fingert JH, Alward LM, Nguyen TD, Polansky JR, Sunden SLF, Nishimura D, Clark AF, Nystuen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC. Identification of a gene causing primary open angle glaucoma (GLC1A). *Science* 1997;275:668-70.

ii) Alward WLM, Fingert JH, Coote MA, Johnson AT, Lerner F, Junqua D, Durcan FJ, McCartney PJ, Mackey DA, Sheffield VC, Stone EM. Clinical features associated with mutations in the chromosome 1 open angle glaucoma gene (GLC1A). *N Eng J Med* 1998;338:1022-7.

iii) Fingert JH, Héon E, Liebmann JM, Yamamoto T, Craig JE, Rait J, Kawase K, Hoh S-T, Buys YM, Dickinson J, Williams-Lyn D, Trope G, Kitazawa Y, Ritch R, Mackey DA, Alward WLM, Sheffield VC, Stone EM. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum Mol Genet* 1999; 8:899-905

- **The most common mutation is the Gln368STOP mutation, which causes a milder form of glaucoma than most other mutations in the GLC1A gene, which tend to cause severe glaucoma.**

iv) Craig JE, Baird PN, Healey DL, McNaught AI, McCartney PJ, Rait JR, Dickinson JL, Rowe L, Fingert JH, Stone EM, Mackey DA. Evidence for genetic heterogeneity within 8 glaucoma families with the GLC1A Gln368STOP mutation being an important phenotypic modifier. *Ophthalmology*. 2001;108:1607-1620.

v) Baird PN, Dickinson J, Craig JE, Mackey DA. The Taal restriction enzyme provides a simple means to identify the Q368STOP mutation of the myocilin gene in primary open angle glaucoma. *Am J Ophthalmol* 2001; 131:510-1.

- **From the GIST we found that 50% of people with glaucoma have a positive family history of glaucoma. This work was awarded a prize for the best scientific paper at the 2000 meeting of the European Glaucoma Society in London. Interestingly even in large glaucoma families many people were unaware of glaucoma running in the family. Improving family awareness of glaucoma is a major campaign of Glaucoma Australia.**

vi) McNaught AI, Allen JG, Healey DL, McCartney PJ, Coote MA, Wong TL, Craig JE, Green CM, Rait JL, Mackey DA. Accuracy and implications of a reported family history of glaucoma: experience from the glaucoma inheritance study in Tasmania. *Arch Ophthalmol* 2000; 118:900-904.

- **Although we know glaucoma runs in families, it tends to be rather complex. There are many families where glaucoma is found on both the father's and the mother's sides of the families. This makes identification of glaucoma genes much harder than we anticipated at the start of the study and suggests that different glaucoma genes may interact.**

vii) Sack J, Healey DL, de Graaf AP, Wilkinson RM, Wilkinson CH, Barbour JM, Coote MA, McCartney PJ, Rait JL, Cooper RL, Ring MA, Mackey DA. The problem of overlapping glaucoma families in the glaucoma inheritance study in Tasmania (GIST). *Ophthalmic Genet* 1996;17:209-14.

- A major impact of glaucoma is loss of peripheral vision to the extent that sufferers are unable to hold a drivers licence. 10% of people with glaucoma involved in the GIST did not have visual fields adequate to drive.

viii) McLean IM, Mueller E, Buttery RG, Mackey DA. Visual field assessment and the Austroad driving standard. Clin and Exp Ophthalmol. (in press).

- In addition to primary open angle glaucoma there are other subgroups of glaucoma such as congenital glaucoma (affecting babies), Rieger syndrome, iridogoniodysgenesis and nail-patella syndrome. GIST is also studying the genes involved in these conditions.

ix) Nishimura DY, Searby CC, Alward WLM, Walton D, Craig JE, Mackey DA, Kawase K, Kanis AB, Patil SR, Stone EM, Sheffield VC. A spectrum of FOXC1 mutations suggests gene dosage as a mechanism for developmental defects of the anterior chamber of the eye. Am J Hum Genet 2001; 68:364-372.

x) Craig JE, Mackey DA. Glaucoma Genetics: where are we? Where will we go? Curr Opin Ophthalmol 1999;10:126-34.

- We have also been investigating the association of corticosteroids with glaucoma. It would seem that taking these medications locally or systemically may predispose development of glaucoma in some people.

xi) Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history and risk of glaucoma. Ophthalmology 1999; 106:2301-6.

xii) Fingert JH, Clark AF, Craig JE, Alward WLM, Snibson GR, McLaughlin M, Tuttle L, Mackey DA, Sheffield V, Stone EM. Evaluation of the myocilin (MYOC) glaucoma gene in monkey and human steroid-induced ocular hypertension. Invest Ophth Vis Sci 2001; 42:145-52.

1) What is Glaucoma & where to find information about it?

Glaucoma is an eye disorder where the pressure in the eye is too high for the safety of the optic nerve. If left untreated, this pressure can cause damage to the nerve at the back of the eye and result in loss of peripheral (side) vision. If this loss of peripheral vision progresses, people may no longer be able to hold a driver's licence. Late in the progression of glaucoma, central vision may be lost as well, and once vision is lost through glaucoma, it can never be restored.

[Glaucoma Australia](#) provides further information on glaucoma. There are also web page links to various other glaucoma web sites from the United States [Glaucoma Research Foundation](#) and the United States [National Institutes of Health](#). Tasmanian Eye Clinics, Hobart Eye Surgeons and The Eye Hospital, Launceston, The Royal Australian & New Zealand College of Ophthalmologists as well as the institutions listed on the first page.

3) Do I have Glaucoma?

This is not always an easy question to answer especially in the early stages of the disease. There are many subsets of the glaucomatous disease process, such as a) ocular hypertension (this is where the eye pressure is high but no glaucoma damage has yet occurred), or b) normal (or low) tension glaucoma (where there is glaucoma damage but the pressure is not high). Many people with early or mild changes may be labelled as glaucoma suspects. It is possible to have glaucoma that is completely asymptomatic or to be completely blind. Several major studies have used different definitions for glaucoma. Thus researchers may not always agree with the treating doctor as to whether someone is affected by glaucoma or is a glaucoma suspect.

xiii) Coote MA, McCartney PJ, Wilkinson RM, Mackey DA. The GIST score: ranking glaucoma for genetic studies. Ophthalmic Genet 1996;17:199-208.

4) What are My Results from the DNA Test?

It has been a slow process to test participants for changes in the GLC1A gene. This has been difficult due to such large numbers of samples and limited funding for this part of the project. When a positive result is identified we contact the families concerned. We discuss the finding, ask if they wished to know about the results and if other family members would like to be involved in the study now that we know about the gene mutation. Almost all people who have had blood or mouth swab DNA taken have wanted to know the results of their testing.

If we have not yet identified a gene mutation in the affected family members we have not yet gone on to test the unaffected family members. As new glaucoma genes are identified we will test all affected members for these new mutations.

There are some important issues related to predictive DNA testing for glaucoma and thus people may not wish to know that they may get the disease at a later date. We have prepared an information sheet for patients wishing to know the results of DNA testing:

If I have the gene mutation will I get glaucoma?
Results from some of the families studied suggest although most people with the gene mutation get glaucoma, not everyone who inherits the mutation will get glaucoma. Further studies should allow us to say exactly what this risk is.

We have now streamlined our methods of collecting DNA samples and although a blood sample provide more DNA it is possible to collect a sample from a cheek swab that can be posted.

xiv) Dickinson JL, Sale MM, Craig JE, Mackey DA. Laboratory methods in ophthalmic genetics: obtaining DNA from patients. Ophthalmic Genetics 2001; 22:49-60.

Information for Patients Receiving Results of Glaucoma DNA Testing

This is the information the GIST gives to patients who request results of DNA testing for glaucoma.

Glaucoma can be treated by lowering the pressure in the eyes and, if the pressure is lowered, this slows further visual loss. This is usually done with eye drops, but sometimes surgery is required.

Early diagnosis and treatment is therefore essential in preventing visual loss from glaucoma. Large studies show that half the people in Australia who have glaucoma are unaware of the condition, because there are usually no symptoms. This is why glaucoma is often called “the sneak thief of sight”.

Ophthalmologists (eye specialists) diagnose glaucoma with three tests: a test of eye pressure to see if it is raised, a test of the visual field to test the amount (if any) of the peripheral vision that has been lost, and signs of “cupping” or damage to the optic nerve.

In the later stages, glaucoma is easy to diagnose, but it is far more difficult in the early stages. Thus, many people in the early stages are labelled as “glaucoma suspects” and, as treatment of glaucoma with drops carries some risks of side effects (as does treatment with surgery), ophthalmologists may not start treatment until they are certain of the diagnosis.

REACTIONS TO KNOWING YOUR TEST RESULTS

Before giving you the results of your personal DNA testing, we need to inform you of some of the issues involved in knowing the results.

Medical research has now been able to identify the gene responsible in a number of diseases, and has gained some experience in passing on the findings to the family members who have been tested for the gene. Previously, most genetic testing involved serious diseases where there has been no effective treatment, and some people did not want to know the results of their tests. Many guidelines have been developed with the experience of these disorders.

With diseases which are life-threatening, some family members chose not to be told whether they carried the gene or not; some people who chose to be told were very distressed to know they carried the gene; others who were told they carried the gene used this information to make certain arrangements in their lives; and of course those who were told they did NOT carry the gene were delighted. Some were prepared to be told that they did carry the gene, and were at first disconcerted to find they did not.

Similar reactions may arise with glaucoma gene testing, but of course the big difference is that **glaucoma is not life-threatening**, and can be treated to prevent or delay visual loss.

CHOOSING TO KNOW YOUR TEST RESULTS - IF YOU CARRY THE GENE

People who already have glaucoma and are told they carry the abnormal gene will have confirmation of something they already suspected. People who were “glaucoma suspects” or were “normal” and are told

they carry this gene will know they are at high risk of progressing to glaucoma. We do not yet know if all the people with the abnormal gene will get glaucoma, but we currently recommend that they are screened regularly, at least once a year if they are over 18 years of age.

Treatment is likely to be recommended at the first signs of glaucoma, and the treatment given will depend on the ophthalmologist who is treating you.

We will be happy to discuss the research and the results of your tests with your doctors. Because the gene may respond to the use of cortisone steroids, we recommend that all patients, especially those who carry the abnormal gene, discuss the matter of steroid use with their doctor. Steroid use may be in the form of steroid eye drops, steroid asthma puffers, steroid creams, steroid injections, and steroid tablets.

CHOOSING TO KNOW YOUR TEST RESULTS - IF YOU DO NOT CARRY THE GENE

For those people who do not carry the abnormal gene, this does not mean that the risk of glaucoma is zero. In several families in this research, there were people, with glaucoma, who did not carry the gene. We suggest that those people whose test shows they do not carry the abnormal gene are in the same low risk group (3%) as the general population for developing other forms of glaucoma. However, because people in this low risk group can develop glaucoma, this may indicate that there are other glaucoma genes that we have not yet discovered.

There is probably no need for non-carriers to be checked routinely prior to the age of 40 years, unless there are other suspicious signs, but ALL people over 40 should be tested every two to three years.

CHOOSING NOT TO KNOW YOUR TEST RESULTS

If you decide not to be told the results of your test, we would recommend that you continue to have a thorough glaucoma eye examination every year. You can always change your mind and be told at a later date. As there is always the slight possibility of a testing error with your result, we will repeat the test if there is any doubt or confusion.

BENEFITS OF KNOWING YOUR TEST RESULTS

As we have explained, there are major benefits of knowing that you may develop glaucoma, because early diagnosis and treatment are so important in controlling it and preventing severe visual loss.

At present, there are usually no obvious disadvantages in terms of lifestyle or in terms of insurances (Life, Disability or Health), but in future this situation may change and individuals known to carry abnormal genes may be subject to policy restrictions.

Please feel free to ask any questions. We will endeavour to provide any further information you would like. You may contact our research office on (03) 9929 8713 at any time to discuss any concern.

5) Future aims of GIST

- Identifying new glaucoma genes by linkage and association studies
- Establishing the magnitude of the role of individual glaucoma genes and mutations
- Examining genotype-phenotype correlations
- Establishing ethnic origins and role of founder effects
- Investigating the natural history of different subgroups of hereditary glaucoma
- Evaluating the sensitivity and specificity of clinical examination and investigations compared to gene status
- Evaluating of pre-symptomatic genetic testing
- Creating a population, family and genetic database for investigation of new diagnostic & treatment modalities

6) Future Research

We will continue laboratory work to look for any other glaucoma genes.

We will continue clinical work to characterise families with glaucoma and to better understand the clinical features and associations of hereditary glaucoma.

7) Can We Help You?

Please let us know if:

- you require more information about glaucoma, glaucoma genetics, a copy of any of the papers mentioned or have specific questions about your own glaucoma, genetic results or family.
- you would like us to send a report to your eye doctor.

Our contact address, phone, fax and email details are listed on the first page.

8) Can you help us?

Please let us know if:

- any of your address or name details are incorrect or have changed
- your glaucoma status or treating doctor has changed
- there are any of your relatives seen in the study who have moved, died or developed glaucoma

Any people in the family who we have not seen and who would like further information may contact us.

If you would be interested in participating in an advisory group on issues relating to the GIST research please let us know.

9) People working on GIST

Our work has attracted international attention with several members of our team presenting numerous talks at conferences in Europe, America and Asia. Talks about the GIST work have also received awards. In 1996, Robin Wilkinson, a Tasmanian orthoptist, was awarded the prize for the best scientific paper at the European Glaucoma Society meeting in Paris. In 2000 Dr David Mackey, on behalf of the group, was

awarded the prize for the best scientific paper at the European Glaucoma Society meeting in London.

Working on the GIST project has attracted people from all over Australia and the world. Many have freely given their time and expertise.

Our ophthalmology research fellows have been, 1995, Dr Michael Coote, (Vic), 1996, Dr Cathy Green, (Tas), 1997, Dr Jamie Craig, (SA); 1997-98, Dr Andrew McNaught, (UK); 1999 Dr Elisabeth Mueller (Austria); 2001 Dr Johnny Wu (Tas). Our medical students have been, 1995-96 Pauline de Graaf (Netherlands), 1995, David Platts, (Tas), 1997, Jenny Allen, (Tas), 2000 Joseph Sze, (Tas). In 2001, ophthalmologist-in training, Dr John Fingert (USA) spent a month in Australia seeing the GIST patients. Dr Fingert was the first to identify the *GLC1A* gene in the University of Iowa laboratories. Ophthalmologists Paul McCartney, (Tas), Richard Cooper (Tas), Robert Buttery (Tas) and Julian Rait (Vic) have also been closely involved in the GIST. All Tasmanian Ophthalmologists have been very supportive of the project, by allowing us to use their clinics and see patients under their care.

Orthoptists Colleen Wilkinson, Robin Wilkinson, Julie Barbour, Joanne Lynch & Tiffany Wong, genealogist Maree Ring & research assistants Danielle Healey & Sue Stanwix have been our main clinical research team.

In the laboratory Dr Joanne Dickinson, Shelly Brown Michele Sale and Jacinta Charlesworth have extracted and helped analyse the DNA samples. We will continue our successful international collaboration with Professors Edwin Stone and Val Sheffield at the University of Iowa. We have also collaborated with Dr Paul Baird and Andrea Richardson in Melbourne. There are dozens of other people who have donated their time and resources to assist with the GIST project, and we are very grateful to them for giving their weekends to help with the field work and the energy and commitment they have given to the study.

The main people who have made the GIST such a successful project have been all the participants.

On behalf of the research team employees and volunteers we would like to thank you very much for your help with the Glaucoma Inheritance Study in Tasmania. We welcome any comments about the glaucoma project.

10) Major GIST Supporters

[Glaucoma Australia](#)

[US National Institutes of Health](#)

[US Glaucoma Research Foundation](#)

[Royal Victorian Eye and Ear Hospital](#)

[Clifford Craig Medical Research Trust](#)

[Ophthalmic Research Institute of Australia](#)

[Royal Hobart Hospital Research Foundation](#)

11) Can I Make a Donation?

The main thing you can help us with is your continuing co-operation and support of the project.

We do however, need research funds to continue the work. If you would like to make a financial contribution to the GIST this can be arranged through [Glaucoma Australia](#), a not-for-profit charity, PO Box 420, Crows Nest NSW 1585

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