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Guest Editorial

## Deafness in blue-eyed white cats: The uphill road to solving polygenic disorders

The pure white cat with luminous blue eyes is an attractive image familiar to many. These animals are well-known to be commonly affected by a congenital hereditary deafness that may affect one or both ears; the deafness is linked to the so-called W gene. Reports of this condition date back to at least the 1930s (Bamber, 1933), and many investigators have studied it in subsequent years (Wolff, 1942; Wilson and Kane, 1959; Boshier and Hallpike, 1965; Bergsma and Brown, 1971; Mair, 1973; Mair and Elverland, 1977; Pujol et al., 1977; Rebillard et al., 1981a,b; Saada et al., 1996; Ryugo et al., 1998, 2003).

The white (W) pigment gene in cats is autosomal dominant over colour, and is unrelated to albinism (Little, 1957; Searle, 1968). Cats carrying the W gene are not always solid white, often having coloured spots on their heads that may fade or disappear with age. Unlike dogs homozygous with the dominant merle pigmentation gene, homozygous white cats do not typically have visual or reproductive defects, but they are prone to the occurrence of blue irises (one or both) and deafness (either unilateral or bilateral), and the deafness likelihood increases with the number of blue eyes (Delack, 1984). Whether the cat is heterozygous or homozygous for W, the blue eyes and deafness have incomplete penetrance. It has been suggested that long-haired cats have a higher prevalence of blue eyes and deafness than short-haired cats (Mair, 1973), but this has not been confirmed. Cats instead carrying the underlying *c<sup>s</sup>* Siamese dilution pigment gene can have blue eyes without deafness, and it has been suggested that the presence of this gene explains why purebred white cats are less often deaf than mixed-breed white cats (Pedersen, 1991), but no studies have documented this assertion about prevalence. The white gene is present in many cat breeds, but unfortunately no data have been available on relative rates of occurrence of deafness among them (see below). A dominant piebald gene (S), also known as white spotting, is also found in various cat breeds (Pedersen, 1991; Searle, 1968), but there has been no report of deafness associated with its presence.

Delack (1984) analyzed three studies of deafness in non-pure breed white cats that included a total of 256 cats

(Boshier and Hallpike, 1965; Mair, 1973; Bergsma and Brown, 1971); 12.1% were unilaterally deaf and 37.9% were bilaterally deaf, or a total of 50% were affected. When cats that were the offspring of two white parents were examined, the prevalence of deafness (unilateral or bilateral) ranged from 52% to 96%. Two of the studies (Mair, 1973; Bergsma and Brown, 1971) examined the effect of blue eye colour on deafness, finding (respectively) a prevalence of deafness (unilateral and bilateral combined) of 85 and 64.9% in cats with two blue eyes, 40 and 39.1% in cats with one blue eye, and 16.7 and 22% in cats with no blue eyes. So, not all white cats are deaf and not all blue-eyed white cats are deaf, but a great many of them are so-affected. The mechanism of inheritance of deafness in white cats has not been determined to date, and advanced statistical genetic analyses, such as complex segregation analysis, have not previously been applied. Analyses of this sort in Dalmatian dogs have supported a non-Mendelian mode of inheritance (Cargill et al., 2004). Analyses in cats is complicated by the recognition that, unlike pigment-associated deafness in dogs, deafness in white cats may be partial or complete in a given ear (Rebillard et al., 1981a), and more than one type of underlying cochlear pathology may exist (Ryugo et al., 2003).

Despite the long recognition of deafness in white cats and many descriptive studies, few mechanistic studies have been performed to determine the cause and genetic origin of the disorder. More such studies of pigment-associated deafness have been performed in dogs, perhaps because the impact of deafness can be more devastating in dogs than in cats where the cat may more likely be an indoor pet. Pigment-associated deafness in dogs is known to be associated with two genes: the recessive alleles of the piebald gene S and the dominant allele of the merle gene M. Recent studies have identified the genomic identities of these genes. The merle gene is a retrotransposon insertion in the SILV pigmentation gene (Clark et al., 2006) and the piebald gene is the MITF pigmentation gene (Karlsson et al., 2006). Both of these genes have been identified in other species, and mutations in MITF have been identified

86 as causative for deafness in humans and mice; MITF is one  
87 of the six genes identified to date as being responsible for  
88 the four forms of Waardenburg syndrome (Van Camp  
89 and Smith, 2007). To date no mutation in SILV or MITF  
90 has been identified as causative for canine deafness.

91 The study by Geigy et al. (2007) reported in this issue of  
92 *The Veterinary Journal* examined deafness in a German  
93 colony of cats, most of them white, finding deafness prev-  
94 alence values consistent with earlier reports. Complex seg-  
95 regation analysis, using maximum likelihood procedures,  
96 was performed to determine the most probable mode of  
97 inheritance of deafness and blue eyes. Their results sug-  
98 gested the best model to be a pleiotropic gene segregating  
99 for deafness and blue irises, with additional polygenic ef-  
100 fects. This recognition that deafness in blue-eyed white cats  
101 does not follow simple Mendelian genetics is not surpris-  
102 ing, as a simpler mode of inheritance would probably have  
103 been recognized long ago and used to reduce deafness prev-  
104 alence. Progress in reducing deafness will most likely re-  
105 quire identification of the genomic identity of W – like  
106 the SILV or MITF genes in dogs – followed by identifica-  
107 tion of changes in that gene causative for deafness. Studies  
108 to identify W are in progress, and may in fact be complete  
109 by the time of this publication.

110 A bonus in the study by Geigy et al. (2007) was the re-  
111 port of hearing prevalence data for three specific cat  
112 breeds: Norwegian Forest, Maine Coon, and Turkish An-  
113 gora, with deafness prevalence rates of 18%, 17%, and  
114 11%, respectively, based on 329, 134, and 474 subjects.  
115 Analyses of iris and coat colour were not reported, but  
116 the subjects included both white and pigmented variants,  
117 so the deafness prevalence among the whites was likely sim-  
118 ilar to that reported for mixed-breed white cats, belying the  
119 assertion that deafness prevalence rates are lower in pure  
120 breed white cats (Pedersen, 1991). Although the data are  
121 limited (underestimates) because some are based on behav-  
122 ioural assessments instead of the more reliable brainstem  
123 auditory evoked response, they still represent the first pub-  
124 lished data on pure breed cats instead of the usually mixed-  
125 breed cats of the Geigy colony and earlier studies. More  
126 data and studies along these lines would be welcome.

127 The great number of hereditary disorders in domestic  
128 species is finally beginning to come under scrutiny with  
129 the new availability of genome maps and a rapidly expand-  
130 ing collection of tools for molecular genetics – and a grow-  
131 ing cadre of clinical scientists eager to tackle them. Since  
132 the great majority of these disorders are polygenic or fail  
133 to follow Mendelian genetics, the road to solving their  
134 causes will not be easy or straightforward. Nevertheless,  
135 the rewards are there and it is gratifying to see the progress  
136 that is already being made.

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