COUNSELING FOR INHERITED KIDNEY AND LOWER URINARY TRACT DISEASES

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INTRODUCTION

Veterinarians are often asked their opinion regarding which individual dogs and cats to breed and with which mates, in order to perpetuate characteristics of interest and to avoid predispositions for breed-associated health concerns. Or perhaps an owner was notified that a littermate or other relative of their pet has been diagnosed to be affected with a problem and they seek advice regarding screening tests and possible early interventions. Screening and staging tests for inherited renal disease or other urinary tract abnormalities may involve blood and urine samples, imaging, blood pressure measurements, renal biopsy, stone analysis, and/or possibly specific DNA testing.

INVESTIGATING THE MODE OF INHERITANCE

When breeders and veterinarians recognize a familial predisposition for renal or urinary tract disorders, patterns of inheritance and predictive markers are sought, to try to prevent production of at-risk individuals while still maintaining genetic diversity. Veterinarians are in a good position to advise breeders, bank DNA from dogs and cats with well-characterized phenotypes, and work with theriogenologists, geneticists, and other veterinary specialists to help identify genotypes of breeds at risk for inherited abnormalities, as they arise in breeding programs. With genomic tools such as gene sequencing (fine mapping) of candidate genes, some DNA tests are now available for breeds and mixbreeds, and the molecular basis for defects may be realized or at least a linked gene may be found. When candidate genes are too numerous to study, genome-wide association studies may reveal a statistically significant interval (with fewer candidate genes for study) on one or more chromosomes which are different in affected animals compared with non-affected relatives. It is important to choose proper control animals of the same population, well past the age of onset for the phenotype, and with documentation of phenotypic information (normalcy vs. affectation, possibly by blood and urine tests, imaging, stone analysis, and/or renal biopsy results, and ruling out other [acquired] differential diagnoses). Conscientious breeders often want to share information with researchers and will provide information including pedigrees of affected and control cases for analysis. Mendelian and complex modes of inheritance need to be carefully explained to breeders, e.g., autosomal vs. sex-linked, simple recessive, simple dominant, incomplete penetrance, variable expression, environmental triggers, multigenetic traits, modifying genes, epigenetic influences, etc., and the impact of breeding various genotypes to one another. If a DNA test or other predictive marker is available, and if the variant allele or test result is uncommon in the breed, then animals with the marker can be culled from the breeding program. But if the variant marker is relatively common in the population, care must be used not to remove too many animals from the breeding pool, lest genetic diversity be lost, possibly selecting for more genetic problems in the future. Characteristics which are important to perpetuate, including health, personality, performance, conformation, and breed standards are all important concerns and need to be considered for the good of the individual animal as well as the breed community as a whole. Veterinarians are needed to help animals, educate owners/breeders, and help investigate genetic predispositions in potential animal models.

DNA TESTING

Genetic counseling can now be offered with additional support from the information gleaned from studies utilizing genomic tools such as genome-wide association studies, fine sequencing of candidate genes, and specific DNA tests available for variant alleles associated with breed predispositions. For instance, for familial kidney diseases, DNA tests are available for some breeds with protein-losing nephropathy (PLN), e.g., due to 1) hereditary nephritis with different collagen IV abnormalities (and different DNA tests) in the glomerular basement membrane (similar to Alport syndrome) for Samoyeds, Navasota mixbreeds, English Cocker Spaniels, and English Springer Spaniels; or 2) podocytopathy associated with glomerulosclerosis due to the same slit diaphragm protein abnormalities (and same DNA test available) in Soft Coated Wheaten Terriers and Airedale Terriers. There are also DNA tests for polycystic kidney disease in Bull Terriers and many cat breeds, for hyperuricosuria in many dog breeds (with the same mutation and therefore the same DNA test is useful for many breeds), and for cystinuria in a number of breeds (with many different mutations so that there are different DNA tests used depending on the breed; some phenotypes are testosterone dependent). See Table 1 and on-line resources at http://www.wsava.org/Guidelines/Hereditary-Disease-Guidelines, http://research.vet.upenn.edu/penngen, or https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen/tests-worldwide to find DNA testing services. DNA samples are usually submitted as cheek swabs (use cytology brushes), blood, or semen samples. Information regarding submitting samples for Soft coated Wheaten terrier dogs for the PLN-associated variant alleles is at www.scwtca.org/health/dnatesting.htm. Care must be taken when submitting cheek swabs to avoid oral contamination of others' DNA from multipet households with shared toys/chews, water/food bowls, or licking one another, coprophagia, excretions or discharges, etc. Puppies need to be separated from each other and the dam for 3-4 hours before swabbing (blood samples may be more reliable).

SOME EXAMPLES OF SCREENING TESTS OTHER THAN DNA TESTING

It is a good idea to screen and monitor animals for abnormalities known to be affecting relatives or which are commonly seen in their breed. Some disorders are seen early in life, but others may not be seen until much later in life, even though the trait is inherited. An animal may be known to be affected If there is a DNA test available and if the trait is inherited by simple Mendelian inheritance. But if there is complex mode of inheritance, e.g., multigenic, with incomplete penetrance, variable expression, or perhaps with environmental triggers, then DNA testing may show increased risk for development of the phenotype but perhaps not all cases will be affected even with a high risk genotype.

Urinalysis - Screening for proteinuria – Occult proteinuria is the earliest warning for affectation with glomerular diseases. A dipstick protein of +2 or higher with any USG or +1 in USG of 1.012 or lower may be significant. Better than dipstick/USG ratio determinations would be MA (microalbuminuria) or UPC (urine protein/creatinine ratio). Onset and frequency of monitoring for proteinuria depends on the usual age of onset for the breed. For instance, in SCWT for which the average age of onset of genetic PLN is 4-8 years old (range 2-14 years), screening for proteinuria is recommended annually, and possibly more frequently in dogs known to have an at-risk genotype (homozygous positive dogs have the highest risk for developing PLN in their lifetimes, and heterozygous dogs have an intermediate risk). Whenever proteinuria is found, it needs to be localized and other causes of proteinuria ruled-out.(See references for diagnosis and treatment of PLN at https://onlinelibrary.wiley.com/toc/19391676/27/s1) and www.iris-kidney.com). Blood test changes which may eventually be seen with PLN include hypoalbuminemia, hypercholesterolemia, high SDMA, creatinine, and BUN, possibly with other chronic renal disease changes. Blood pressure should be monitored. Decreased USG is a late finding in PLN later than onset of azotemia. Urine SDS-PAGE may help differentiate glomerular from tubular proteinuria (contact Mary Nabity at mnabity@cvm.tamu.edu for special instructions).

Screening for decreased GFR in renal diseases: High SDMA is likely the earliest warning for decreased GFR and may be seen with 25-40% decline. With 66% decline, a concentrating defect (low

USG with PU/PD) may be observed, and a 75% decline of GFR is associated with high BUN and serum creatinine. See guidelines at www.iris-kidney.com.

Blood pressure measurements - Hypertension is associated with renal diseases. If BPM is monitored and part of a routine visit for an animal at risk for renal disease, it will become accustomed to the procedure and the results will be more reliable and able to be followed over time with more confidence.

Imaging – Radiography may see gross renal size changes, but ultrasonography is preferred to monitor early changes of JRD (if affected seriously enough, there may be hyperechoic cortical changes or small kidneys), for PCKD (at 10 months), for urinary calculi, or for some lower urogenital abnormalities. Vaginal examination and endoscopy (cystoscopy, urethroscopy, vaginoscopy) may be helpful in cases of structural abnormalities of the urogenital system such as ectopic ureters.

Screening for urine COLA (cystine, ornithine, lysine, arginine) or nitroprusside test for cystine

Urine uric acid/creatinine ratio – for Dalmatians, Dalmatian mixbreeds (including low uric acid dalmatians), and other breeds with hyperuricosuria. See https://luadalmatians-world.com/enus/

Urine metabolic screen for Fanconi (also includes nitroprusside test for cystinuria)

Urine glucose – for inherited glucosuria

Renal biopsy – A wedge biopsy (cortex) is best to document JRD since we need to view architecture as well as numerous glomeruli to check for percentage of fetal glomeruli. For glomerular diseases a Tru-cut core biopsy (cortex) will do. It is recommended to submit the sample to the Ohio State University for electron microscopy, immunofluorescence, and thin section light microscopy, to differentiate ultrastructural abnormalities of the glomerular basement membrane, immune-complex disease, glomerulosclerosis, minimal change disease, amyloid, and non-amyloid fibrillary deposition. Contact Rachel Cianciolo for special kit and instructions for submission (rachel.cianciolo@cvm.osu.edu).

TABLE 1*: INHERITED URINARY TRACT ABNORMALITIES IN DOGS AND CATS

Breed	Phenotype	Site	Mode of Inheritance	DNA test available
Airedale Terrier	Podocytopathy/GS (as SCWT)	G	Complex	+
Akita	Possibly amyloidosis	K		
Alaskan Malamute	JRD	K		
American Foxhound	ICGN (Leishmaniasis)	G		
American Staffordshire Terrier	Cystinuria Hyperuricosuria	T T	AR	+
Australian Cattle Dog & Stumpy Tail Cattle Dog	Cystinuria, Type II-A	T	AD (IP)	+
Australian Labradoodle	Cystinuria, Type I-A	T	AR	+
Australian Shepherd	Cobalamin mal. and mild proteinuria Cystinuria Hyperuricosuria	GI/K T T	AR AR	+ +
Basenji	GN (with SIIPD) Fanconi syndrome Cystinuria	G T T	AR	+
Bassett Hound	Cystinuria	T		

Beagle	Renal agenesis Amyloidosis Glomerulopathy (HN?) Cobalamin mal. and mild proteinuria TCC	K K G GI/K L	AR	+
Bernese Mountain Dog	MPGN	G	AR, possible sex-linked modifier	
Black Russian Terrier	Hyperuricosuria	T	AR	+
Border Collie	Cobalamin mal. and mild proteinuria	GI/K	AR	+
Border Terrier	JRD/Fanconi syndrome Ectopic ureter	K,T L		
Boston Terrier	Urethral prolapse Hypospadias	L L		
Boxer	JRD/Reflux nephropathy	K		
Briard	Ectopic ureter	L		
Brittany Spaniel	MPGN - Complement deficiency	G	AR	+
Bullmastiff	Glomerulopathy/FSGS	G	AR	
Bull Terrier, English Bull Terrier	GBM defect PCKD	G K	AD AD	+
Cairn	PCKD (infantile)	K	AR	
Cavalier King Charles Spaniel	Renal agenesis Xanthinuria	K T		
Chihuahua	Cystinuria	T		
Chow Chow	JRD, cystic glomeruli	K		
Coton de Tulear	Hyperoxaluria (infantile)	T	AR	+
Dachshund	Cystinuria	T		
Dalmatian	GBM defect Hyperuricosuria Hypospadias	G T L	AD AR	+
Doberman	Renal agenesis JRD/Glomerulopathy/HN? GN (sulfonamides) Urinary incontinence/ intrapelvic bladder?	K K,G G L		
Dutch Kooiker	JRD	K		
English Bulldog	Renal/ureteral duplication Cystinuria, Type III Hyperuricosuria Ectopic ureter, urethrorectal fistula, urethral prolapse, urethral duplication	K T T L	Sex-limited AR	+ +

English Cocker Spaniel	GBM defect	G	AR	+
English Foxhound	Amyloidosis	K		
English Springer Spaniel	GBM defect	G	AR	+
Entlebucher Mountain Dog (Swiss dog)	Ectopic ureter	L	Complex	
Finnish Harrier	JRD (Davidson)	K		
Fox Terrier	Ectopic ureter	L		
French Bulldog	Cystinuria III, as English Bulldog Hyperuricosuria	T T	Sex-limited AR	+ +
French Mastiff (Bordeaux)	Juvenile glomerulopathy	G	AR	
German Shepherd	ICGN (*Ehrlichia canis*) Cystadenocarcinomas (with nodular dermatofibrosis, uterine leiomyomas) Hyperuricosuria	G K T	AD (homo-zygous lethal in embryo) AR	+ +
German Spitz	Hyperuricosuria	T	AR	+
Giant Schnauzer	Cobalamin mal. and mild proteinuria Hyperuricosuria	GI/K T	AR AR	+ +
Golden Retriever	ICGN (Lyme nephritis) JRD Ectopic ureter	G K L		
Gordon Setter	JRD/Reflux nephropathy	K		
Greyhound	Vasculopathy (skin, renal)	G		
Griffon	Ectopic ureter	L		
Irish Terrier	Cystinuria, Type III	T	Sex-limited	
Jack and Parson Russell Terrier	Hyperuricosuria	T	AR	+
Keeshond	JRD	K		
Labradoodle	Cystinuria, Type I-A	T	AR	+
Labrador Retriever	ICGN (Lyme nephritis) Liver disease/Fanconi Cystinuria, Type I-A Ectopic ureter	G T T L	AR	+
Landseer	Cystinuria, Type I-A	T	AR	+
Large Munsterlander	Hyperuricosuria	T	AR	+
Lhasa apso	JRD	K		
Mastiff	Cystinuria, Type III	T	Sex-limited	+
Miniature Pinscher	Cystinuria, Type II-B	T	AD (homo-zygous lethal)	+

Miniature Poodle Miniature and Toy Poodle	Urethrorectal fistula, urethroperineal fistula, urethral duplication Ectopic ureter	L L		
Miniature Schnauzer	GS or possibly HN JRD Persistent Muellerian Duct Syndrome	G K L	AR (sex-limited)	+
Native American Indian Dog	2-8 dihydroxyadenine urolithiasis	L	AR	+ but NA
Navasota, TX mixbreed	GBM defect	G	X-linked dominant	+
Newfound-land	Juvenile collagenofibrotic glomerulopathy Cystinuria, Type I-A Ectopic ureter	G T L	AR AR	+
Norwegian Elkhound	Periglomerular fibrosis Glucosuria	G T		
Pekingese	Renal agenesis	K		
Pembroke Welsh Corgi	Glomerulopathy Renal telangiectasia Cystinuria	G K T		
Rottweiler	Glomerulopathy (HN?)	G		
Samoyed	GBM defect (females are mosaics)	G	X-linked recessive	+
Scottish Deerhound	Cystinuria, Type III	T	sex-limited	
Scottish Terrier	Cystinuria Glucosuria TCC	T T L	AR	
Shar pei (Chinese)	Amyloidosis	G		+ but NA
Shetland Sheepdog	ICGN (Lyme nephritis) Renal agenesis TCC	G K L		
Shih Tzu	JRD	K	AD (IP)	
Siberian Husky	Ectopic ureter	L		
Skye terrier	Ectopic ureter	L		
Soft Coated Wheaten Terrier	Podocytopathy/GS JRD	G K	Complex	+
South African Boerboel	Hyperuricosuria	T	AR	+
Standard Poodle	JRD	K		
Weimeraner	Hyperuricosuria	T	AR	+
West Highland White Terrier	PCKD (infantile) Ectopic ureter TCC	K L L	AR	
Wire Hair Fox Terrier	TCC	L		

CATS				
Abyssinian	Amyloidosis (T > G) Proliferative glomerulopathy	K G	AD (IP) AR	
British Long- hair; British Shorthair	PCKD	K	AD	+
Burmilla	PCKD	K	AD	+
Domestic Shorthair	Hyperoxaluria (infantile) Cystinuria	T T	AR	+ but NA + but NA
Exotic Shorthair	PCKD	K	AD	+
Himalayan	PCKD	K	AD	+
Maine Coon	PCKD (this is a different mutation)	K		
Persian	PCKD	K	AD	+
Ragdoll	PCKD	K	AD	+
Scottish Fold	PCKD	K	AD	+
Selkirk Rex	PCKD	K	AD	+
Siamese	Amyloidosis (T>G)	K		

*See Reference[1] for more details regarding specific variant alleles involved if DNA tests are available.
**See http://research.vet.upenn.edu/penngen for available laboratories for individual DNA tests.
A: autosomal; D: dominant; G: glomerular; GBM: glomerular basement membrane; GI: gastrointestinal; GS: glomerulosclerosis; ICGN: immune-complex glomerulonephritis; IP: incomplete penetrance; JRD: juvenile renal disease; K: kidney; L: lower urinary tract; mal.: malabsorption; MP: membranoproliferative; PCKD: polycystic kidney disease; R: recessive; SIIPD: small intestinal immunoproliferative disease; T: tubular; TCC: transitional cell carcinoma

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Helpful websites:

www.iris-kidney.com
https://onlinelibrary.wiley.com/toc/19391676/27/s1
http://research.vet.upenn.edu/penngen
http://www.wsava.org/Guidelines/Hereditary-Disease-Guidelines
www.scwtca.org/health/dnatest.htm