TFT Genetics
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Part 2: CHG in TFTs - To Test or Not to Test, That is the Question

Introduction

In the first essay of this series, I introduced several genetic terms and the principles of their application. That information will be very useful for understanding this discussion. If you haven't yet read that essay you may want to do so before reading this one.

An article in the January 2003 issue of the *AKC Gazette*, discussed genetic disorders, how the defective genes can be identified, and how genetic tests for those disorders can be developed. It was accompanied by a table that listed the currently available genetic tests for dogs by disorder, breeds in which they can be tested, and which testing facility(ies) can perform the various tests. However, the article did not discuss the specific disorders in any detail nor made recommendation about the necessity or desirability for testing. In this essay and in several others, I am going to discuss the disorders associated with the Toy Fox Terrier, and my recommendations for testing. The first disorder that I want to discuss is one that has become a major topic of conversation among TFT breeders and would-be breeders. The disorder is called Congenital Hypothyroidism with Goiter (CHG). It is with some interest that I have been following the information presented about the occurrence of this particular disorder. As a breeder of Toy Fox Terriers I have a deep, abiding interest in the improvement of the breed. This includes the elimination, wherever possible, of genetic disorders. However, as a geneticist with over 30 years of experience in teaching and research in genetics I understand at least some of the complexities of even attempting such an elimination process. With that in mind, what is CHG and what can be done about it?

Congenital Hypothyroidism with Goiter (CHG)

CHG is a condition that results in excessive lethargy, failure to nurse well, and delayed openings of the ear canals and eyes. Affected puppies usually die by 3 weeks of age. Those that do not die naturally are usually euthanized. Therefore, it is rare for an affected puppy to survive long enough to reach reproductive maturity. Furthermore, even if a dog were to survive that long, the obvious goiter (enlargement of the thyroid) would prevent any conscientious breeder from using that dog as breeding stock. Unfortunately, those that die as puppies (or are euthanized early) can easily be misdiagnosed as "puppy-failure-to-thrive" (sometimes referred to as "fading puppy"). Therefore, for some years the existence of the problem was only vaguely recognized but rarely confirmed. Thanks to the work of Dr. John C. Fyfe at Michigan State University we now know that CHG is an **autosomal recessive** genetic disorder (All of the terms in **boldface** type were either explained in the first essay in this series or will be explained in this one). Until very recently there has been no way to detect **clinically normal heterozygous carriers** of the disorder except when the breeding of two such carriers results in one or more puppies that are affected with CHG. Dr. Fyfe changed that situation by developing a DNA-based test that will detect **clinically normal heterozygous carriers**. In my last essay I indicated that I would

address several questions about this disorder and the test that Dr. Fyfe has developed. The questions to be addressed are:

1) How accurate is the test?
2) Should you test all your TFTs (at $40 per dog)?
3) Should you test any?
4) If you test all or some of your dogs and they test positive as heterozygous carriers, what should you do about it?

Definitions and Basic Genetic Principles as Applied to CHG

As I indicated above, CHG is an autosomal recessive genetic disorder caused by a mutation in a single gene. The gene involved controls the production of an enzyme called Thyroid Peroxidase (TPO). This enzyme is needed for normal thyroid development and function. It is the lack of this enzyme that results in CHG. The normal allele specifies production of the enzyme, while the mutant allele results in no production. The normal condition is dominant therefore, because even a single normal allele directs the production of enough TPO to allow normal thyroid development and function. ONLY when individuals are homozygous for the mutant allele is there absolutely no TPO production and therefore abnormal development and functioning of the thyroid that is manifested as CHG. Therefore, CHG is a recessive disorder. This was originally determined from the observation that affected pups could result from the mating of two clinically normal parents (the classic way of identifying recessive disorders). Further pedigree analysis and the enzyme studies confirm this. We can represent this symbolically (go back to the first article in the series for a discussion of the symbolic representation of genes and alleles) as follows:

T = normal allele that can direct production of **TPO**

t = mutant allele that cannot direct production of **TPO**

TT = genotype of individuals that can produce normal **TPO** from either (or both) of the alleles **(homozygous normal)**

Tt = genotype of individuals that can produce normal **TPO** from the **T allele** but not from the **t allele (heterozygous carriers;** these individuals are **phenotypically normal** but are **carriers** of the **mutant allele** and, as such, can pass that allele on to their offspring)

tt = genotype of individuals that cannot produce **TPO** at all **(homozygous abnormal;** these dogs will be **affected** with **CHG)**

Since affected TFT puppies (**homozygous tt**) will die or will not be bred we need only consider the following possible matings between individuals with clinically normal phenotypes. Whenever more than one outcome is possible, then the percentages are estimates based on probability (remember the genetic gamble) and not absolute numbers.

TT x **TT** ➔ **100%** of offspring will be **TT**; All are therefore **phenotypically normal;** Furthermore, they are not carriers and cannot produce CHG-affected pups even if bred to a carrier

TT x **Tt** ➔ **50 %** of offspring will be **TT** (**homozygous normal**); **50%** will be **Tt** (**heterozygous carriers**); **All** are **phenotypically normal** (i.e. **no pups affected with CHG will be produced from this type of breeding**)

Tt x **Tt** ➔ **25%** of offspring will be **TT** (**homozygous normal**); **50 %** will be **Tt** (**heterozygous carriers**); **25%** will be **tt** (**affected pups with CHG**); therefore **75%** will be **phenotypically normal** and **25%** will be **CHG-affected**.

Therefore, only when two **clinically normal heterozygous carriers** are bred is it possible to get pups with CHG. However, I remind you that since we are dealing with probabilities and not absolutes, it is possible that some such matings will produce no CHG-affected pups while other similar matings (or even the same mating repeated) may produce more than 25% that are CHG-affected (even as much as 100%). This is the part of the "**genetic gamble**" that we cannot control. We can only breed "**the best to the best and hope for the best**".

Until Dr. Fyfe's test became available recently, the only way to identify **heterozygous carriers** was when a breeding of clinically normal dogs produced CHG-affected pups that were correctly diagnosed. Therefore many carriers may exist in the TFT population that are unknown even to their owners because:

1. they may never have been bred to another carrier
2. they may have been bred to another carrier but not produced any CHG-affected pups
3. they may have been bred to another carrier and produced CHG-affected pups that were misdiagnosed

Dr Fyfe, in an effort to help breeders systematically eliminate this condition has developed a DNA-based test that identifies clinically normal heterozygous carriers. I won't go into the technical details but, at my request, Dr. Fyfe sent me the results of his investigations and all of the information necessary for me to perform the test in my own lab. I have now tested a number of TFTs that had previously been tested by Dr. Fyfe in a series of blind studies (I did not know Dr Fyfe's results until after I made my own determination). In every case my determination was identical to Dr. Fyfe's. I then tested the offspring of several matings. Some of those matings were between two homozygous normal individuals. As predicted, no carriers were detected among their offspring. Some of the matings involved one parent who was a heterozygous carrier and one who was homozygous normal. Also as predicted, some of the offspring from these matings were found to be heterozygous carriers while the rest of the offspring were homozygous normal. Therefore, the test appears to be accurate with very clear results not easily subject to misinterpretation. In fact, the results are so clearly interpreted that I have adopted this assay as a lab exercise for a course that I teach on methods used in molecular diagnostics.

To Test or Not To Test?

Given the existence of a simple, reliable, accurate test the first response to the above question is likely to be: test all breeding dogs and eliminate all carriers from a breeding program (i.e. spay or neuter them and place them in pet homes; they can be excellent pets with no health problems; at least none caused by the carrier condition that resulted in the decision to spay or neuter them). Pups destined for pet homes can be spayed or neutered without testing since their individual health is not in question. If every breeder were to do this, the disorder would be wiped from the population in a single generation. This seems like a desirable goal, but is it practical? Let's consider all of the ramifications of this situation. Unfortunately, for some of you, I am probably going to raise more questions than I answer. There are really two separate questions (or sets of questions) that need to be asked and answered:

1. Should all breeding dogs be tested; If not why not?
2. Should all dogs identified as CHG carriers be automatically eliminated from breeding; If so, what will be the consequences to the breed?

To answer the first question consider the following:

- The cost of having Dr. Fyfe do the test is $40 per dog. Dr. Fyfe indicates that this only covers the cost of materials and technician time to do the test. Having done similar kinds of work, and having repeated the specific test involved, I can attest to the accuracy of that estimate. Dr. Fyfe is not making a huge profit; he is barely covering his expenses and some of the cost of the research.
- For many of us who have only a few breeding animals, $40 per dog is not prohibitively expensive.
- Given the concern over CHG, those who have had their dogs tested will probably find that they have a competitive edge when it comes to selling dogs as show/breeding prospects or for standing a dog for stud service.

That's the positive aspect. However, let me play Devil's Advocate for a minute:

- The flip side of the situation is that for some larger breeders with many breeding dogs, testing could get quite expensive and will probably drive the price of show/breeding puppies upward in order to recover some of the expense.
- Where does it stop? How many genetic disorders exist? If 4 more are identified in the next few years and the test for each one is $40, that's $200 per dog. What if the next set of tests are more expensive? What happens when the volume of CHG-testing needed becomes too much for Dr. Fyfe and other, commercial, labs begin offering the test at a higher price, in order to make a profit? – PS. The latter part of this question has already happened
- Therefore, are we setting a dangerous precedent if we insist that all breeding dogs be tested or we won't use them? Or that we won't buy breeding stock that has not been tested?
- There are many genetic disorders known in humans. Yet we don't routinely test for all of them. We usually only test for the most devastating of them or for those that we have

some reason to believe may exist in a particular family. Maybe we should follow the same principle here and only test where there is reason to suspect that the problem exists.

While the last bullet raises an interesting point marketing pressure has resulted in most breeders testing their breeding stock.

This brings us to the second, and probably more problematic question. Once carriers have been identified (either through testing or through the production of CHG-affected pups) what should be done about it? One article on ***TheDogPlace*** web site suggested that we should maybe let nature take its course. That is don't test. Carriers are healthy and affected pups will die anyway so the problem will stay uncommon. For any of us who have ever tried unsuccessfully to nurse a sick newborn to health and then had to euthanize it after several weeks of intense effort, this cavalier attitude does not begin to address the emotional drain and physical strain that such heroic efforts at resuscitation levies upon us. Even if we don't make any effort to save the pup, it is still emotionally draining. Common sense would therefore suggest that carriers should be identified and at least never be bred to another carrier. That way no one has to go through the trauma of dealing with an affected pup. What about breeding carriers to non-carriers? Granted, such breedings can, and probably will, produce more carriers. In fact, approximately 50% of the offspring from such matings will be carriers. However, no affected pups will be produced. Furthermore, while elimination of the mutant allele is a desirable goal, we must be careful not to "throw the baby out with the bath water". What I mean by that is that you have to look at the total dog. If the dog is outstanding with respect to the breed standard and/or other desirable characteristics, you may not want to eliminate it from the gene pool just because it is a carrier of CHG. All dogs are probably carriers of some genetic disorder (most likely several) that we do not know about. For an excellent discussion of this you should read: **George A. Padgett, DVM, *Control of Canine Genetic Diseases*, 1998.** The only way to prevent previously unknown genetic disorders from surfacing is to not breed at all. Just because we know about a specific disorder does not mean we should treat it any differently. Remember, every time you breed two dogs, especially if you **linebreed** or **inbreed**, you run the risk of observing a recessive disorder by producing individuals homozygous for recessive alleles. This is another part of the "**genetic gamble**" that we live with. The advantage with CHG testing is that we never again have to produce a pup that is affected with CHG. Just don't breed two carriers together. So, what is my recommendation?

1. Test your foundation breeding stock. If none are carriers then you never have to test any of their offspring because only carriers can produce more carriers (or produce CHG-affected pups).
2. If you bring a new dog into your kennel as a breeding dog, be sure that it has been certified not to be a carrier (either it has been tested and found not to be a carrier or its parents were tested and neither one was a carrier).
3. If you breed one of your dogs to one at another kennel be sure that the other dog has been certified not to be a carrier.
4. Under these circumstances, testing is a one-time thing that you will not have to do again as long as you never breed to a carrier.
5. However, if you test one of your dogs and it is a carrier you have several options:

- If it does not have other characteristics that you really want as part of your breeding program then don't breed it; have it spayed or neutered and place it as a pet.
- If it has some desirable characteristics but so do others of your dogs that are not carriers then don't breed it; have it spayed or neutered and place it as a pet; use the other, non-carrier dogs instead.
- If it has desirable characteristics that you do not have in other dogs, or that you know from previous breedings it readily passes on to its offspring, then breed it (but not to another carrier unless you are willing to face the emotional stress and physical strain of dealing with one or more CHG-affected pups). However, remember that if you do breed it (even to a non-carrier), you should, as an ethical and responsible breeder, test any offspring that will be kept or sold as breeding stock, since they have the potential to be carriers. You should also inform prospective buyers of the results. If you do not want to test such offspring yourself then you should at least inform prospective buyers that the offspring may be CHG carriers and let the buyers make an informed decision as to whether to buy. Remember that you do not need to test puppies that will be sold as pets and spayed or neutered. Even though there is the possibility that they may be carriers, they will have no CHG-related health problems and therefore, do not represent any increased risk of veterinary expenses to the new owners.

Having said all that, the decision to test or not to test is a personal one that only you can make. However, if you do not test you may someday face the prospect of dealing with a CHG-affected puppy and all the stress that entails. Also, don't be surprised if you have trouble selling your dogs to anyone as breeding stock (or getting anyone to breed their dogs to one of yours). If you intend to sell only pets that will be spayed/neutered and keep any breeding quality dogs (and if you are willing to face the prospect of dealing with a CHG-affected puppy) then you can probably save the expense of testing. But if you are going to sell puppies as potential breeding stock then you should probably test as indicated above.

The bottom line is that testing and elimination of carriers from your breeding stock is best, if you can do so without losing desirable characteristics that you may have worked long and hard to bring into your breeding lines. If you cannot eliminate a carrier without losing something else important to your breeding program then at the very least don't breed it to another carrier and be prepared to test all offspring that will be kept (or sold) as breeding stock.

Finally, let me state clearly that this is just one person's opinion. Others may feel differently. I look forward to hearing from any of you who agree or disagree with what I have written. Please feel free to contact me at daralstft@comcast.net.