A Study of Renal Dysplasia

by Dr. Catherine Marley

The data for this brief article were collected from a moderately closely related group of 69 Lhasas. Only 9 of these animals had any clinical symptoms of renal failure. Accurate diagnoses of Hereditary Renal Dysplasia status were obtained by wedge biopsy in 24 of the 69. No biopsy was done on 4 of the 9 animals with symptomatic kidney disease.

Distribution of Glomerular Abnormalities
(lethal grades of HRD are in blue, asymptomatic HRD in green)

% Fetal Glomeruli	0%	1-5%	6-15%	15-30%	>30%	No Biopsy clinically normal	No biopsy Renal Failure	Total
Numbers of Dogs	**6**	**8**	**5**	**0**	**5**	**41**	**4**	**69**

The results in this population indicate that of the 24 biopsied, 6 (25%) were biopsy free of kidney disease and 18 (75%) were affected to varying degrees. 13 of the biopsy positive animals had no clinical evidence of disease. 5 of the biopsy positive animals had >30% fetal glomeruli and those were in renal failure, but those with a smaller percentage of fetal glomeruli were asymptomatic. 32% (6 of 19) of clinically "normal" (biopsy negative and lo-grade biopsy positive) dogs were in fact biopsy-clear and 68% were not. This means that in this group of animals, two thirds of the dogs that appeared perfectly healthy, were actually affected with Hereditary Kidney Dysplasia. Only one third of the apparently healthy dogs were in fact free of kidney disease.

Of the unbiopsied dogs, 41 were clinically normal and 4 had symptoms of kidney failure. Since both the biopsied and unbiopsied groups were all close blood relatives, we can infer that a similar distribution of the gene exits in both groups. By inference, we can apply the ratios in the biopsied group, and expect to find roughly two thirds of the 41 clinically normal animals to be affected, and one third to be clear.

Based on the results of the biopsied group, it would seem that the ratio of affected to unaffected in this group of dogs is exactly the ratio of 3 affected to 1 normal that we would expect from a mendelian dominant gene, if each of the parents carried one copy of the gene. It is very unlikely that a recessive gene would be able to affect 75%. It thus becomes more likely that the gene responsible for Hereditary Renal Dysplasia is a dominant with poor penetrance, as some investigators have suggested.

Parent Status vs Puppy Status
(numbers of lethally affected are in blue, asymptomatic affected in green)

Parent Status	**Biopsy-Clear Pups**	**Biopsy-Affected Pups**	**Unbiopsied No failure**	**Unbiopsied Renal Failure**
Clear x Clear	1	0	0	0
Affected x Affected	0	8 **(6) (2)**	0	0
Clear x Unbiopsied	2	4 **(3) (1)**	14	**2**
Unbiopsied x Unbiopsied	1	5 **(3) (2)**	20	**1**
Affected x Unbiopsied	1	1	9	**1**

When we consider the distribution of the affected dogs in relation to the breedings done, we find we are missing a very important piece of the puzzle. There are no results of a proven clear and a proven affected dog. What we do see is that 2 affected dogs only produced affected, and the one mating of two proven clear dogs produced one clear puppy.

Admittedly, the sample is too small to be significant, but there were no affected pups born to two biopsy-clear parents. On the other hand, No clear pups were born to parents, both of whom were biopsy-positive. Since the "Unknown" (unbiopsied) group are surmised to be about 2/3 affected and 1/3 clear, the mixed results involving breedings with Unknowns are in agreement with

expectations.

Could this be a partial recessive, which would give a mild degree of dysplasia in the heterozygous state, and a severe, lethal degree in the homozygous state? Clear x Clear would always be clear. We would then expect the heaviest concentration of severe cases in litters having an affected parent. What we see is:

- In matings of Clear to Unknown, 4 of 6 pups are known to be affected, 1 lethally so. 2 of 6 are clear. Of the unbiopsied dogs, 2 are lethally affected, 12 are not. The 1 in 6 lethals in the biopsied group is startling similar to the 2 in 14 lethals in the unbiopsied group, suggesting that this group, if biopsied, would yield the same distribution of sub clinically affecteds as the biopsied group - ie. 2/3 with microscopic evidence of disease.

- In matings of Unknown to Unknown we find 5 out of 7 affected, 3 of those lethal, and only 1 proven clear. There is no essential difference from the Clear to Unknown combination.

- In mating Affected to Unknown, we find 2 out of three affected, 1 of these fatally. Again the ratios are pretty stable.

It has been suggested by geneticists looking at these data, that the gene is a recessive. That the sub clinically affected individuals may be those carying only one copy of the gene, wheras the ones in kidney failure may be carrying 2 copies. The biopsy negative ones would be clear of the gene. I cannot accept that theory because it cannot explain how matings between clears (KK) and unknowns, even if every one of the unknowns was a carrier (Kk), could produce 3 lethally affected pups (kk) out of 20. It should be impossible to produce any homogygous recessives from a carrier x clear mating.

If, on the other hand, the gene is dominant, we see 4 out of 6 affected and one clear in the biopsied group resulting from a clear x unknown mating. If the unknown parent is also clear, we would expect none of the offspring to be affected. If the unknown parent were affected carrying one copy of the gene, we would expect 50% affected, and if carrying two copies, 100% affected. In our biopsied group we found 2/3 affected offspring, suggesting that at least one of the unbiopsied parents was carrying one copy.

The problem that remains is: - why such a wide range of expression of the gene? Affected animals go from almost no kidney defect, to nearly total absence of functional kidney. The notion of "poor penetrance" is one with rather shaky foundation in fact. It means a "dominant gene that sometimes doesn't work". Nevertheless, in the case of HRD this may be the best explanation. We have so many affected animals with very small percentages of their kidneys affected, that indeed there may be some affected animals with biopsy normal kidneys, thereby fulfilling the definition of a gene with "poor penetrance"

I think that the best fit of these data is a "dominant with poor penetrance" model. What we really need to know is the ratio produced when mating a known affected to a known clear. To be statistically significant, at least 16 pups would be needed. Please, if anyone has any data they think might be useful, please contact me. We need to at least know the mode of inheritance if we are ever to select against this disease.