# Polycystic kidney disease in Bull Terriers: an autosomal dominant inherited disorder

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The prevalence, mode of inheritance and urinalysis findings in Bull Terriers with polycystic kidney disease were assessed by screening 150 clinically normal dogs. The disorder was diagnosed in 39 dogs on the basis of renal ultrasound results and family history of the disease. In equivocal cases confirmation required gross and histopathological renal examination. Necropsy was performed on nine affected dogs and the kidneys from another five affected animals were also examined. Renal cysts were usually bilateral, occurred in cortex and medulla and varied from less than 1 mm to over 2.5 cm in diameter. Cysts were lined by epithelial cells of nephron origin. Abnormal urine sediment and proteinuria were common in affected dogs. The disease appears to be inherited in a highly penetrant autosomal dominant manner.

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Key words: Dog, Bull Terrier, polycystic kidney disease, inherited renal disease, canine, autosomal dominant.

ADPKD	Autosomal dominant polycystic kidney disease	MSB	Martius Scarlett blue
BTPKD	Bull Terrier polycystic kidney disease	PKD	Polycystic kidney disease
H&E	Haematoxylin and eosin	UPC	Urine protein to creatinine ratio

KD has been reported in many species including Persian cats,1 Cairn Terriers,<sup>2</sup> West Highland White Terriers,<sup>3</sup> a raccoon,<sup>4</sup> a Nubian goat.<sup>5</sup> rats.<sup>6</sup> mice,<sup>7</sup> pigs<sup>8</sup> and humans.<sup>9</sup> However, autosomal dominance and adult onset disease have only been demonstrated in the Persian cat, one strain of rat, one strain of mouse and humans. PKD was first reported in eight related Bull Terriers in 1994.<sup>10</sup> The diagnosis was made by renal ultrasonography or at necropsy. All affected dogs had multiple bilateral macroscopic renal cysts and all dogs for which data were available had proteinuria, haematuria and pyuria. Pedigree analysis suggested an autosomal dominant mode of inheritance.

In recent years, extensive breeding of Bull Terriers with PKD has occurred. As the disease may now be prevalent in Australia, clinicians need to be aware of the clinical and pathological features, mode of inheritance and methods of diagnosis. This study was undertaken to provide this information by examining Bull Terriers in three-generation pedigree structures for evidence of BTPKD, using renal ultrasonography, urinalysis and in some cases necropsy.

## Materials and methods Experimental design

The study was carried out at The Universities of Queensland and of Sydney. Breeders and owners of Bull Terriers were requested to present dogs from three-generation pedigree structures for examination. Some animals came from breeding lines known to be affected by BTPKD and pedigrees were obtained for all 150 dogs. Dogs' ages ranged from 8 weeks to 13 years and 11 months.

#### Criteria for diagnosis of BTPKD

The presence or absence of BTPKD was determined using diagnostic criteria established from studies of human ADPKD, requiring demonstration of at least three cysts distributed between two kidneys, together with occurrence of other affected family members.<sup>11,12</sup> In cases where fewer than three cysts could be detected, or if only one kidney appeared affected, results were classed as equivocal and retesting was recommended in 6 to 12 months. Animals with equivocal results were regarded as likely to be affected if they had an affected first degree relative (parent, sibling, or offspring from a mating to an unaffected animal).

Renal ultrasound

An ATL Ultramark 9 (Advanced Technology Laboratories) with a 5 MHz annular array transducer, a 7.5 MHz mechanical sector transducer and 5, 7.5 and 10 MHz mechanical sector transducers were used for renal ultrasonography in Queensland. In Sydney, an ATL Ultramark 9 with a variable frequency 4 to 7 MHz curvilinear array or a 3 to 5 MHz phased array transducer was used. All dogs were scanned in lateral recumbency on both sides of the upper cranial flank to obtain sagittal, dorsal and transverse images of both kidneys.

# *Criteria for grading severity of renal cystic change*

To allow comparison of disease severity between individuals, affected dogs were graded according to size and number of renal cysts detected by renal ultrasonography (Table 1).

### Urinalysis

Urine samples were obtained from 34 affected dogs. Urine was collected midstream and from the first urination of the day where possible. Otherwise, samples were collected by cystocentesis. Most urine samples were collected on the day of renal ultrasonography. All samples were refrigerated or stored on ice and tested within 36 h of collection.

All urinalyses were performed by the same person (CO), using Ames multiple reagent strips (Bayer Diagnostics), a haemocytometer for microscopic

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Table 1. Ultrasonographic criteria for grading BTPKD.			
Grade	Description <sup>a</sup>		
1	1 or 2 cysts		
2	4 to 7 cysts, usually less than 1 cm diameter		
3	8 or more cysts, kidneys not greatly enlarged		
4	Kidneys greatly enlarged and distorted by over 20 cysts		

<sup>a</sup>Number of renal cysts are the total number detected for both kidneys.

examination of sediment, a Reichert veterinary refractometer for USG determination (Cambridge Instruments) and a digital pH meter (TPS). After measuring urine protein and creatinine concentrations, UPC was calculated. The creatinine concentration was measured using the picric acid method and the Jaffe reaction with a creatinine reagent kit (Trace Scientific) and protein was measured using the pyrogallol method and urinary protein kit (Randox Laboratories) on a Cobas Mira (Roche Diagnostics Systems) wet chemistry analyser.

Reference UPC ratios were established from 71 voided urine samples collected from dogs hospitalised at The University of Queensland Veterinary Teaching Hospital and a private veterinary clinic. These dogs were not Bull Terriers and were free of any condition known to cause proteinuria.

Unpaired two-tailed t tests and chisquared analyses were performed using

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#### Pathology

Full necropsy was performed on nine dogs. Tissue samples were fixed in 10% neutral-buffered

formalin. Formalin-fixed kidneys from a further five affected dogs were also obtained. Samples were processed for paraffin embedding and 5  $\mu m$  sections were cut and routinely stained with H&E and MSB. Semi-quantitative estimates of glome-rular tuft size were made using a 125  $\mu m$  graticule with a total magnification 20 x.

#### Results

# Diagnosis of BTPKD using renal ultra - sonography

Renal ultrasonography (Figure 1) allowed clear distinction between 34 affected (grade > 1) and 111 unaffected animals. The remaining five animals, all having affected first degree relatives, were diagnosed as equivocal. Two of these cases were young pups with less than three detectable cysts in one kidney, and BTPKD was confirmed on histopathological examination after necropsy. One adult is undergoing further tests. Two other adults were lost to follow-up. One of these had unilateral disease and the second had one detectable cyst in each kidney. Parentage was not verified in any of these cases.

#### Renal pathology

Fourteen of the 39 affected dogs were euthanased. In 13 of these, the kidneys appeared either normal or larger than normal in size. The remaining dog had one kidney that was smaller than normal, because of scarring. Architectural distortion due to multiple renal cysts (< 1 mm to > 2.5 cm diameter) was not always evident on initial inspection, but became obvious on sectioning. The cysts contained clear-to-cloudy, strawcoloured, serosanguinous or brown fluid, the latter presumably resulting from prior intracystic haemorrhage. The renal capsule was occasionally adherent to underlying parenchyma or cysts. In 12 cases the cysts were distributed randomly throughout both kidneys, with many located in the cortex or at the corticomedullary junction (Figure 2).

Histopathological examination of affected kidneys showed many circular and irregularly ovoid cysts, uni- or multi-loculated, with thin walls and usually a single lining layer of flattened squamous to low cuboidal epithelial cells (Figures 3 and 4). Occasional cysts had a stratified lining of cuboidal cells. Lining cells appeared to be derived from nephron elements. The epithelial cyst lining was supported by variable amounts of collagenous connective



Figure 1. Ultrasonographic image of a kidney from an animal with BTPKD showing cysts as anechoic lesions (hollow arrow) in the hypoechoic renal cortex.



Figure 2. Sagittal section of a kidney from a dog with BTPKD showing multiple variable sized cysts in the cortex and medulla.



Figure 3. Histological section showing a multiloculated renal cyst with squamous lining, supported by a collagenous wall of varying thickness. H & E, x 20.



Figure 4. Histological section showing a renal cyst lined with a cuboidal (black arrowhead) and focally stratified (black arrow) lining. The cyst contains sloughed cells (hollow arrow) and remnants of amorphous eosinophilic coagulum. H & E, x 20.

tissue demonstrable in sections stained with MSB. In many sections the cysts appeared empty, but some were filled with an eosinophilic homogeneous coagulum presumed to be proteinaceous. Some also contained red blood cells, inflammatory cells (macrophages and neutrophils), and sloughed epithelial cells.

Varying degrees of interstitial lymphocytic-plasmacytic infiltration were present in renal cortex and medulla of most animals, particularly adults, with a superimposed neutrophilic infiltrate in some areas and focal fibrosis. Radial tracts of inflammation and fibrosis of cortex and medulla, and dense medullary fibrosis, appeared more severe in adults. In one case diffuse interstitial oedema and scattered recent interstitial haemorrhages were present. A focal area of myxoid connective tissue was observed in another.

In general, cysts were not associated with glomeruli, although in six cases glomeruli in focal areas showed some cystic change associated with tuft atrophy and mesangial sclerosis. Glomerulocystic changes generally appeared in association with marked interstitial lymphocytic-plasmacytic infiltration and fibrosis. In three cases only one kidney showed such interstitial inflammation and glomerulocystic change, with the other uninflamed kidney showing negligible glomerulocystic change. A number of glomerular changes were evident, including hypercellularity, segmental sclerosis and global enlargement. Normal adult canine glomerular tufts are approximately 170 um in diameter (JC Hood unpublished), but many of these glomeruli were over 200 µm in diameter. In addition, in 13 cases, small, dark-staining foetal-type glomeruli were numerous, and in 5 dogs 10 to 15% of glomeruli were of this type; however one of these dogs was 2 months old. These glomerular changes have been described as characteristic of hereditary nephritis in this breed,13 suggesting that the lesions may occur in both diseases or that some dogs may have had both diseases.

#### Urinalysis

The mean UPC from voided urine samples in 71 normal dogs was 0.13 (SD 0.09). Accordingly the maximum normal UPC value (determined as two SDs above the mean), was 0.31 (95% confidence limit). A significantly higher proportion of BTPKD dogs (38%) had increased UPC ratios in voided urine samples ( $\chi^2$ =65.8, P=0.0001) when compared to normal dogs (4%) (Table 2). The method of urine collection did not appear to affect UPC ratios in BTPKD dogs of either sex. Increased UPC ratios were found in 6 of 9 affected male dogs (67%) and 7 of 25 affected female dogs (28%). There was no clear correlation between ultrasonographic grade of renal cystic disease and increased UPC in BTPKD dogs, but the number of affected dogs in each group was small.

Dogs with BTPKD had increased numbers of red and white blood cells in urine compared with normal dogs (Table 3). One animal from which a very small volume of urine was collected was excluded from the analysis, as the sample yielded great numbers of cells.

There were too few dogs for statistical analysis, but urine collected by cystocentesis from dogs with BTPKD tended to have lower epithelial cell counts (mean 4, SD 5) than did voided samples (mean 24, SD 21). No other differences were noted between collection methods. Males and females with BTPKD did not appear to differ in the prevalence of abnormal sediment in urine collected by either method.

# Prevalence and mode of inheritance in BTPKD

BTPKD was diagnosed in 26% (39 of 150) of Bull Terriers examined. The prevalence in males (27%, 13 of 48), was similar to that in females (26%, 26 of 102).

All affected dogs were descended from two closely related Bull Terriers, one of which had previously been diagnosed with BTPKD.<sup>10</sup> The other dog was not available for testing. Sixty-three dogs in this study also had renal ultrasonography results available for both parents (Table 4). X-linked inheritance could be eliminated since there were equal proportions of affected male and female offspring in litters born to affected parents, and either dam or sire could transmit the disease to offspring of each

Table 2. Comparison of numbers of normal dogs or dogs with BTPKD with UPC ratios above or below 0.31.

Group	Total no.	$\text{UPC} \leq 0.31$	UPC > 0.31	
Normal dogs	71	68	3	
BTPKD dogs	34	21	13	

Table 3. Cell numbers in urine of normal dogs and dogs with BTPKD.<sup>a</sup>

Group	Erythrocytes	Leukocytes	Epithelial cells
Normal dogs	0 - 53 (1)	0 - 520 (10)	0 - 143 (7)
BTPKD dogs	0 - 1517 (13)	3 - 1655 (123)	0 - 75 (10)

<sup>a</sup>Values are ranges, medians in parentheses, expressed as cells x 10<sup>6</sup>/L.

sex. A recessive mode of inheritance was eliminated because normal offspring that were adult at the time of testing could be produced from two affected parents. Furthermore many affected offspring arose from matings between one affected and one unaffected parent, with some of these matings being between animals unrelated to each other or to the affected line for five or more generations. Overall, these data strongly suggest an autosomal dominant mode of inheritance for BTPKD. Whether homozygous affected dogs with BTPKD survive the neonatal period remains unknown. However, PKD homozygous affected rats are severely affected and die very young.6

## Discussion

Diagnosis

Renal ultrasonography is the preferred method of diagnosis for PKD because of its high sensitivity, specificity and noninvasiveness.<sup>12,14</sup> Ultrasonography also uses neither radiation nor contrast material, is fairly inexpensive, quick to perform and readily available.<sup>12</sup>

Ultrasonographically, cysts appear as smooth, round, focal anechoic structures with sharply marginated walls.<sup>15-17</sup> As the renal cortex is more echogenic than the renal medulla,<sup>18</sup> cysts are more difficult to detect in the medulla than in the cortex. The presence of a cyst is confirmed by through-transmission and acoustic enhancement distal to and consistent with the size of the lesion.<sup>1</sup> Distortion of parenchyma<sup>15</sup> and alterations in renal structure can occur with severe disease and multiple cysts.

Diagnostic criteria for BTPKD were extrapolated from data published for

human ADPKD and feline PKD. Diagnosis of ADPKD is based on the presence of at least three cysts distributed between both kidneys, and a family history of the disease which confirms cysts to be inherited rather than acquired during the patients lifetime.12,19 A recent study reported a diag-

nostic sensitivity of 89% at age 15 to 29 years, and 100% at 30 years and older for the most common form of ADPKD.<sup>14</sup> In less severe ADPKD, renal cysts may appear later in life.<sup>20</sup> A false-positive rate of 2% has been reported.<sup>21</sup>

One cause of false positive diagnoses is the presence of simple renal cysts, which occur sporadically in many species and are usually an incidental finding.<sup>22</sup> The prevalence of simple renal cysts is low in children<sup>23</sup> but increases with age.<sup>14</sup> In view of this, recognition of ADPKD has been improved in patients younger than 30 years by requiring detection of two renal cysts (unilaterally or bilaterally distributed),<sup>14</sup> or any number of renal cysts in children,<sup>23</sup> together with a history of affected family members.14 Renal imaging of first-degree relatives can be useful to establish a family history.<sup>19</sup> Patients 30 to 59 years old require demonstration of two or more cysts in each kidney, and older patients at least four cysts in each kidney<sup>14</sup> for diagnosis of ADPKD.

In Persian cats the diagnosis of PKD by renal ultrasonography is possible as early as 7 weeks of age with a sensitivity of 91% at 36 weeks.<sup>1</sup> Using ultrasonography, simple renal cysts are infrequently detected in cats,16 but in dogs simple renal cysts are reported to be common.24 Although simple renal cysts have been observed in dogs at necropsy, in our experience and the experience of others they are relatively uncommon.<sup>22</sup> In this study involving renal ultrasonographic examination of dogs of many ages, while it was not possible to distinguish simple renal cysts from PKD definitively, all dogs with any renal cysts had an affected firstdegree relative. Hence any dog with an affected first-degree relative and detectable renal cysts was regarded as at risk, especially if it was less than 3 years old.

Variation in the echotexture of normal kidneys in Bull Terriers was noted, and may make definitive diagnosis of BTPKD difficult. Definitive diagnosis requires distinguishing this normal variation from other disease processes such as neoplasia, nephritis, <sup>16</sup> haematomas, abscesses<sup>16,17</sup> and true cystic change.

The gradual or late enlargement of renal cysts in ADPKD may cause variation in the age at which cysts become detectable.<sup>12,19,25</sup> Such variation in severity of disease at a given age makes diagnosis difficult in mildly affected individuals and may explain the few equivocal cases in this study. Bilateral asymmetry of cystic involvement has been reported in ADPKD,<sup>9,26</sup> and was observed in one Bull Terrier over 3 years of age in this study.

Alternative testing modalities such as magnetic resonance imaging<sup>27</sup> or computed tomography<sup>28</sup> may be useful in resolving these equivocal cases. Conventional radiology and intravenous urography are reportedly less sensitive than ultrasonography for detection of renal cysts.<sup>16,17</sup> Renal biopsy is unnecessary for diagnosis in most cases of PKD, and in early ADPKD no obvious histological changes may be present and the lesions may not be generalised in distribution.<sup>29</sup>

Trial matings may or may not help establish a diagnosis, as the significance of a negative renal ultrasound in young offspring is unknown. However, the affected status of an equivocal animal could be established definitively if it were mated with an unequivocally normal animal and affected offspring were produced.

Repeated examination or alternate testing procedures may be necessary in equivocal cases. If renal ultrasonography detects no change over a prolonged period, it would suggest either the presence of simple renal cysts, another renal disease, or biological variation in a normal Bull Terrier.

# Predicted clinical signs and association with renal lesions

Renal interstitial oedema and haemorrhage and cortical and medullary parenchymal inflammation have been observed in BTPKD, and may be associated with interaction of cysts with the

## Table 4. Analysis of the pattern of inheritance of BTPKD.<sup>a</sup>

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Type of mating	Code for parents affected/ nonaffected status	Offspring with BTPKD proportion	Offspring with BTPKD percentage	Predicted percentage of affected offspring if autosomal dominant inheritance <sup>b</sup>
2 parents diagnosed as not having BTPKD	n x n	0 of 31	0	0
1 parent diagnosed as not having BTPKD and 1 parent diagnosed as having BTPKD	n x N	17 of 27	63	50
1 parent diagnosed as having BTPKD and other parent strongly suspected as normal or vice versa	n? x N or N? x n	32 of 60	53°	50
2 parents diagnosed as having BTPKD	N x N	3 of 5	60	75
1 parent strongly suspected as having BTPKD 1 parent diagnosed as having BTPKD.	N? x N	7 of 9	78	75

<sup>a</sup>n is animal diagnosed as not having BTPKD, n? is animal from breeding line not known to be affected by BTPKD, N is animal diagnosed as having BTPKD, N? is animal strongly suspected as having BTPKD on the basis of having produced affected offspring when mated to unaffected animals.

<sup>b</sup>On the assumption that dogs with BTPKD are heterozygous.

<sup>c</sup>Five equivocal cases included here as affected.

renal parenchyma, as is thought to occur in ADPKD.<sup>30,31</sup> The high prevalence of pyelonephritis, renal fibrosis and renal cyst inflammation suggests that secondary bacterial urinary tract infection and renal disease are likely to occur in BTPKD.

In Persian cats with PKD, clinical renal disease typically becomes evident at 3 to 10 (mean 7) years.<sup>1</sup> In the most common form of human ADPKD, renal function is impaired in more than 60% of affected people 40 years of age or older: 15% of these patients enter end stage renal failure by age 40 and 75% develop failure at 41 to 65 years.<sup>32</sup> Renal disease may also occur in affected children.<sup>26</sup>

#### Urinalysis

Proteinuria is reported in human ADPKD, most commonly in the later stages of disease.<sup>33</sup> More severe proteinuria is associated with poor prognosis.<sup>33</sup> In a prior study, all dogs with BTPKD, for which urinalysis results were available, were proteinuric.<sup>10</sup>

The UPC allows an accurate estimation of proteinuria from a single urine sample in dogs,<sup>35</sup> but an increased UPC does not indicate whether the source of the protein is prerenal, renal or postrenal. A high proportion of dogs with BTPKD had increased UPC. The source of proteinuria may be a primary abnormality associated with BTPKD, or it might also be due to the renal inflammation observed histopathologically, or to another disease such as bacterial pyelonephritis or hereditary nephritis. UPC is a currently used screening test for hereditary nephritis in Bull Terriers: increased UPC in the absence of increased urine cell numbers suggests the presence of this disease, which is common in Australia.<sup>36</sup>

An increased UPC in a Bull Terrier, with or without active urine sediment, may thus be due to hereditary nephritis, BTPKD, another urogenital or prerenal disease or a combination of these. Definitive diagnosis would involve physical examination of the animal, complete urinalysis and further diagnostic testing.

In patients with ADPKD, haematuria is often associated with more severe disease,<sup>23,34</sup> and urinary tract infections<sup>34,37</sup> are also common. In a prior study, all four animals with BTPKD, for which urinalysis results were available, were haematuric and pyuric, and three of these also had bacteria in the urine or other evidence of urinary tract infection.<sup>10</sup> In this study, increased numbers of red and white blood cells in the affected dogs' urine may result from BTPKD itself, or may reflect a higher prevalence of urinary tract inflammation as was observed histopathologically. Since no microbiological data were collected on urine, further work in this area is necessary.

#### Inheritance mechanism

Autosomal dominant transmission is likely and while disease penetrance appears high, it may not be complete. Definitive diagnosis was difficult in 13%of cases using renal ultrasonography, and in one of three of the equivocal cases that went to necropsy. Difficulties in diagnosing early cases with renal ultrasonography or with renal biopsy have also been reported in ADPKD.<sup>29</sup> The occurrence of unilateral disease (one dog) and fewer than three renal cysts in dogs over 3 years of age (two dogs), raises the possibility of variable disease expression or variable penetrance of the mutant gene. Other possible explanations for equivocal cases include sampling areas of the kidneys with no detectable cysts, incorrect recording of parentage, or the presence of early renal changes that may have progressed with age.

#### Disease monitoring and treatment

Bull Terriers with BTPKD should be monitored for signs of renal disease and urinary tract infections. Serial monitoring of renal function, UPC and urinalysis, and renal ultrasonography may help to monitor disease progression. Increasing azotaemia, proteinuria and renal size, or the development of haematuria, are likely to be bad prognostic indicators. Early detection of this disease and prevention of complications may improve the quality and length of life for affected dogs.

#### Conclusion

BTPKD is a relatively recently reported inherited disease in Bull Terriers. Clinicians should be aware of this disease because of its high prevalence in some lines of show and breeding Bull Terriers in Australia. As the disease appears to be inherited in a highly pene-

trant autosomal dominant manner, the numbers of affected Bull Terriers and their crosses may increase unless determined efforts are made to discourage breeding of affected animals. Bull Terrier breeders and owners should be encouraged to prevent breeding of affected animals and to promote breeding of dogs prescreened using renal ultrasonography.

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