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Review

Congenital sensorineural deafness in dogs: A molecular genetic approach toward unravelling the responsible genes

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Abstract

Deafness is often diagnosed in different dog breeds and has been identified as a significant problem for breeders, owners and clinicians. The aetiology can be inherited or acquired, and a distinction must be made between sensorineural and conductive forms of deafness. This paper provides a brief overview of the varieties of findings in different dog breeds and in one breed in particular including prevalence, phenotypic and gender associations, histology, modes of inheritance and the number of contributing genes in congenital sensorineural deafness. We have also described molecular genetic approaches to canine hearing loss and discuss how comparative genomics could help reduce the prevalence of deafness in affected breeds leading to new insights into the molecular mechanisms of auditory function in both dogs and humans.

Keywords: Dog; Deafness; Heredity; Candidate gene approach; Comparative genomics

1. Introduction

The prevalence of congenital sensorineural deafness (CSD) in dogs has increased in recent decades, primarily as a result of heightened awareness of the disorder among dog breeders, owners and clinicians (Strain, 2004). Animals with hearing impairment are hardly suitable for use as working dogs as they are at a higher risk from traffic accidents, often seem to be easily startled and have an increased tendency to bite. A bilaterally deaf puppy requires specialised training by a responsible owner. As a result, most puppies with bilateral deafness are euthanased.

In the present study, we give a short overview of the aetiology, prevalence, phenotypic and gender associations, mode of inheritance and histological pattern of CSD in different dog breeds and discuss a molecular genetic approach to canine deafness using comparative genomics.

2. Sensorineural and conductive deafness

Canine hearing loss can be inherited or acquired. The most commonly seen forms are: (1) inherited congenital sensorineural; (2) acquired later-onset sensorineural and (3) acquired later-onset conductive deafness (Strain, 1996). A more simplified classification distinguishes between conductive and sensorineural deafness (Steffen and Jaggy, 1998). Conductive deafness is the result of a dysfunction caused by problems in the external ear canal or the middle ear space, and often results in an incomplete hearing loss (Eger and Lindsay, 1997). For example, chronic otitis externa and otitis media with ensuing stenosis and possible occlusion of the external ear canal, impaction from excess cerumen accumulation, rupture of the tympanic membrane, or stiffening or fractures in the bony ossicles can cause this type of deafness. Sensorineural deafness may be caused by dysfunction of the cochlea of the inner ear, by alterations of the cochlear nerve or of portions of the auditory pathway within the central nervous system. The causes of sensorineural deafness are diverse, and an inherited alteration of the inner ear structures is only one possibility. Otitis interna, tumours, ototoxic agents (e.g., aminoglycoside

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antibiotics), trauma and presbycusis can also result in this form of deafness (Strain, 1996).

In cases of suspected sensorineural deafness a conductive form of hearing impairment must first be excluded. Different examinations can be performed, such as otoscopy of the ear canal with an examination of the tympanic membrane, radiography and computerised tomography of the middle ear, or myringotomy to specify the bacteriological/cytological content of the tympanic bullae. A reliable method for the diagnosis of sensorineural deafness has shown to be the brainstem auditory evoked response (BAER) test, which is a reflection of electrical events within the brainstem as they ascend through the auditory pathway (Sims and Moore, 1984). The BAER test can be carried out either with a bone stimulator, particularly when there is reason to suspect conductive deafness, or with an air-conducted click produced by earphones (Strain et al., 1993). It is also possible to diagnose dogs suffering from unilateral hearing impairment with this test.

3. Prevalence of canine deafness

Canine congenital deafness has often been reported in the literature and occurs in 80 different breeds of dogs (Strain, 2004). However, because of the various possible acquired causes of congenital deafness and in the absence of breeding studies for many breeds, it cannot be confirmed that all of those cases were inherited. The breeds with the highest observed prevalence of deafness include Dalmatian, Bull Terrier, English Cocker Spaniel, English Setter and Australian Cattle Dog (Table 1).

The prevalence of deafness in studied dog breeds is highest in Dalmatian dogs, in which 16.5% to 29.9% exhibit unilateral or bilateral hearing loss (Famula et al., 1996; Holliday et al., 1992; Juraschko et al., 2003b; Muhle et al., 2002; Strain, 2004; Wood and Lakhani, 1997) (Table 2). In an American study, Strain (2004) demonstrated that the prevalence of deafness in other BAER-tested dog breeds appeared to be approximately half of that of Dalmatians. The frequency of unilaterally affected animals is generally higher than that of totally deaf animals. Indeed, most of the studies mentioned above show that about two to three times more Dalmatians are unilaterally rather than bilaterally deaf.

Table 1
Breed-specific deafness prevalence in dogs (adapted from Strain, 2004)

Breed	Dogs tested	Unilaterally deaf (%)	Bilaterally deaf (%)	Total deaf (%)
Australian cattle dog	296	12.2	2.4	14.6
Bull terrier	665	9.9	1.1	11.0
White	346	18.0	2.0	20.0
Coloured	311	1.3	0.0	1.3
English setter	3656	6.5	1.4	7.9
English cocker spaniel	1136	5.9	1.1	7.0
Parti-coloured	1067	5.9	1.1	7.0
Solid-coloured	60	1.7	0.0	1.7

4. Pigmentation and gender associations

Numerous investigators have looked for phenotypic associations of other traits with deafness. The association of CSD with pigmentation pattern in dogs has been described in published reports for more than a century (Rawitz, 1896). In breeds with white and non-white phenotypes (e.g., Bull Terrier, English Cocker Spaniel), there is a clearly increased prevalence in the white phenotype (Strain, 1999, 2004). The most commonly observed association is between blue eyes (heterochromia iridis) and deafness (Famula et al., 2000; Greibrokk, 1994; Holliday et al., 1992; Juraschko et al., 2003a,b; Mair, 1976; Strain et al., 1992; Strain, 2004). Another characteristic that has been shown to be associated with deafness in Dalmatians is the presence or absence of a patch, a visible pigmented area of hair, present at birth. Indeed, Strain et al. (1992), Strain (2004) and Juraschko et al. (2003b) demonstrated that patched Dalmatians were less likely to be deaf than unpatched animals and that the absence of iris pigmentation had a significant association with hearing disorder in this breed.

It is suspected that the observed association of CSD with pigmentation is related to the three different recessive alleles of the *S* locus. The extreme white piebald allele s^w is seen for example in Dalmatians, Bull Terriers, English Setters and Dogo Argentinos. The s^i allele produces Irish spotting and is responsible for white pigmentation in bloodhounds, whereas the beagle is an example that is usually homozygous for the piebald spotting allele s^p (Strain, 2004). A second pigmentation locus associated with deafness is the merle locus *M*. Different dog breeds such as the Collie, Shepherd Dog, Dachshund or Great Dane are known to be heterozygous for merle (*Mm*) (Strain, 1996). The question of the causal relationship between CSD and the recessive *S* alleles still remains controversial. These alleles are suspected of producing white colouration by acting on the differentiation and/or migration of melanocyte precursor cells from the neural crest during embryogenesis. It is likely that in Dalmatians a strong expression of s^w results in a reduction of melanocytes, e.g., in the eye and inner ear, thus leading to blue eyes and deafness, and that a weak expression of s^w results in a pigmented area, such as the patches seen in this breed (Strain, 2004). In fact, mouse models have shown melanocytes to be essential for normal hearing function (see below). The assumption that CSD is related to white producing genes and not to other coat pigmentation varieties was