A detailed explanation of the VetGen DNA-based marker test for renal dysplasia and recommendations for its use. DNA, VetGen, Renal dysplasia, Genetics

GUIDELINES FOR USAGE OF THE VETGEN DNA MARKER
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Introduction
Renal dysplasia (RD) has been a cause of premature death in Soft Coated Wheaten Terriers of British lineage since the 1950s. Independent work on progressive renal nephropathy of the juvenile Soft Coated Wheaten Terrier was reported on by both Nash et al (1984) in the UK and Ericksen and Grondalen (1984) in Scandinavia. Similar conditions have been widely reported in other breeds of dogs (Picut & Lewis, 1987).

Renal failure is a chronic condition associated most frequently with older dogs of all breeds with a wide range of causative factors identified. A specific progressive renal disease of young dogs has been reported on for the following breeds: Bedlington Terrier, Bull Terrier (miniature), Cocker Spaniel, Doberman Pinscher, Keeshond, Lhasa Apso, Malamute, Norwegian Elkhound, Samoyed, Shih Tzu, Soft Coated Wheaten Terrier, Standard Poodle, Swedish Foxhound, Vizsla and Yorkshire Terrier (Hoppe et al. 1990). Only in a subset of these breeds has a progressive renal nephropathy been identified as familial, but the Soft Coated Wheaten Terrier is one in which the familial nature has been established beyond doubt. Only dogs of a particular lineage developed in the UK and isolated from the Irish and early American populations have shown a susceptibility to developing RD.

Early research by the UK Soft Coated Wheaten Terrier Club suggested a possible recessive mode of inheritance for RD, but the number of affected puppies seemed much higher than the 25% expected and many breedings with “carriers” identified from other mating combinations did not result in RD cases when some were expected if the parents were carriers. Since RD pathology appears identical in some other dog breeds, work on the Shih Tzu breed, done in Sweden suggesting a recessive defective allele for RD in that breed (Hoppe et al. 1990) is pertinent to this work done on Soft Coated Wheaten Terriers. It is to be expected that RD in some breeds will be the result of similar deleterious mutations in genes involved in either development and maturation and/or repair of glomeruli.

This report is designed to provide a background and discussion on RD in Soft Coated Wheaten Terriers (SCWT) and the use of the DNA Marker now available from VetGen. The introduction of a DNA-based Marker test for RD has moved the SCWT breeder one step closer to being able to eliminate affected puppies from this breed. Insight gained from recent studies on the inheritance of RD in the Soft Coated Wheaten Terrier give strong evidence for RD being a polygenic trait controlled by two genes which segregate independently. JRD1, (A1 being a co-dominant defective allele, and A2 the normal Allele) and JRD2 (with B dominant normal allele and b being an autosomal defective allele) with a Marker linked to JRD1 that can be utilized to eradicate the illness from the breed. The purpose of this document is to provide a working approach for breeders to utilize the test and have the optimum impact with respect to both RD incidence and maintenance of genetic diversity of the SCWT gene pool.

Discussion
The available marker is for the JRD1 locus (allowing us to distinguish between A1 and A2 alleles) giving us a partial picture. Remember this is more information than breeders had in the past, so it is a start. The marker is stated to be accurate to 80% of the tests run by VetGen. The marker is for a co-dominant allele, so more detail on understanding the genetics of RD (as we understand it today) will help to make decisions more clear cut for breeders. VetGen are testing for the presence or absence of a Marker (M, N) which are linked to the A1 or A2 alleles of the JRD1 gene. The 80% accuracy means that more than 80% of the time both the M marker is linked to the A1 allele and the N marker is linked to the A2 allele. In genetics terms the marker and the gene of interest (JRD1) are tightly linked leading to a combined total of less than 20% false negatives and positives from using this test. A crossover (which is a rare event) will occur when the N marker and the M marker get moved from their original chromosome on to the other
chromosome as the chromosomes are being replicated in the gonads. This leads to the M marker no longer being accurate for the presence of the A1 allele.

**Genetics of RD**

Dogs affected with RD may be one of two genotypes with respect to the JRD1 and Jrd2 loci

\[
\begin{align*}
A1A1 \text{ bb} \\
A1A2 \text{ bb}
\end{align*}
\]

It is of interest to note we see differences in % fetal golmeruli, normals have 0% fetal glomeruli, and among affected two groups seem to occur in those in the 7-12% range and those in the 25-40 % range. It will be of interest to see if the A1A1bb genotype correlates with one phenotype and the A1A2bb genotype with the other phenotype. Age of onset of clinical signs of RD might also be correlated with these genotypes to see if they account for differences seen.

Carrier dogs, (i.e. dogs which can produce RD if mated to the appropriate genotypes) are one of the following types:

\[
\begin{align*}
A1A1 \text{ Bb} \\
A1A2 \text{ Bb} \\
A1A1 \text{ Bb} \\
A2A2 \text{ bb}
\end{align*}
\]

Now let us examine the various carrier matings that can produce RD affected progeny. I list first the parent’s genotypes, then the possible genetic types of sperm or eggs (gametes) that can produce and finally the various genotypes of progeny.

**Mating 1**

\[
\begin{align*}
A1A1 \text{ Bb} \quad x \\
A1B, A1b
\end{align*}
\]

\[
\begin{align*}
A1A1 \text{ Bb} \\
A1B, A1b, A2B, A2b \\
A1A1 \text{ Bb}, A1A1 \text{ Bb}, A1A2 \text{ BB}, A1A2 \text{ Bb}
\end{align*}
\]

This mating has 25% of the puppies affected with RD (A1A1 bb)

**Mating 2**

\[
\begin{align*}
A1A1 \text{ Bb} \quad x \\
A1A2 \text{ Bb}
\end{align*}
\]

\[
\begin{align*}
A1A1 \text{ BB}, A1A1 \text{ Bb}, A1A2 \text{ BB}, A1A2 \text{ Bb}
\end{align*}
\]

This mating has 25% of the puppies affected with RD (A1A1 bb, A1A2 bb)

**Mating 3**

\[
\begin{align*}
A1A1 \text{ Bb} \quad x \\
A2A2 \text{ Bb}
\end{align*}
\]

\[
\begin{align*}
A1A2 \text{ BB}, A1A2 \text{ Bb}, A1A2 \text{ BB}, A1A2 \text{ Bb}
\end{align*}
\]

This mating has 25 % of the puppies affected with RD (A1A2 bb)

**Mating 4**

\[
\begin{align*}
A1A2 \text{ Bb} \quad x \\
A2A2 \text{ bb}
\end{align*}
\]

\[
\begin{align*}
A1A2 \text{ Bb}, A1A2 \text{ bb}
\end{align*}
\]

This mating has 50% of the puppies affected with RD (A1A2 bb)

**Mating 5**

\[
\begin{align*}
A1A2 \text{ Bb} \quad x \\
A1A2 \text{ Bb}
\end{align*}
\]

\[
\begin{align*}
A1A1 \text{ Bb}, A1A1 \text{ Bb}, A1A2 \text{ Bb}, A1A2 \text{ Bb}
\end{align*}
\]

This mating has 50% of the puppies affected with RD (A1A2 bb)
A1A2 BB, A1A2Bb, A2A2 BB, A2A2 Bb
A1A2Bb, A1A2 bb, A2A2 Bb, A2A2 bb

This mating has 18 3/4 % of the puppies affected with RD (A1A1 bb, A1A2 bb, A1A2 bb)

Mating 6
A1A2 Bb     x     A2A2 Bb
Parents
A1B, A1b, A2B, A2b
A2B, A2b

A1A2 BB, A1A2 Bb, A1A2 Bb, A1A2 bb

This mating has 12 1/2% of the puppies affected with RD (A1A2 bb)

Mating 7
A1A2 Bb     x     A2A2 bb
Parents
A1B, A1b, A2B, A2b
A2b

A1A2 Bb, A1A2 Bb, A2A2 Bb, A2A2 bb

This mating has 25% of the puppies affected with RD (A1A2 bb, A2A2 bb)

All other mating combinations will not produce RD. These include the following mating combinations.
A1A1 Bb x A1A1 BB
A1A1 BB x A2A2 bb
A1A1 BB x A1A1 Bb, and
A1A1 BB x A2A2 bb

Since the current Marker test give us information on JRD1 gene (A1 or A2 allele) but we still remain in the dark about JRD1 (B or B allele) we must test but use the information wisely. Clearly we need a Marker for the different JRD2 alleles also. This will allow greater flexibility for different mating combinations and ensuring we do not produce affected offspring.

Recommendations
1) Test all individuals possible, especially in affected families. If a comprehensive testing of the SCWT population occurs, we can use this data to get a gene frequency of the defective allele of the JRD1 locus in the SCWT. This will allow progress to be measured in the future.
2) Breeders need to be realistic about the dogs they are breeding from with respect to RD risk. Families (or lines) exist within this breed which differ markedly in RD risk. This must be taken into consideration when decisions are made.
3) Breed A1A1 (MM) or A1A2 (MN) individuals to others coming from low risk families.
4) Avoid breeding A1A1 (MM) to A1A1 (MM) individuals unless family history is virtually RD free, this is not wise in moderate or high-risk families at all.
5) By supporting the currently available test for JRD1, SCWT breeders will give financial incentive for development of the test for JRD2 as well as PLE and PLN genes in the future.
6) Testing litters will allow selection to include information on JRD1 status of the puppies.
7) Remember this is a linked marker. Errors due to “crossovers” will occur. This does not prove the test to be worthless, just that we must bear in mind the 80% accuracy statistic given by VetGen.

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References

