Inheritance of Polycystic Kidney Disease in Persian Cats


Polycystic kidney disease in Persian cats culminates in chronic renal failure after a variable clinical course. An affected 6-year-old Persian cat was used to establish a colony of cats with polycystic kidney disease. In affected cats, cysts could be detected by ultrasonography as early as 7 weeks of age. Absence of cysts on ultrasound examination at 6 months of age was correlated with absence of polycystic kidney disease at necropsy. Both male and females were affected and, of progeny from affected × unaffected crosses, 42% were affected and 58% were unaffected. In affected × affected crosses, 73% of progeny were affected and 27% were unaffected. These results are compatible with autosomal dominant inheritance of this trait. Polycystic kidney disease in Persian cats resembles autosomal dominant polycystic kidney disease (ADPKD) in human beings, and represents a valuable animal model of the human disease.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder of human beings, occurring in 1 in 200 to 1 in 1,000 people (Kimberling et al. 1991; Welling and Grantham 1991). The disease occurs in all races, affecting as many as 5 million people worldwide. It is one of the most common causes of end-stage renal disease in the United States, and accounts for approximately 10% of patients on dialysis (Welling and Grantham 1991).

Polycystic kidney disease has been described in adult male and female long-haired, Persian-type cats (Battershell and Garcia 1969; Lulich et al. 1988; Northington and Juliana 1977; Stebbins 1989), and a family of affected Persian cats has been described (Biller et al. 1990). In affected cats, the kidneys are enlarged and irregular, and renal failure develops after a variable number of years. Azotemia [creatinine 2.6 mg/dL (normal, 0.8–1.8 mg/dL), BUN 69 mg/dL (normal, 15–35 mg/dL)] and decreased renal concentrating capacity [urine specific gravity 1.012 (normal, > 1.045)] were present. Abdominal radiographs showed bilateral renomegaly, and multiple well-circumscribed, round filling defects caused distortion of the renal pelvis on excretory urography. Multiple cysts were observed in both kidneys on ultrasonography. At necropsy, the cortex and medulla of both kidneys contained many epithelial-lined cysts that ranged from 5 mm to 10 mm in diameter. Cysts were not observed in other organs.

Offspring from two litters born to this affected queen and an unaffected male Persian cat were used to establish a colony of cats with polycystic kidney disease (Figure 1). The sire used in these breedings was determined to be unaffected by renal ultrasonography. One litter was comprised of one affected male (#473) and one affected female (#475). The affected male (#473) served as sire for nine breedings.

Materials and Methods

Description of Propositus and Establishment of Breeding Colony

The propositus was a 6-year-old female Persian cat referred to the Ohio State University Veterinary Teaching Hospital in 1987 for evaluation of polyuria and polydipsia (Biller et al. 1990). The cat was thin and both kidneys were enlarged. Azotemia [creatinine 2.6 mg/dL (normal, 0.8–1.8 mg/dL), BUN 69 mg/dL (normal, 15–35 mg/dL)] and decreased renal concentrating capacity [urine specific gravity 1.012 (normal, > 1.045)] were present. Abdominal radiographs showed bilateral renomegaly, and multiple well-circumscribed, round filling defects caused distortion of the renal pelvis on excretory urography. Multiple cysts were observed in both kidneys on ultrasonography. At necropsy, the cortex and medulla of both kidneys contained many epithelial-lined cysts that ranged from 5 mm to 10 mm in diameter. Cysts were not observed in other organs.

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The affected female (#475) from this litter was euthanatized due to renal failure at 10 years of age. The second litter was comprised of one affected male (#472) and two unaffected females (#474, #476). The affected male (#472) served as sire for three breedings and one unaffected female (#474) served as queen for one breeding. The remaining unaffected female (#476) in the second litter was lost to follow up. The affected male (#472) died of renal failure at 8 years of age. The domestic shorthaired cats (#038, #045, #127, #224, #296, #340, #464) used in this study were unrelated individuals donated from a multiple cat household by a private individual. These domestic shorthaired cats, and cats in the F1 generation (#472–#476) were not included in the data analyzed for the present study.

Of the remaining 115 cats in Figure 1, 75 had renal histopathology (N = 54) or complete necropsy (N = 21) performed, 11 remain in the colony, 17 were provided as research animals to other investigators, and 12 were adopted as pets and lost to follow up. The colony is being maintained, and blood and tissue samples are available for collaborative research.

Ultrasonography
Ultrasonography was used to establish or eliminate a diagnosis of polycystic kidney disease in 102 of 115 cats in this study. These 102 cats included 62 of those with renal histopathology or necropsy data, all 11 cats remaining in the colony, all 17 cats provided as research animals to other investigators, and all 12 cats adopted as pets. In the remaining 13 cats, ultrasonography was not performed, and the diagnosis was confirmed or eliminated by gross and microscopic pathology. Renal ultrasonography was performed using a 7.5 MHz transducer and an ATL UltraMark 4 high-resolution real-time ultrasonography unit with videotape and multifomat camera for hard copy backup. Cats were scanned in dorsal recumbency in the awake state or sedated with ketamine (10 mg/kg) administered intramuscularly. Longitudinal and transverse plane images of the kidney were examined.

Cysts were identified as anechoic, spherical structures with smooth, sharply margined walls and through-transmission (acoustic enhancement posterior to and consistent with the size of the lesion). Ultrasonography was performed on cats ranging in age from 7 weeks to 12 months, and ultrasound examinations were repeated two to five times over several months.
In 62 cats, both ultrasonography and renal histopathology were performed.

Pathology
Renal histopathology (N = 54) or complete necropsy (N = 21) were performed in 75 cats at ages ranging from 1 day (neonatal deaths) to 6 years. The light microscopic, electron microscopic, and immunohistochemical findings in the 21 cats that had complete necropsies performed and in one cat from the F1 generation (#472) have been reported elsewhere (Eaton et al., in press). In the remaining 54 cats, renal tissue was examined by light microscopy, but complete necropsy examinations were not performed. For histologic examination, selected tissue samples collected at necropsy were fixed in neutral buffered 10% formalin, embedded in paraffin, cut in 6 μm sections, and stained with hematoxylin and eosin.

Statistics
Affected cats were identified by renal ultrasonography, gross and microscopic pathology, or both as described above. Results of breeding trials were subjected to standard chi-square analysis. A P value of less than .050 was considered significant.

Results
Breeding Studies
Breeding studies were carried out in which affected cats were bred to affected and unaffected cats. From these breedings, 115 kittens were born of which 71 (62%) were males and 44 (38%) were females ($\chi^2 = 2.755, P = .097$). Of the 115 kittens, 52 (45%) were affected and 63 (55%) were unaffected. Of the 52 affected cats, 29 (56%) were male and 23 (44%) were female ($\chi^2 = 0.154, P = .694$). Of the 63 unaffected cats, 42 (67%) were male and 21 (33%) were female ($\chi^2 = 2.947, P = .086$).

There were 11 offspring from breedings of affected cats to affected cats. In all instances, these breedings were backcrosses in which affected Persian cats were bred to affected mixed breed cats. The affected mixed breed cats were offspring of outcrosses of affected Persian cats to unaffected domestic shorthaired cats. Of these 11 cats, 8 (73%; 5 male, 3 female) were affected and 3 (27%; 1 male, 2 females) were unaffected. The observed sex ratios did not differ significantly from the expected ratios when all offspring ($\chi^2 = 0.046, P = .831$), affected offspring ($\chi^2 = 0.000, P = 1.000$), or unaffected offspring ($\chi^2 = 0.171, P = .679$) were considered. Chi-square analysis of the results for the polycystic kidney disease phenotype was performed using a null hypothesis of dominant inheritance and the assumption of lethality for the homozygous genotype. This analysis yielded $\chi^2 = 0.024 (P = .877)$. The same data were subjected to chi-square analysis using a null hypothesis of dominant inheritance and the assumption of nonlethality for the homozygous genotype. This analysis yielded $\chi^2 = 0.132 (P = .716)$.

There were 104 offspring from breedings of affected to unaffected cats. Of these 104 cats, 44 (42%; 24 males, 20 females) were affected and 60 (58%; 41 males, 19 females) were unaffected. The observed sex ratios did not differ significantly from the expected ratios when all offspring ($\chi^2 = 2.813, P = .093$), affected offspring ($\chi^2 = 0.046, P = .831$), or unaffected offspring ($\chi^2 = 3.449, P = .063$) were considered. Chi-square analysis of the results for the polycystic kidney disease phenotype using a null hypothesis of dominant inheritance yielded $\chi^2 = 0.948 (P = .330)$. The offspring in this group were derived from outcrosses of affected Persian cats or affected mixed breed cats to unaffected domestic shorthaired cats. Of 61 offspring produced by breedings between affected Persian cats and unaffected domestic shorthaired cats, 29 (48%) were affected and 32 (52%) were unaffected. Chi square analysis of this data using a null hypothesis of dominant inheritance yielded $\chi^2 = 0.008 (P = .928)$.

In affected × unaffected crosses, there were 65 offspring (31 affected, 34 unaffected) from breedings in which the male parent was affected and 39 offspring (13 affected, 26 unaffected) from breedings in which the female parent was affected. On chi-square analysis, the proportions of affected offspring in these different types of crosses did not differ significantly ($\chi^2 = 1.513, P = .219$).

Imaging Studies
The earliest age at which cysts could be detected by ultrasound examination was 7 weeks. In seven cats, ultrasound examinations initially were negative, but a diagnosis of polycystic disease was made at a later age by repeated ultrasound examination or by gross and microscopic pathology. One cat (#744) was negative on ultrasound examination at 10, 17, and 27 weeks of age, but was determined to have polycystic disease at necropsy performed at 44 weeks of age. Another cat (#791) was negative on ultrasound examination at 7 and 22 weeks of age but was positive when ultrasound examination was performed at 35 weeks of age. This cat was confirmed as affected when necropsied at 5 years of age. Two cats (#782 and #786) were negative on ultrasound examination at 7 and 8 weeks of age but had gross and microscopic evidence of polycystic kidney disease when necropsied at 10 and 11 weeks of age, respectively. In the remaining three cats (#789, #803, and #806), ultrasound examination for cysts was negative at 7 to 8 weeks of age, but positive when repeated at 17 to 22 weeks of age. Cat #789 is still in the colony, cat #803 was confirmed to be affected at necropsy performed at 3 years of age, and cat #806 was studied by another investigator and confirmed to be affected at the time of euthanasia.

Both ultrasonography and renal histopathology were performed in 62 of the 115 cats in Figure 1 that comprise the present study. The sensitivity and specificity of ultrasonography for the diagnosis of polycystic kidney disease were calculated using data from these 62 cats. Sensitivity was defined as the number of affected cats positive on ultrasound at or younger than a specified age divided by the total number of cats positive for polycystic kidney disease on renal histopathology. Specificity was defined as the number of unaffected cats negative on ultrasonography divided by the total number of cats negative for polycystic kidney disease on renal histopathology. Using these definitions, ultrasonography had a sensitivity of 75% (15/20) and a specificity of 100% (21/21) when performed at ≤16 weeks of age and a sensitivity of 91% (29/32) and a specificity of 100% (30/30) when performed at ≤36 weeks of age.

Pathologic Findings
At necropsy, polycystic kidney disease was diagnosed by the presence of renal cysts ranging in size from <1 mm to approximately 20 mm and in number from 20 to >200 per kidney (Figure 2) (Eaton et al., in press). Cysts were present in the renal cortex and medulla of both kidneys, and their number, size, and appearance varied markedly among cats. In spite of marked individual variation in cyst size, cysts tended to be larger in older cats. Histologic lesions were confined to the kidneys and liver. Renal cysts were lined by epithelium which varied from cuboidal to squamous. Some cysts were surrounded by interstitial fibrosis or lymphoplasmacytic inflammation, and some cysts com-
pressed adjacent renal parenchyma. Many cysts, however, were not accompanied by lesions in the adjacent parenchyma. In addition to renal cysts, mild to severe widespread multifocal chronic tubulointerstitial nephritis was present in affected cats, and was more common in older cats. Chronic tubulointerstitial nephritis was characterized by lymphoplasmacytic interstitial infiltration, interstitial fibrosis, and associated tubular epithelial atrophy and regeneration. Small hepatobiliary cysts were observed in the livers of 2 cats, and mild to marked, widespread biliary hyperplasia and fibrosis were observed in the livers of 10 affected cats.

Discussion

Animal models of polycystic kidney disease include chemically induced and spontaneously occurring genetic forms of the disease in mice and rats (Gattone and Grantham 1991). Chemically induced models include those produced by administration of diphenylthiazole, nordihydroguaiaretic acid, and corticosteroids. Cpk and pcy strains of mice develop polycystic kidney disease that is inherited as an autosomal recessive trait. A form of autosomal dominant polycystic kidney disease has been described in the Han:SPRD rat (Cowley et al. 1993; Kaspireit-Rittinghausen et al. 1989; Schafer et al. 1994). This disease leads to massive renal enlargement, uremia, and death by 2 to 3 weeks of age in affected homozygotes. Heterozygous males develop renal cysts, progressive interstitial fibrosis, and azotemia by 6 months of age whereas heterozygous females develop stable renal disease without azotemia (Cowley et al. 1993).

The gene responsible for the most common form of ADPKD in human beings has been localized to the short arm of chromosome 16 in the region of the α-globin and phosphoglycolate phosphatase genes (ADPKD1) (Reeders et al. 1985, 1986). Genetic heterogeneity for ADPKD was soon recognized (Kimberling et al. 1988) and a second ADPKD gene (ADPKD2) was assigned to chromosome 4 (Kimberling et al. 1993; Peters et al. 1993). Other genetic forms of polycystic kidney also may exist (Daoust et al. 1993). Recently, the complete structure of the ADPKD1 gene and its protein product have been reported (Consordium 1994, 1995). The amino acid sequence predicted by the ADPKD1 gene does not show homology with known proteins. Carriers of the ADPKD1 gene are thought to account for approximately 85% of ADPKD in human beings, with most of the remaining cases being associated with ADPKD2 (Peters and Sandkuil 1992).

Several adult cats with polycystic kidney disease have been reported in the veterinary literature in the past 30 years (Battershell and Garcia 1969; Caputo 1980; Lulich et al. 1988; Northington and Juliana 1977; Rendano and Parker 1976; Stebbins 1989). Speculation that polycystic kidney disease in Persian cats is an inherited trait was based on its common occurrence in longhaired or Persian-type cats and identification of the disease in a family of related Persian cats (Biller et al. 1990). Until now, however, the mode of inheritance was unknown.

Results of the present study support the conclusion that polycystic kidney disease in Persian cats is inherited as an autosomal dominant trait. Chi-square analysis indicated that the observed distribution of offspring in affected × unaffected crosses was not significantly different from the 50% predicted by the assumption of dominant inheritance. The percentage of affected offspring did not differ significantly whether the affected parent was male or female. The distribution of offspring in affected × affected crosses also was consistent with autosomal dominant inheritance. On chi-square analysis, these results were not significantly different from the 75% of offspring expected to be affected with simple dominant inheritance or from the 67% of offspring expected to be affected with dominant inheritance and lethality of the homozygous genotype. The occurrence of unaffected cats in these breeding effectively eliminated the possibility of autosomal recessive inheritance. In addition, the breeding experiments in this study demonstrated male-to-male, male-to-female, female-to-male, and female-to-female transmission, effectively eliminating X-linked inheritance. Finally, the trait of polycystic kidney disease has been maintained in the colony for four generations and all affected kittens have had at least one affected parent.

In the Han:SPRD rat, homozygotes are easily recognized because their kidneys enlarge rapidly and constitute 25%–30% of body weight by 3 weeks of age (Cowley et al. 1993). In human beings with ADPKD, the homozygous state has not yet been recognized despite the fact that ADPKD is a relatively common disease. In Persian cats with ADPKD, individual cats with extremely rapid disease progression (i.e., development of renal failure by 1 year of age) have not been observed, and the homozygous genotype has not yet been identified. Of six cats with polycystic kidney disease previously reported in the veterinary literature, four were longhaired or Persian-type (Battershell and Garcia 1969; Lulich et al. 1988; Northington and Juliana 1977; Stebbins 1989) and two were shorthaired cats (Caputo 1980; Rendano and Parker 1976). Polycystic kidney disease also has been reported in a shorthaired cat with renal lymphosarcoma (Podell et al. 1992). These observations still are compatible with dominant inheritance of this trait in Persian cats. Many cats in the colony described in this report have short hair and lack the typical brachycephalic facial conformation of Persian cats. Presumably, long hair coat and brachycephalic facial conformation do not segregate with polycystic kidney disease in the cat.

The variable number and size of renal cysts in the Persian cats of this study resemble what is observed in human beings with ADPKD, and the rate of progression of renal disease is highly variable in both species. Hepatic cysts commonly complicate ADPKD in human patients, especially women (Gabow 1993; Kaehny and Everson 1991), but were uncommon in Persian cats of either sex (Eaton et al., in press). Hepatobiliary fibrosis was a common lesion in affected cats, but its presence was not correlated with the severity of the renal lesions. Both hepatic fibrosis and chronic tubulointerstitial nephritis were more common in older cats. Hepatic fibrosis is uncommon, but has been reported in human patients with ADPKD (Cobben et al. 1990; Ramos et al. 1990). The occurrence of extrarenal lesions in Persian cats with ADPKD further supports its validity as an animal model of the human disease.

The penetrance (i.e., presence or ab-
sence of cysts) and expression (i.e., severity of the disease) of ADPKD are age-dependent in human patients (Kimerling et al. 1991). In ADPKD1, approximately 90% of presumed gene carriers will have cysts that can be identified by ultrasound by age 20 (Bear et al. 1992). In most affected cats subjected to ultrasound at <16 weeks of age, the renal parenchyma appeared normal except for the presence of small (1–2 mm) cysts. Only two cats that were negative on ultrasound examination at 6 months of age were later found to have ADPKD at subsequent ultrasound examination or at necropsy. This suggests that absence of renal cysts in young adulthood is associated with a low risk of later development of ADPKD both in human patients and cats.

Approximately 45% of human patients with ADPKD will develop renal failure by age 60, but the age of onset ranges from 2 to 80 years (Gabow 1993). In adult patients with renal cysts on ultrasonography, the risk of developing renal failure was estimated to be 2% by age 40, 23% by age 50, and 48% by age 73 (Churchill et al. 1984). The age at which renal failure develops in Persian cats with ADPKD also is variable. The average age of onset of renal failure in affected cats is 7 years, with a range of 3 to 10 years.

There are several possible explanations for variability in the clinical progression of ADPKD. Environmental factors may play a role. Hypertension, multiple pregnancies, and urinary tract infections were some factors potentially influenced by environment that were associated with more rapid progression in one study of affected human patients (Gabow et al. 1992). Genetic factors also may contribute to variability in expression of ADPKD. Different genetic loci for ADPKD can result in variations in clinical course. For example, the age of onset of renal failure is later in patients with non-ADPKD1 genotypes (Parfrey et al. 1990). Interactions with other genes or different alleles at a single ADPKD locus also may occur (Kimerling et al. 1991). Even within ADPKD1 families, there may be marked variation in the severity of the disease and the age of onset of renal failure (Muttilinovic et al. 1992). One possible explanation for such variation within families is unstable DNA with varying numbers of triplet repeat sequences within the gene (Fick et al. 1994).

In summary, polycystic kidney disease in Persian cats closely resembles ADPKD in human beings. Both diseases are inherited as autosomal dominant traits. Both diseases are characterized by development and enlargement of cysts in the renal cortex and medulla resulting in progressive renalmegaly. Finally, both diseases usually are accompanied by onset of renal failure late in life, although, in both species, there is marked variability in the clinical course of the disease.

References

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