Genetic testing and counselling in inherited eye disease

Inherited eye disease is common. Monogenic inherited retinal degeneration affects about 1 in 2500 of the population. Common eye diseases such as age-related macular degeneration and glaucoma often have a genetic component although only a small proportion of cases show monogenic inheritance.

Over the last few years genetic testing in eye disease has evolved very rapidly from being available on a research basis only for a few conditions, to provision of specific tests on the NHS in accredited laboratories. The importance of inherited eye disease was highlighted by a publication entitled," Genetic Ophthalmology in focus, a needs assessment and review of specialist services for genetic eye disorders". A copy of this report is available at www.Phgfoundation.org/. This document was written at the request of the UK Genetic Testing Network (UKGTN) (www.ukgtn.nhs.uk/) by a working group charged with evaluating clinical and laboratory provision of ophthalmic genetic testing in the UK. The benefits of genetic testing in ophthalmic disease have been highlighted in the report and include diagnostic and prognostic information, information regarding reproductive risks, and access to prenatal diagnosis in some instances. A follow up document entitled 'Genetics and mainstream medicine' raises the issue of formalised commissioning for specialist genetics services such as Ophthalmic Genetics: ' *We suggest that in the services examined, commissioning for inherited disease within a specialty should be led by that specialty'* and the document goes on to say: '*This service should now be formally included in commissioning documents, contracts service specifications and standards and should include explicit arrangements for clinical and laboratory genetics elements to be provided as part of a multidisciplinary team'.*

Original document 2008 (2008/PROF/067)
Review 2011 (2011/PROF/150) (Idiopathtic nystagmus FRMD7 added 31 January 2012)

A list of genetic tests, which are currently available or are being developed in UK research laboratories are shown in the appended table. This is expected to expand as more tests become available. Outside the UK there are laboratories offering tests either as a service or on a research basis. Further information may be found on the following websites: European directory of DNA diagnostic laboratories (www.eddnal.com/) or Gene Clinics, which includes an International directory of genetic testing laboratories www.geneclinics.org, the UKEGG.com website gives a list of helpful website contacts.

The purpose of this paper is to raise awareness of the genetic basis of many eye diseases so that ophthalmologists can advise patients and their families when a referral to a genetics service may be beneficial. Genetic testing should be done in the context of a specialist ophthalmic genetics services, partly because many of the tests are expensive to perform, but more importantly because the implications of test results need to be discussed accurately and sensitively with patients and families.

This service usually comprises an ophthalmologist with specialist genetics expertise who has access to clinical genetics service, or a combined clinic where an ophthalmologist and a clinical geneticist work together. Either of these models will provide specialist care with particular knowledge and experience in the diagnosis and management of these conditions. The majority of centres offering this specialty have a Regional Genetics Service with access to laboratory molecular diagnostics, and visual electrophysiology testing to ISCEV standards. There should be well established referral networks from these specialist services for patients with syndromal conditions to other appropriate medical specialist services including paediatrics, endocrinology, neurology, hepatology and nephrology. This list is not exhaustive. In addition there should be provision of rehabilitation services such as low vision services and Social Services.

Patients receive genetic counselling prior to genetic testing to provide them and their families with information on the nature, inheritance, and implications of the genetic disorder. Genetic counselling can be fraught with difficulty in some conditions. For example, some patients may have no family history of the disorder. This may be due to reduced penetrance (where gene carriers show little or no evidence of disease), or age related penetrance. Determining the risks to offspring in such cases can be extremely difficult. However, a lack of family history can also be the result of a *de novo* mutation, non-paternity or the result of an alternative pattern of inheritance (for example some "sporadic" cases of RP are caused by mutations in X-linked genes, autosomal recessive or mitochondrial genes. Finally a lack of family history may reflect more complex interactions between genes and the environment.

Future developments include new technologies for identifying mutations such as high-throughput sequencing and new funding initiatives such as the National Institutes of Health Research (http://www.nihr.ac.uk/infrastructure/Pages/infrastructure_biomedical_research_units.aspx). This institution is supporting projects related to ocular genetics and new therapeutic avenues based on genotype-specific molecular diagnosis such as the RPE 65 trial for Leber Congenital Amaurosis, and the Choroideremia trial (start date 2011).

Ophthalmic genetic tests currently available in the UK					
	Clinical indication	**Gene**	**Blood sample tube**	**Provider(s)**	Turnaround time (CL: contact laboratory)
Anterior segment					
Aniridia	Postnatal diagnosis	PAX 6	EDTA	9	CL
Anophthalmia Microphthalmia	Prenatal and postnatal diagnosis	SOX2	EDTA	9	CL
Retina and **Vitreous**					
Stickler	Prenatal and postnatal diagnosis	STL1, STL2 and STL3	EDTA	3	3-10 days
Marfan	Prenatal and postnatal diagnosis	MFS1	EDTA	9 10 2	3-14 days (known mutations) 21 days (postnatal diagnosis only) 5-30 days
RP autosomal dominant RP autosomal dominant RP X-linked RP X-linked RP X-linked	Postnatal diagnosis	RHO RDS/Peripherin RP2 RPGR/RP3 RPGR/ORF15	EDTA	5	Up to 120 days (complete analysis)
Pattern dystrophy	Postnatal diagnosis	RDS/Peripherin	EDTA	5	10-40 days
Doyne Honeycomb Retinal Dystrophy	Postnatal diagnosis	EFEMP 1	EDTA	9 5	CL 10 days
Stargardt disease		CL	EDTA	7	CL
X-linked retinoschisis	Prenatal and postnatal diagnosis	RS1	EDTA	5	3-10 days (known mutations) Up to 40 days (complete analysis)

Ophthalmic genetic tests currently available in the UK					
	Clinical indication	**Gene**	**Blood sample tube**	**Provider(s)**	Turnaround time (CL: contact laboratory)
Sorsby Fundus Dystrophy	Postnatal diagnosis	TIMP 3	EDTA	5	10-40 days
Leber congenital amaurosis	Postnatal diagnosis	AIPL1, CRB1, CRX, GUCY2D, LRAT, MERTK, RPGRIP1 and RPE65	EDTA	5	CL
Norrie disease	Prenatal and postnatal diagnosis	NDP	EDTA	1	3-40 days
Optic nerve					
Leber hereditary optic neuropathy	Prenatal and postnatal diagnosis	Multiple mitochon drial mutations	EDTA	1,2,4,6,7,8,10	10-40days
Autosomal dominant optic atrophy	Postnatal diagnosis	OPA1	EDTA	11	Up to 42 days (express service available)
Primary open angle glaucoma	Postnatal diagnosis	MYOC	EDTA	9	35 days
Idiopathic nystagmus					
X linked congenital nystagmus, idiopathic infantile nystagmus, OMIM number 310700	Post natal	FRMD7	EDTA	12	Up to 40 days; testing for a familial mutation up to 10 days

Important information

Ophthalmic genetic tests should be performed as part of a specialist genetics assessment, though clinicians are welcome to contact the relevant laboratories for further information ..

Turnaround times are only indicative, as they may vary depending on clinical details and the genetic analysis that is required.

Contact details of providers (laboratories):

1. Cheshire and Merseyside Regional Molecular Genetics Laboratory (Liverpool)
   - http://www.lwh.me.uk/html/genetics.php or roger.mountford@lwh.nhs.uk
2. Dundee Molecular Genetics Laboratory
   - http://www.humangenetics.org.uk/molgenwlcm.htm or phone 01382 496271
3. East Anglian Molecular Genetics Laboratory (Cambridge)
   - www.addenbrookes.nhs.uk/moleculargenetics or becky.treacy@addenbrookes.nhs.uk
4. London Institute of Neurology
   - Phone 0845 155 5000 ext 4250
5. North West Regional Genetics Centre (Manchester)
   - www.mangen.co.uk or phone 0161 2766122 or 0161 2766605
6. Nottingham Regional Molecular Genetics Service
   - Phone 0115-9627743
7. Oxford Regional Genetics Centre
   - dutyscientist.dnalab@orh.nhs.uk or phone 01865 225594
8. Sheffield Molecular Genetics Service
   - Phone 0114 2717003
9. Wessex Regional Genetics Laboratory (Salisbury)
   - www.wrgl.org.uk or wessex.genetics@salisbury.nhs.uk
10. West Midlands Regional Genetics Laboratory (Birmingham)
    - www.bwhct.nhs.uk/regionalgenetics or genetics.lab@bwhct.nhs.uk
11. Asper Biotech (Estonia)

- www.asperbio.com or info@asperophthalmics.com

12. Head of East Midlands Regional Molecular Genetics Service Nottingham University Hospitals NHS Trust
    - Gareth Cross PhD FRCPath, Consultant Clinical Scientist and Head of East Midlands Regional Molecular Genetics Service Nottingham University Hospitals NHS Trust Molecular Genetics Department Centre for Medical Genetics City Hospital Campus Hucknall Rd Nottingham UK, NG5 1PB

    gareth.cross@nuh.nhs.uk
    Telephone 0115 9627743
    Fax 0115 9627711

As this is a rapidly advancing field, interested laboratories are encouraged to email any updates, corrections or omissions to the authors:

Susan Downes (susan.downes@orh.nhs.uk) Aris Konstantopoulos (ariskons@yahoo.com), Andrew Lotery (a.j.lotery@soton.ac.uk) or Graeme Black (graeme.black@manchester.ac.uk).

Authors:

Ms Susan Downes, Oxford Radcliffe Trust
Prof Andrew Lotery, University of Southampton
Prof Graeme Black, University of Manchester
Mr Aris Konstantopoulos, University of Southampton