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Topical Review

A Review of the Genetics of Hypoadrenocorticism

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Hypoadrenocorticism is an uncommon disease in dogs and rare in humans, where it is known as Addison disease (ADD). The disease is characterized by a deficiency in corticosteroid production from the adrenal cortex, requiring lifelong hormone replacement therapy. When compared with humans, the pathogenesis of hypoadrenocorticism in dogs is not well established, although the evidence supports a similar autoimmune etiology of adrenocortical pathology. Several immune response genes have been implicated in determining susceptibility to Addison disease in humans, some of which are shared with other autoimmune syndromes. Indeed, other types of autoimmune disease are common (approximately 50%) in patients affected with ADD. Several lines of evidence suggest a genetic component to the etiology of canine hypoadrenocorticism. Certain dog breeds are overrepresented in epidemiologic studies, reflecting a likely genetic influence, supported by data from pedigree analysis. Molecular genetic studies have identified similar genes and signaling pathways, involved in ADD in humans, to be also associated with susceptibility to canine hypoadrenocorticism. Immune response genes such as the dog leukocyte antigen (*DLA*) and cytotoxic T-lymphocyte–associated protein 4 (*CTLA4*) genes seem to be particularly important. It is clear that there are genetic factors involved in determining susceptibility to canine hypoadrenocorticism, although similar to the situation in humans, this is likely to represent a complex genetic disorder.

Introduction to Hypoadrenocorticism

Hypoadrenocorticism is an uncommon disease in dogs and is rare in humans, where it is known as Addison disease (ADD). It is characterized in both humans and dogs by a deficiency in corticosteroid production from the adrenal cortex, requiring lifelong hormone replacement therapy. Hypoadrenocorticism is a challenging disease for dog owners, breeders, and veterinary surgeons, often with waxing and waning nonspecific clinical signs that can become severely life threatening. Anecdotally and based on postmortem data, it is likely that hypoadrenocorticism is underdiagnosed.[1,2] For these reasons, there is interest in developing genetic[3-5] or serologic tests[6,7] that might be employed in identifying dogs at risk. These would be useful tools, both for diagnosis of individuals in veterinary clinical practice and for informing selective breeding programs.

Dogs have a high prevalence of spontaneous primary hypoadrenocorticism compared with other species. Adrenal gland pathology is similar to that seen in human autoimmune ADD, with lymphocytic adrenalitis progressing to adrenocortical atrophy,[1,8,9] as the adrenal cortex is destroyed by an immune-mediated inflammatory process. The condition has been identified as an inherited disease with a moderate-to-severe effect on dog health and welfare affecting a wide range of popular breeds.[10] Further evidence of an autoimmune pathogenesis has been shown recently, whereby circulating autoantibodies against the steroid synthesis enzymes 21-hydroxylase[11] and p450 side chain–cleavage enzyme (p450scc)[7,11,12] have been demonstrated in dogs affected with hypoadrenocorticism, both of which are also seen in humans with ADD.[13-15]

Secondary hypoadrenocorticism, resulting from nonadrenal disease, is even less common than primary hypoadrenocorticism, accounting for approximately 2%-4% of cases of hypoadrenocorticism in referral populations.[16,17] Reported causes of secondary hypoadrenocorticism include head trauma[18,19] and withdrawal of steroid administration,[20,21] although in most case reports, the underlying cause is not identified.[16,17,22] Given the limited information available, secondary hypoadrenocorticism has not been considered further in this review.

Comparative research into canine hypoadrenocorticism has great potential for better understanding of genetic susceptibility to autoimmune disease,[23] and interest in using canine models of human disease is increasing as part of the "One Biology, One Health" strategy. Such comparative and collaborative research has the potential to improve our understanding of both canine and human diseases to the benefit of both species.[8]

Autoimmune Polyglandular Syndromes

In humans, AAD not only manifests as an isolated condition but also occurs in association with other autoimmune disorders, termed autoimmune polyglandular or polyendocrine syndrome (APS).[24] Approximately 50% of patients with ADD have a

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Table 1
Criteria of Multiple Autoimmune Syndrome (MAS) Types in Humans. (Modified With Permission From Betterle et al. 2002.[28])

Type	Inclusion Criteria
MAS type 1	At least 2 present: of chronic candidiasis, hypoparathyroidism, or AAD
MAS type 2	AAD and either T1D or ATD
MAS type 3	ATD and other autoimmune disease(s) (excluding AAD, hypoparathyroidism, and chronic candidiasis)
MAS type 4	Two or more organ-specific autoimmune diseases (which do not fall into type 1, 2, or 3)

concurrent autoimmune disorder, most commonly autoimmune thyroid disease (ATD) or type 1 diabetes (T1D).[8,25] The prevalence of autoimmune comorbidity in a recent Norwegian study[26] was 66%, with 47% having ATD, 12% T1D, 11% vitiligo, 10% vitamin B12 deficiency, and 6.6% of women with premature ovarian failure. Female AAD patients are reported to be more likely to be affected with a concurrent immune-mediated disorder (72%) than men are (42%).[26] Owing to the range of autoimmune diseases exhibited by these patients, there has been a recent move to rename APS as multiple autoimmune syndrome (MAS).[27]

A standardized nomenclature has been adopted to classify patients with autoimmune comorbidities, categorizing them under APS/MAS types 1-4 (Table 1).[28] Clinically, the classifications MAS types 3 and 4 are not in common usage and are often combined with MAS type 2.[24]

In the veterinary literature, there are relatively few published reports of multiple endocrinopathies affecting dogs. There are a number of case reports of dogs with concurrent hypoadrenocorticism and hypothyroidism, including an 8-year-old female boxer,[29] a 9-year-old female Weimaraner,[30] a 3-year-old male Doberman,[31] a 4-year-old female Great Pyrenees,[32] a 6-year-old female Russian black terrier,[33] and a 2-year-old female standard poodle.[34] In a case series of related Leonburgers with hypoadrenocorticism, 2 of the 4 dogs had concurrent hypothyroidism.[35] The largest case series of concurrent hypoadrenocorticism and hypothyroidism was of 10 dogs that had thyroid function testing performed after being diagnosed with hypoadrenocorticism due to poor response to steroid replacement therapy.[36]

Concurrent endocrinopathies in dogs are mentioned in 2 large retrospective studies. In 1 report of 187 cases of hypoadrenocorticism, 28 (15%) had at least one other endocrinopathy, 16 (8.6%) had hypothyroidism, 14 (7.5%) diabetes, 3 (1.6%) hypoparathyroidism, and 2 (1%) had azoospermia.[16] In the second of these studies, which included data from 225 dogs with hypoadrenocorticism, 11 (4.9%) had a concurrent endocrinopathy noted, 10 had hypothyroidism, 2 had diabetes, and 1 had hypoparathyroidism.[17] A cross-sectional analysis of dogs with hypoadrenocorticism found an odds ratio for concurrent hypothyroidism of 4.65 (95% CI; 3.04-7.12); however, the author advised caution in interpretation owing to potential measurement bias.[37] An examination of concurrent autoimmune diseases in Italian greyhounds has shown 9% prevalence in a retrospective, hospital-based analysis and approximately 2%-4% of individuals affected in a cross-sectional breeder-based analysis; half of this population had more than one concurrent autoimmune disorder.[38] Hypoadrenocorticism was the third most prevalent problem, with immune-mediated hemolytic anemia and a systemic lupus erythematous–like disease more common; thyroiditis was less commonly noted.[38]

These findings suggest that concurrent autoimmune diseases might be more common in the canine population than previously recognized. The underlying genetic associations discussed later in this review might explain these findings in dogs, as in the situation in humans, autoimmune susceptibility genes are likely to be common to several immune-mediated diseases, including AAD, ATD, and T1D.

Epidemiology of Canine Hypoadrenocorticism

The incidence of AAD in the human population is estimated to be approximately 0.4-1 per 100,000 people per year,[26,28] giving a reported prevalence of approximately 40-144 per 1,000,000, but with wide geographic variance. The estimated prevalence of canine hypoadrenocorticism is greater, with cross population estimates between 0.3% and 1.1%.[37,39] The incidence of hypoadrenocorticism has been estimated at approximately 0.5 per 1000 dogs per year.[16] The age of onset is typically between 2 and 6 years;, however, the diagnosis can be made at almost any age with a range of 3 months to 14 years reported.[17,40] ADD is more common in women than in men,[28] and there might be a similar sex bias in dogs, with bitches having a higher incidence of disease[17,37]; though this is not always consistent with some breed-specific studies showing equal sex split.[5,41-43]

A wide range of breeds are affected with hypoadrenocorticism, but the most commonly diagnosed breed classification in larger studies is the crossbreed.[16,17,37,41] In these analyses, there is significant overrepresentation and underrepresentation of certain breeds, as shown in Tables 2 and 3. Table 4 shows data from a study by Kelch,[37] detailing breed-specific incidence estimates in a US referral population. Some breed-specific studies of hypoadrenocorticism have reported higher prevalence estimates, including standard poodles (10%),[5] Portuguese water dogs (PWDs) (minimum of 1.5%),[44] and bearded collies (3.4%).[45] There are also family-based case series reported in the literature including lines of Leonbergers,[35] Nova Scotia duck tolling retrievers (NSDTRs),[46] soft-coated wheaten terriers,[43] and Pomeranians.[47] These breed-specific differences strongly suggest a genetic predisposition to hypoadrenocorticism.

In addition to breed-specific prevalence and risk, evidence of a genetic component to hypoadrenocorticism is seen in a number of pedigree analysis studies. High estimates of heritability are seen in a number of breeds, including of 0.76 for bearded collies,[45] 0.75 for standard poodles,[5] 0.49 in PWDs,[48] and 0.98 for NSDTRs.[42] The study of PWDs analyzed the effect of inbreeding, revealing that the more inbred the individual, the more likely they were to develop hypoadrenocorticism.[48] The analyses for standard poodles, PWDs, and NSDTRs supported an autosomal recessive mode of inheritance, although data from 2 of these studies are also consistent with a more complex pattern of inheritance, as seen in human AAD and APS/MAS type 2.[45,48]

Genetics of ADD and APS/MAS in humans

Although AAD, the most common form of adrenal deficiency in humans, is a complex genetic disorder, there are other disease

Table 2
Breeds Significantly Overrepresented for Hypoadrenocorticism in Epidemiologic Studies

Breeds Significantly Overrepresented for Hypoadrenocorticism	
Airedale[37]	Poodle—unspecified[37]
Basset hound[37]	Poodle—standard[17,39]
Bearded collie[37,39]	Portuguese water dogs[17,39]
Border terrier[39]	Rottweiler[17]
Brussels Griffon[39]	SCWT[17]
English pointer[39]	Springer spaniel[37]
German SH pointer[37]	St Bernard[41]
Great Dane[17]	WHWT[17,37]

SCWT, soft-coated wheaten terrier.