



GLEN OF IMAAL TERRIER

Progressive Retinal Atrophy

From the first diagnosis of PRA to DNA testing for GPRA-crd3

2011

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Introduction

Generalised progressive retinal atrophy (GPRA or PRA) was first recognised in the Glen of Imaal Terrier in the mid 1990's. This condition causes gradual loss of vision. To develop PRA, an affected Glen has to have inherited two copies of the disease gene ... one from each parent. Up until recently, the only way to diagnose PRA in the Glen was by eye testing. Glen PRA is late onset, with some affected Glens not showing any clinical signs of disease (by eye examination) until seven years old and older ... in many cases after breeding duties were completed. This made it almost impossible to “breed out” PRA from the Glen gene pool.

In 2010, the gene that causes Glen PRA was identified. The Glen is the only breed with this particular variant of PRA ... cone-rod dystrophy 3 (crd3). The development of a DNA test means that we need never again breed a Glen that is at risk of developing crd3; and we can work towards eliminating crd3 from our gene pool. As long as breeders have at least one DNA-tested or hereditary Clear parent in a pairing, the puppies will not develop crd3.

- ❖ It is not necessary for all Glens to be DNA tested for GPRA-crd3 but **any Glen that is to be used for breeding must be DNA tested, (unless it is already known to be Hereditary Clear).**
- ❖ However, **ALL** Glen owners are encouraged to have their dogs eye tested at regular intervals throughout their lives:

Professor Bedford, a veterinary eye specialist and patron of the Glen of Imaal Terrier Association (UK) writes on GOITA's Glen Health page, “As a breed you have already developed the discipline of eye examination and you should continue to be certain that another problem does not become entrenched within the breed Eye examination is essential to ensure that our delightful breed remains free from other potential ocular [eye] disease.”

There is no consensus as to how often eye testing should be done, but at 2-3 years, 5 – 7 years and over 10 years is a suggestion that covers the age range at which late onset PRA has been diagnosed in the Glen. Eye testing is generally recommended on an annual basis and so most responsible breeders will eye test their breeding stock on a more regular basis.

Encouraging everyone to have their Glens eye tested will enable us to identify a problem early. Hopefully, though, we will not be like some other breeds and be affected by more than one variant of eye disease.

This booklet aims to provide an overview of Glen PRA, inheritance, DNA testing for breeders, safe breeding strategy, information for puppy buyers, and where/how to find further information and results of UK tested Glens.

What is PRA?

- ❖ Generalised progressive retinal atrophy (GPRA or PRA) is an “umbrella term” for a number of canine inherited eye diseases that cause **blindness**.
 - ❖ PRA causes degeneration (dying off) of specialised photoreceptor cells – cones (daytime vision) and rods (night and dim light vision) – in the retina, leading to gradual deterioration in eyesight and eventual loss of vision.
 - ❖ Ophthalmoscopic (eye) examination provides evidence that Glen PRA is late onset. Retinal degeneration can begin in some affected Glens at around 2 years of age, but other affected Glens may not show any signs of retinal degeneration until they reach 7+ years of age.
 - ❖ As with age of onset, progression of the disease can also be quite variable, with some affected Glens losing their sight completely, but other affected Glens losing their sight so slowly that they never go completely blind during their lifetime.
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History of PRA and the Glen

- ❖ **Mid 1990's** – the first diagnosis of progressive retinal atrophy (PRA) in a Glen was made, by ophthalmoscopic examination.
- ❖ **Late 1990's** – research to find the DNA mutation for Glen PRA began at Cornell University, USA under the leadership of Dr Greg Acland and principal researcher, Orly Goldstein.
- ❖ **Late 2006** – another research project at Ruhr University, Bochum, Germany, under the leadership of Professor Joerg Epplen and principal researcher, Regina Kropatsch, commenced.
- ❖ **June 2010** – both research teams announced that they had identified a single gene mutation that causes PRA in the Glen of Imaal Terrier and developed a direct mutation test, with **OptiGen** offering the test in the USA.
- ❖ **August 2010** – the research papers from both teams were published; and it was confirmed that both teams had identified the ADAM9 gene mutation (deletion) as being responsible for the cone-rod dystrophy variant of PRA in the Glen of Imaal Terrier (**GPRA-crd3**):
 - ❖ **BOCHUM** – Available online from 4th August and for publication in the bi-monthly journal ‘Molecular and Cellular Probes’ : **Generalized progressive retinal atrophy in the Irish Glen of Imaal Terrier is associated with a deletion in the ADAM9 gene**
 - ❖ **CORNELL** – Published on 11th August in the journal ‘Molecular Vision’ : **An ADAM9 mutation in canine cone-rod dystrophy 3 establishes homology with human cone-rod dystrophy 9**

Inheritance of GPRA-crd3

Mode of inheritance of GPRA-crd3 is **autosomal recessive**.

To develop GPRA-crd3, a Glen must have 2 copies of the ADAM9 gene mutation i.e. it will have inherited 1 copy of the gene mutation from each parent.

- ❖ A Glen with no copies of the gene mutation i.e. 2 normal genes will not develop GPRA-crd3
- ❖ A Glen with 1 copy of the gene mutation (and 1 normal gene) is a **carrier** but will not develop GPRA-crd3
- ❖ A Glen with 2 copies of the gene mutation is very likely to develop GPRA-crd3, although age of onset and progression of disease is highly variable

Parent 1 Carrier		Parent 2 Carrier	
+	-	+	-
<ul style="list-style-type: none"> ❖ A carrier has 1 normal gene (+) and 1 gene mutation (-) ❖ In this scenario, each parent will pass on either a normal gene (+) or a copy of the gene mutation (-) to each of its progeny (offspring) ❖ There are 4 possible “gene combinations” : the outcomes are outlined in the table below 			
Puppy outcome 1	Puppy outcome 2	Puppy outcome 3	Puppy outcome 4

Parent 1 Carrier		Parent 2 Carrier					
+	-	+	-				
+	+	+	-	+	-	-	-
Puppy outcome 1 Clear		Puppy outcome 2 Carrier		Puppy outcome 3 Carrier		Puppy outcome 4 Affected	

Each puppy (in this **Carrier** x **Carrier** scenario) has a:

- 1:4 (25%) chance of being **Clear** (+ +)
- 1:2 (50%) chance of being a **Carrier** (+ -)
- 1:4 (25%) chance of being **Affected** (- -)

This scenario is an **UNSAFE** mating – please see page 7

DNA mutation test – what does this mean?

If breeders have their Glens DNA tested for GPRA-crd3 and employ **SAFE** breeding strategies, this means that:

- ❖ We need never again produce puppies that are at risk of developing GPRA-crd3

This is the short term objective of the majority of Glen breeders

- ❖ We can eventually eliminate the disease gene from the gene pool

This is the long term objective of the majority of Glen breeders



DNA mutation test for GPRA-crd3

Breeders have two options for DNA testing their Glens for GPRA-crd3:

- ❖ OptiGen, USA
- ❖ Ruhr University, Bochum, Germany

The DNA test determines whether a Glen of Imaal Terrier has two, one or no copies of the gene mutation (ADAM9 deletion):

A Glen with 2 copies of the gene mutation is very likely to develop GPRA-crd3, although age of onset and progression of disease is highly variable

These Glens will always pass on a copy of the gene mutation to their offspring

A Glen with 1 copy of the gene mutation (and 1 normal gene) is a **carrier** but will not develop GPRA-crd3

These Glens will pass on either a normal gene or a copy of the gene mutation to their offspring

The offspring of these Glens **must** be DNA tested for GPRA if they are to be used for breeding, to ascertain whether they are Clear or Carrier status

A Glen with no copies of the gene mutation i.e. 2 normal genes will not develop GPRA-crd3

These Glens will always pass on a normal gene to their offspring

DNA testing options

OptiGen

www.optigen.com/opt9_crd3_test.html

Name of test:	Cone rod dystrophy (crd3) ~ Normal/Clear : Carrier : Affected
Submission form:	www.optigen.com/opt9_request.html
Sample required:	Only blood samples accepted ~ Minimum of 3mls EDTA
Price:	\$120.00 [2011] Discount available for online submission (5%) Discounts available for group testing (20+ dogs)
Group testing sessions:	www.optigen.com See under CLINIC SCHEDULE where UK sessions are also listed

OptiGen, Cornell Business & Technology Park, 767 Warren Road, Suite 300, Ithaca, New York 14850, USA
Tel: (001) 607 257 0301 ~ Fax: (001) 607 257 0353 ~ Email: genetest@optigen.com

Please contact Mrs Anne Hardy, GOITA Secretary for further information about OptiGen testing:

Email: anmeha@aol.com

Tel: 01777 703417

Bochum

www.ruhr-uni-bochum.de/mhg/MITARBEITER/ARBEITSGRUPPEN/PRA/Glen%20Form%20english.pdf

Name of test:	GPRA ~ (++) : (+-) : (--)
Submission form:	See link above
Sample required:	Blood sample preferred ~ 2 x 2 – 5mls EDTA
Price:	€70.00 [2011]
Group testing sessions:	Please enquire about discounts for group testing

Humangenetik, Gebaeude MA 5, Ruhr-Universitaet, Universitaetsstr. 150, 44801 Bochum, Germany
Tel: 00 49 234 32-23839 ~ Fax: 00 49 234 32 14-196 ~ Email: joerg.t.epplen@ruhr-uni-bochum.de

Please contact Mrs Jean Rogers, EFG Acting Secretary for further information about Bochum testing:

Email: jean@e-f-g.co.uk

Tel: 01205 820791

NB. Dogs submitted for DNA testing need to have some form of permanent identification (PI).

- ❖ Most vets offer a microchipping service
- ❖ Some DNA testing sessions also offer a microchipping service

Breeding strategy

- ❖ **SAFE** matings are those that do not produce Glen puppies that are at risk of developing GPRA-crd3
- ❖ **SAFE** matings must have at least one parent that has been DNA tested Clear, or is known to be hereditary Clear for GPRA-crd3

- ❖ These **SAFE** matings will not produce puppies that are at risk of developing GPRA-crd3
- ❖ A **SAFE** mating must have at least one parent that is **Clear (++)**

SCENARIO 1

	Parent 1 Clear (++)		Parent 2 Clear (++)	
Puppies ↓	Outcome 1 Clear (++)	Outcome 2 Clear (++)	Outcome 3 Clear (++)	Outcome 4 Clear (++)

SCENARIO 2

	Parent 1 Clear (++)		Parent 2 Carrier (+-)	
Puppies ↓	Outcome 1 Clear (++)	Outcome 2 Carrier (+-)	Outcome 3 Clear (++)	Outcome 4 Carrier (+-)

SCENARIO 3

	Parent 1 Clear (++)		Parent 2 Affected (--)	
Puppies ↓	Outcome 1 Carrier (+-)	Outcome 2 Carrier (+-)	Outcome 3 Carrier (+-)	Outcome 4 Carrier (+-)

- ❖ These **UNSAFE** matings have the potential to (or will *) produce puppies that are very likely to develop GPRA-crd3
- ❖ A mating where **neither** parent is **Clear (++)** is **UNSAFE**

SCENARIO 4

	Parent 1 Carrier (+-)		Parent 2 Carrier (+-)	
Puppies ↓	Outcome 1 Clear (++)	Outcome 2 Carrier (+-)	Outcome 3 Carrier (+-)	Outcome 4 Affected (--)

SCENARIO 5

	Parent 1 Carrier (+-)		Parent 2 Affected (--)	
Puppies ↓	Outcome 1 Carrier (+-)	Outcome 2 Carrier (+-)	Outcome 3 Affected (--)	Outcome 4 Affected (--)

SCENARIO 6 *

	Parent 1 Affected (--)		Parent 2 Affected (--)	
Puppies ↓	Outcome 1 Affected (--)	Outcome 2 Affected (--)	Outcome 3 Affected (--)	Outcome 4 Affected (--)

Kennel Club (KC) Official DNA Testing Scheme

An official DNA Testing Scheme for the Glen of Imaal Terrier was approved by the Kennel Club in October 2010. Results of DNA testing for **GPRA-crd3** are sent to the owner and to the KC.

- ❖ Results are entered onto the KC's registration database
- ❖ Results are published in the KC's quarterly Breed Records Supplement (BRS)
- ❖ Results are searchable via the KC website's "Health Test Result Finder"
- ❖ Results are published on regularly updated lists [Clear, Carrier & Affected] on the KC website
- ❖ Results are included on any new registration certificates issued and on the registration certificates of any progeny (offspring)

Please see page 11 for **Kennel Club health and breed information** links.

Anyone who had their Glen DNA tested prior to approval of the Official DNA Testing Scheme can now:

- i. submit results for inclusion on the KC's registration database
- ii. have results put onto the registration certificate

Please send (i) a COPY of the DNA test certificate and (ii) the ORIGINAL registration certificate to:

Health & Breeder Services Department, The Kennel Club, 1 – 5 Clarges Street, Piccadilly, London, W1J 8AB

Kennel Club (KC) DNA Control Scheme

The next stage is a DNA Control Scheme for the Glen of Imaal Terrier, where the Kennel Club will only register Glen puppies that are not at risk of developing the crd3 variant of GPRA.

The KC explains the process of working towards a **DNA Control Scheme**:

"The KC has a well-established protocol for using new DNA tests. The first is the establishment of an Official DNA Testing Scheme, which we have now set up for your new PRA test. We normally accompany this with breeding advice, which strongly encourages breeders to have all of their breeding stock DNA tested before they are bred from and, if a carrier is identified, only breed a carrier to a DNA tested normal dog (or an hereditarily normal dog) and then test the resulting progeny to see which are carriers and which are normal. Of course, we can, and have, gone to the next step, which is to link DNA testing to registration (what we call a DNA Control Scheme), but this usually happens at the end of the voluntary period described above. The reason for waiting is to ensure that the vast majority of breeders are complying and using DNA testing as advised."

Kennel Club (KC) DNA Control Scheme contd.

To begin the process of working towards a DNA Control Scheme for the Glen of Imaal Terrier, the majority of Glen breeders in the UK have agreed to the following voluntary scheme (from 2011):

1. Prior to being mated, all Glens to be DNA tested for GPRA-crd3 (or their hereditary status known – please see **BEFORE MATING** 1b and 1c below)
2. At least one of the breeding pair must be DNA tested CLEAR or known to be hereditary CLEAR for GPRA-crd3, to ensure that none of the puppies will be at risk of developing GPRA-crd3
3. In the case of CLEAR x CARRIER matings, where the individual GPRA-crd3 status of each Glen puppy is not known – (the puppies from this mating will be either CLEAR or CARRIER) – the registered owner of the bitch (and puppies) to do the following:

Endorse the puppies' registrations "*Progeny not eligible for registration*" – this must be done with the signed agreement of the new owner and an explanation of the circumstances under which the endorsement can be lifted e.g. when the puppy has been DNA tested for GPRA-crd3

For information on endorsements to registrations – www.thekennelclub.org.uk/item/365

Thinking of breeding from your Glen?

Glen breeders in the UK are encouraged to follow these **BEST PRACTICE** breeding recommendations:

BEFORE MATING:

1. Please ensure that you know the GPRA-crd3 status of your Glen before mating:
 - a. You may need to have your Glen DNA tested for GPRA-crd3
 - b. If your Glen is from a Clear x Clear mating, then it will be **hereditary Clear**
 - c. If your Glen is from a Clear x Affected mating, then it will be **hereditary Carrier status**
2. Please ensure that the GPRA-crd3 status of the stud dog or brood bitch you are using is also known:
 - a. Ask to see the DNA test certificate of the stud dog / brood bitch you are using
 - b. Check the Kennel Club's lists of DNA tested Glens – www.thekennelclub.org.uk/item/3384
3. Please ensure that at least one of the Glens has been DNA tested CLEAR, or is known to be hereditary CLEAR for GPRA-crd3 so that none of the puppies are at risk of developing GPRA-crd3:
 - a. See the table on page 7 for **SAFE** matings

Thinking of buying a Glen puppy?

To make sure that the Glen puppy you welcome into your home is not at risk of developing GPRA-crd3, please get your puppy from a responsible breeder who follows **BEST PRACTICE** breeding recommendations, as outlined on page 9.

- ❖ Glen puppies that are either Clear or Carrier status for GPRA-crd3 are **not** at risk of developing GPRA-crd3:

Glens from a Clear x Clear mating will all be Clear

These **hereditary Clear** Glens can be SAFELY mated to either a Clear or a Carrier

Glens from a Clear x Affected mating will all be Carriers

These **hereditary Carrier status** Glens can be SAFELY mated **only** to a Clear

Glens from a Clear x Carrier mating will either be Clear or Carrier status

Glens from this mating **must** be DNA tested if they are to be used for breeding, to establish whether they are Clear or Carrier status

Please see the table on page 7 for **SAFE** matings.

- ❖ An “endorsement” may be applied to your Glen puppy’s registration:

If your puppy is from a Clear x Carrier mating, your breeder will probably endorse the registration document, “*Progeny not eligible for registration*”.

This means that, if you breed from your Glen with the endorsement still in place, you will not be able to register the puppies with the Kennel Club.

Your breeder should talk this through with you before your puppy is signed over to you, and explain the circumstances under which the endorsement will be lifted e.g. when the puppy has been DNA tested for GPRA-crd3.

- ❖ The Kennel Club website is a useful source of health and breed information.

Please see page 10 for **Kennel Club health and breed information** links.

- ❖ For further information about DNA testing for GPRA-crd3, please contact the breed club secretaries:

Please see page 11 for **Glen of Imaal Terrier breed club websites** links.



Websites & links

Glen of Imaal Terrier breed club websites

www.goita.co.uk
anmeha@aol.com

- ❖ The Glen of Imaal Terrier Association
- ❖ Mrs Anne Hardy, GOITA Secretary

www.e-f-g.co.uk
jean@e-f-g.co.uk
www.glenofimaalterrier.uk.com

- ❖ Enthusiasts and Fanciers of Glens (EFG)
- ❖ Mrs Jean Rogers, EFG Acting Secretary
- ❖ Glen Services

Contact Mrs Hardy for more information about OptiGen testing.
Contact Mrs Rogers for more information about Bochum testing.

DNA testing sessions

www.optigen.com

- ❖ **CLINIC SCHEDULE**
Sort By : [Location](#)
See under **Non-U.S. Locations:** for UK sessions

Kennel Club health and breed information

www.the-kennel-club.org.uk

- ❖ **Health Tests**
Type in the full name of any KC registered dog and find out the results of tests done under the British Veterinary Association / Kennel Club Health Schemes
- ❖ **Breed Information Centre**
Health Information · Accredited Breeders · Breed Standard · Accepted Registration Colours · Pictures · Breed Watch

www.thekennelclub.org.uk/item/3384

- ❖ **DNA Screening : GPRA-crd3**
This page has links to lists of Clear, Carrier and Affected Glens
The lists are updated monthly with any new results

Permanent identification (PI)

www.thekennelclub.org.uk/petlog

PETLOG
The Kennel Club, 4A Alton House, Gatehouse Way, Aylesbury, Bucks HP19 8XU
Tel: 0844 463 3999

www.dog-register.co.uk

THE NATIONAL DOG TATTOO REGISTER
NDTR, PO Box 5720, Harwich, CO12 3SY
Tel: 01255 552455

Your Glen must have some form of PI to be eligible to be tested and certified under the BVA/KC Health Schemes and for DNA testing for GPRA-crd3

Working together to eradicate GPRA-crd3



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