Hereditary Deafness in Dogs and Cats

Sordera Hereditaria en Perros y Gatos

Congreso Internacional de Medicina, Cirugía y Zootecnia en Perros, Gatos y otras Mascotas

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Outline

- anatomy and physiology
- forms of deafness
- hearing testing
- pigment genes and hereditary deafness
- prevalence and breeds
- genetics of deafness
Ear Anatomy:

- outer ear
- middle ear
- inner ear
# Approximate Hearing Ranges (Hz)

<table>
<thead>
<tr>
<th>Species</th>
<th>Human Range</th>
<th>Sheep Range</th>
<th>Mouse Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>64-23,000</td>
<td>100-30,000</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>67-45,000</td>
<td>360-42,000</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>45-64,000</td>
<td>200-76,000</td>
<td></td>
</tr>
<tr>
<td>Cow</td>
<td>23-35,000</td>
<td>1,000-91,000</td>
<td></td>
</tr>
<tr>
<td>Horse</td>
<td>55-33,500</td>
<td>75-150,000</td>
<td></td>
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</tbody>
</table>

(See [www.lsu.edu/deafness/HearingRange.html](http://www.lsu.edu/deafness/HearingRange.html) for more species)
Forms of Deafness

- inherited or acquired

- congenital or later-onset

- sensorineural or conductive

result: eight possible combinations (i.e., acquired later-onset sensorineural deafness)
Definitions

- **sensorineural (nerve) deafness** - loss of auditory function because of loss of cochlear hair cells or the cochlear nerve neurons they connect to.

- **conductive deafness** - blockage of sound transmission through outer and/or middle ear without damage to cochlea.
Most Common Forms of Deafness

- hereditary congenital sensorineural
- acquired later-onset sensorineural
- acquired later-onset conductive
Infectious causes of conductive deafness:

- otitis externa
- otitis media
Hearing Testing

- **behavioral testing** - sound stimuli produced outside of the animal's visual field
  - cannot detect unilateral deafness
  - animals quickly adapt to testing
  - stimuli detected through other sensory modalities

- **electrodiagnostic testing** - brainstem auditory evoked response (BAER, BAEP, ABR)
  - objective, non-invasive
  - detects unilateral deafness
  - limited availability
Brainstem Auditory Evoked Response

Left

Right

Puppy 1
Puppy 2
Puppy 3
Puppy 4

hearing
uni
uni
deaf
Bone stimulus transducer

Silent whistle
Hereditary Congenital Sensorineural Deafness

- usually linked to the genes responsible for white
  - Dog – Recessive alleles of the piebald ($s$) gene: Irish spotting ($s^i$), piebald ($s^p$), extreme-white piebald ($s^w$)
  - Dog – Dominant allele of the merle ($M$) gene
  - Cat – Dominant allele of the white ($W$) gene
- deafness develops at 3-4 weeks of age when the blood supply to the cochlea (stria vascularis) degenerates
- degeneration is thought to result from an absence of pigment cells (melanocytes) which normally help maintain the ionic concentrations of $K^+$ and $Na^+$
- other pigmentation effects are frequently seen
Heterochromia Irides
Dog Breeds With Congenital Deafness

- reported in over 85 dog breeds
- prevalence (unilateral & bilateral) highest in:
  - Dalmatian (n=5,333) 30%
  - white bull terrier (n=346) 20%
  - English setter (n=3,656) 8%
  - English cocker spaniel (n=1,247) 6%
  - Australian cattle dog (n=296) 15%
  - Jack Russell terrier (n=56) 16% *
  - Catahoula leopard dog (n=78) 63% *

(prevalence unknown for most breeds)
Cat Breeds With White Gene

- W is present in at least 17 cat breeds
- prevalence data (unilateral & bilateral) is unknown for most breeds

- DSH and DHL white cats 50-96%
- white Norwegian Forest, Maine coon, and Turkish angora cats 11-18%

(data from owner surveys – likely underestimates)
Genetics of Congenital Deafness

- Doberman – simple autosomal recessive; vestibular dysfunction, not pigment-associated
- “nervous” pointer deafness – dogs bred for anxiety research studies - simple autosomal recessive?
- pigment-associated deafness - ?
  - **merle gene (M)** – dominant gene; homozygous dogs may have additional health problems
  - **piebald gene (s)** – recessive gene, but all white dogs in the breed are homozygous – deafness likely due to a single locus with modifier genes – NOT simple autosomal recessive
  - **white gene (W)** – dominant gene
Piebald Gene
Demi Azure Pedigree
Observations on Pigment-Associated Congenital Hereditary Sensorineural Deafness in the Dalmatian
Dalmatian Deafness Prevalence in the US

- **Bilateral:** 70.1% (3,740)
- **Unilateral:** 21.9% (1,167)
- **Deaf:** 8.0% (426)

N=5,333
Effect of Parent Hearing Status On Deafness Prevalence

B-B Parents (N=2,320)  B-U Parents (N=728)

Percent

Bi: 73%  59%
Uni: 21%  31%
Deaf: 6%  11%

27%  42%
Effect of **Sex** On Deafness Prevalence

Male (N=2,459)  
- Bi: 71%  
- Uni: 22%  
- Deaf: 7%

Female (N=2,424)  
- Bi: 69%  
- Uni: 22%  
- Deaf: 9%

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**Percent**

29%  
31%
Coat Pigmentation Genes In Dalmatians

- base coat - underlying coat color
  - B - black (dominant)
  - b - liver (recessive)
- extreme-white piebald gene - $s^w$ - white covering; recessive but homozygous in all Dalmatians [hair is white if it contains no pigment granules (melanin) or other substances which absorb light.]
- ticking gene - T - dominant, produces holes in white to show underlying coat color
Effect of Varying the Expression of the Extreme-White Piebald Gene

- weak gene expression: failure of the piebald gene to completely suppress the underlying coat color (black or liver) results in a patch; animals are less likely to be deaf

- strong gene expression suppresses pigmentation in the iris (blue eyes) and tapetum (red eye shine), and in the stria vascularis (deafness)
Patches

Present at birth when spots have not yet appeared
Effect of Patch On Deafness Prevalence

Patched (N=436)  Not Patched (N=4,404)

<table>
<thead>
<tr>
<th>Bi</th>
<th>Uni</th>
<th>Deaf</th>
<th>Bi</th>
<th>Uni</th>
<th>Deaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>8%</td>
<td>2%</td>
<td>68%</td>
<td>23%</td>
<td>9%</td>
</tr>
</tbody>
</table>

10% 32%
Effect of **Eye Color** (Brown or Blue) On Deafness Prevalence

<table>
<thead>
<tr>
<th></th>
<th>BR-BR (N=4,246)</th>
<th>BR-BL (N=372)</th>
<th>BL-BL (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi</td>
<td>73%</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>Uni</td>
<td>21%</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Deaf</td>
<td>7%</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Percent

28% 51% 50%
Prevalence of Deafness In Dalmatians By Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
<th>Reference</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>30%</td>
<td>G Strain, N=5,333</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>21%</td>
<td>M Greening, N=2,282</td>
<td></td>
</tr>
<tr>
<td>Holland</td>
<td>18%</td>
<td>B Schaareman, N=1,208</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>19%</td>
<td>L Poncelet, N=122</td>
<td></td>
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</tbody>
</table>
Impact Of Breed Standards

- United States: allows blue eyes
- Europe & Canada: do not allow blue eyes
- Efforts through breeding to reduce blue eyes in Norwegian Dalmatians also reduced deafness prevalence.
Breeding Recommendations

- BEST ADVICE: don't breed affected animals
- A unilaterally deaf animal is genetically the same as a bilaterally deaf animal, and should not be bred!
- It is unwise to repeat a breeding that produced large numbers of deaf animals
- Avoid breeding to animals with a history of producing many deaf offspring
Breeding Recommendations (cont.)

- Do not totally breed away from patches (Dal)

- Avoid breeding blue eyed animals

- If deafness is a problem in your breed, ALWAYS know the hearing status of animals you breed to!

- Breeding decisions should always take into consideration the overall good of the breed
Syndromic and nonsyndromic human hearing loss loci
Identification Of the Piebald Gene

- in the Dalmatian the mode of inheritance is NOT simple autosomal recessive
- best modeled statistically as being inherited as a single “locus” but one that does not follow Mendelian genetics
- human/mouse genes excluded to date: mitf  c-kit  endrb  pax3
- work on isolation continues
Merle Gene
Merle (M)

- homozygous recessive dogs (mm) – uniform pigmentation
- heterozygous dogs (mM) – dappling or alternate body areas of fully pigmented coat and pale or white coat; may be deaf
- homozygous dominant dogs (MM) – usually nearly solid white, may be deaf, blind with microphthalmic eyes, and sterile
Merle Pattern in Various Breeds
Retrotransposon insertion in *SILV* is responsible for merle patterning of the domestic dog

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Edited by Susan R. Wessler, University of Georgia, Athens, GA, and approved November 26, 2005 (received for review August 11, 2005)

Merle is a pattern of coloring observed in the coat of the domestic dog and is characterized by patches of diluted pigment. This trait is inherited in an autosomal, incompletely dominant fashion. Dogs heterozygous or homozygous for the merle locus exhibit a wide range of auditory and ophthalmologic abnormalities, which are similar to those observed for the human auditory-pigmentation disorder Waardenburg syndrome. Mutations in at least five genes have been identified as causative for Waardenburg syndrome; however, the genetic bases for all these have not been determined. Linkage disequilibrium was identified for a microsatellite marker with the merle phenotype in the Shetland Sheepdog. The marker is located in a region of CFA10 that exhibits conservation of synteny with HSA12q13. This region of the human genome contains *SILV*, a gene important in mammalian pigmentation. Therefore, this gene was evaluated as a candidate for merle patterning. A short Interspersed element Insertion at the boundary of Intron 10/exon 11 was found, and this insertion segregates with the merle phenotype in multiple breeds. Another finding was deletions within the oligo(dA)-rich tail of the short Interspersed element. Such deletions permit normal pigmentation. These data show that *SILV* is responsible for merle patterning and is associated with impaired function of the auditory and ophthalmologic systems. Although the mutant phenotype of *SILV* in the human is unknown, these results make it an intriguing candidate gene for human auditory-pigmentation disorders.

short Interspersed element | pigmentation | linkage disequilibrium

of ocular abnormalities, including increased intraocular pressure and anetropic eyes. Microphthalmia and colobomas are well described in merle and double merle Dachshunds and Australian Shepherds (3, 7, 8). In all breeds, the double merle genotype can be sublethal and is associated with multiple abnormalities of the skeletal, cardiac, and reproductive systems (3, 9, 10). For these reasons, merle-to-merle breedings are strongly discouraged (9).

Interestingly, many of the abnormalities associated with merle dogs are remarkably similar to those observed in Waardenburg syndrome (WS) (11). WS is an autosomal dominant auditory-pigmentation disorder in humans (1 per 40,000 live births) that accounts for 2% of all cases of congenital deafness (12). Several genes have been implicated in the four clinical varieties of WS: Mutations in *PAX3* cause WS type 1 and type 3 (13, 14) and mutations in *SOX10, EDNRB*, or *EDNR3* cause WS type 4 (15–17). Mutations in *MITF* cause WS type 2; however, the genetic basis for 85% of type 2 cases remains unidentified (18, 19).

To identify a chromosomal region segregating with merle, we carried out a whole-genome scan for the Shetland Sheepdog by using the multiplexed Minimal Screening Set 2 (20, 21). Linkage disequilibrium (LD) for merle was identified with a microsatellite marker in a region of CFA10 that exhibits conservation of synteny with HSA12q13. This region of HSA12 harbors the *SILV* gene.

*SILV* (also known as *Pmel17, gp100*) is a pigment gene best known as the Silver locus responsible for a recessive trait in an inbred strain of black mice in which the hair color dilutes with

Merle Gene

• located on the centromeric tip of canine chromosome 10
• wild type gene known as SILV (Silver in mice)
  – plays a role in the biogenesis of premelanosomes
  – encodes a protein thought to be necessary for matrix fibrils where melanin is deposited
• SILV mutation responsible for merle consists of a short interspersed element (SINE) insertion at the intron 10/exon 11 boundary
  – SINE size is approximately 253 base pairs
  – variable oligo(dA)-rich tail length
Canine SILV Gene

SINE – short interspersed element, at the inton 10 / exon 11 boundary

A commercial test for merle genotype is now available ($95/dog).
Shetland Sheepdogs

Tricolor (black, sable and white) non-merle ($mm$)

Blue merle ($Mm$)

Double merle ($MM$)

$SILV$ gene Exon 11

PCR products
White Gene
White (W)

- autosomal dominant over color in cats
- cats are not always totally white – may have colored spots on the head that may disappear with age
- homozygous cats do not have visual or reproductive defects, but are more likely to have blue eyes and deafness
- likelihood of deafness increases with number of blue eyes – incomplete penetrance
- blue eyes may also result from the $c^s$ Siamese dilution pigment gene – not associated with deafness
- no molecular genetic studies currently underway
Heterochromia Irides
References:

- Strain GM. Deafness in Dogs & Cats web page: [www.lsu.edu/deafness/deaf.htm](http://www.lsu.edu/deafness/deaf.htm)