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Does a pleiotropic gene explain deafness and blue irises in white cats?

Caroline A. Geigy [a], Silvia Heid [b], Frank Steffen [c], Kristen Danielson [d], André Jaggy [e,*], Claude Gaillard [a]

[a] Institute of Animal Genetics, Nutrition and Housing, Vetsuisse Faculty of the University of Berne, Switzerland
[b] Institute of Physiology II, J.W. Goethe-University of Frankfurt/Main, Germany
[c] Section of Small Animal Surgery/Neurology, Vetsuisse Faculty of the University of Zurich, Switzerland
[d] Fortryllekat Norwegian Forest Cats, Spokane, WA, USA
[e] Division of Clinical Neurology, Vetsuisse Faculty of the University of Berne, Switzerland

Abstract

The prevalence of deafness is high in cat populations in which the dominant white gene is segregating. The objective of this study was to investigate whether there is a gene that is responsible for deafness as well as for blue eyes and to establish a plausible mode of inheritance. For this purpose, data from an experimental colony with deaf cats were analyzed. The hearing status was determined by acoustically evoked brain stem responses (BAER). Complex segregation analyses were conducted to find out the most probable mode of inheritance using maximum likelihood procedures. The prevalence of deafness and partial hearing in the experimental colony was 67% and 29%, respectively. The results of the bivariate segregation analysis support the hypothesis of a pleiotropic major gene segregating for deafness and blue iris colour. The high heritability coefficients for both traits, 0.55 and 0.75 respectively, indicate that beside the major gene there is an important influence of polygenic effects.

Keywords: Deafness; Eye colour; Dominant white; Cat; Prevalence; Pleiotropic gene

1. Introduction

Congenital deafness is especially frequent in cat breeds in which the dominant white gene (W) is segregating. The dominant white gene is present in 14 registered breeds (Gebhardt et al., 1979) but the true prevalence of congenital deafness among those breeds has never been published. Delack (1984) presented proportions of white phenotype cats in urban and rural regions, which ranged from 0-11.1%. In three experimental studies (Bergsma and Brown, 1971; Bosher and Hallpike, 1965; Mair, 1973) matings of two dominant white cats were performed resulting in 89.3%, 95.8% and 52.0% cats, respectively, with impaired hearing (unilateral and bilateral combined). Matings between white cats and cats with a pigmented coat led to a prevalence of 24.6–27.4% of individuals with impaired hearing.

Mair (1973) and Bergsma and Brown (1971) found clear associations between blue eye colour and deafness. The prevalence of deafness (unilateral and bilateral combined) in cats with two blue eyes was 85% and 65%, respectively. In cats with one blue eye it was 40% and 39%, respectively, and in cats with no blue eyes it was 17% and 22%, respectively. Purebred white cats are said to have a lower prevalence of deafness than cross-breed cats (Pedersen, 1991) and long-haired cats are said to have a higher prevalence of blue eyes and deafness than short-hairs (Mair, 1973). Although pigment-associated deafness has been reported since the last century the hereditary mechanisms are not yet fully understood.

In cats, the allele W of the biallelic autosomal dominant white locus is dominant and epistatic over all colour loci (Searle, 1968). This type of white coat is invariably manifested but blue irises and deafness are observed in only a

* Corresponding author. Tel.: + 41 031 631 23 72; fax: + 41 031 631 25 83.
E-mail address: andre.jaggy@itn.unibe.ch (A. Jaggy).

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proportion of the cats with the dominant white allele. The albino locus (C) results in a solid white coat and blue irises too, but deafness does not seem to be associated with albinism. Currently, 12 different genes have been identified that, when mutated, result in an albino coat colour in different species (Oetting et al., 2003) but none of these was associated with deafness.

Typically, deaf cats – and dogs – exhibit cochleo-saccular degeneration of the Scheibe type (Anderson et al., 1968; Bosher and Hallpike, 1965; Brighton et al., 1991; Hudson and Ruben, 1962; Igarashi et al., 1972; Johnsson et al., 1973; Lurie, 1948; Mair, 1973, 1976; Suga and Hattler, 1970). The organ of Corti degenerates during the period in which the normal cochlea matures (Bosher and Hallpike, 1965; Cable et al., 1995). Recently, a distinct type of cochlear pathology associated with congenital sensorineural deafness has been detected consisting of hypertrophy of Reissner's membrane resulting in an irregular and folded structure, eventually filling the scala media, and the tissue exhibits an overall ''spongiform'' appearance. Only some cats showed the well known Scheibe degeneration while others showed both epithelial overgrowth and Scheibe degeneration (Ryugo et al., 2003). In another study, the inner ear of deaf white cats was examined histologically and electrophysiologically. It was clearly demonstrated that hereditary degeneration of the cochlea was – although similar in appearance – not a uniform process. (Rebillard et al., 1981b). In addition, electrophysiological testing of the inner ear in this study revealed that some cats were only partially deaf (Rebillard et al., 1981a). This finding is in contrast to the hereditary, sensorineural deafness in dogs where deafness always seems to be complete and partial hearing suggests that other causes than hereditary sensorineural degeneration must be responsible for the hearing disorder.

The objective of this retrospective study was to investigate whether there is a gene that is responsible (or at least partly responsible) for impaired hearing as well as for blue eyes, and to establish a plausible mode of inheritance of that gene in cat populations in which the dominant white allele W is segregating. For this purpose, phenotype information from an experimental colony was available. Possible modes of inheritance were analyzed by bivariate segregation analyses with hearing status and eye colour.

2. Materials and methods

The Institute of Physiology at the University II of Frankfurt/Main has bred white deaf cats in order to study the maturation of central auditory structures that have never received specific sensory input. The founders of this colony were four white adult females, one deaf and three with partial hearing, and one white deaf male. It was assumed that these founders were unrelated. In order to obtain a large number of deaf cats, inbreeding was performed and a deaf male and his deaf son were used to build up the colony. A total of 16 females, including the four founders, had offspring. A prerequisite for dams to be bred was the presence of severe hearing loss and good mothering abilities. The animals were not exposed to any extreme noise in their environment (mean ambient noise levels were in the range of 60 dB L_{eq}). The pedigree of the colony included 104 cats, for which information on hearing function and eye colour was available. Forty-four percent of the cats were not inbred, 29% had an inbreeding coefficient between 0.1 and 0.2 and 27% an inbreeding coefficient between 0.2 and 0.4.

Hearing assessment was performed by means of acoustically evoked brain stem responses (BAER). For this test, the kittens were anesthetized with Rompun (Bayer; 0.6 mg/kg body weight IM) and Ketavet (Parke–Davis; 15 mg/kg BW IM). Each ear was tested separately. The acoustic stimuli used were clicks (50 μs) at levels up to 120 dB SPL (sound pressure level) peak equivalent, presented through an earphone (inversely driven Band K 1″ condenser microphone). The sound pressure in the ear canal was monitored by a 0.25 in. (6.35 mm) Sennheiser Electret microphone. BAERs were recorded with subcutaneous silver electrodes (Vertex-ear-lobe). The potentials were amplified (500 000×) and bandpass-filtered in the frequency range of 10 Hz–10 kHz. One hundred responses at a rate of 13 s^{-1} were averaged on-line using an Apple Macintosh II computer and a National Instruments AD converter. If some hearing function was found in the first test at an age of 3–6 weeks, further BAER testing was performed at an interval of 6 weeks in order to follow up a possible progressive loss of hearing.

In normal animals, the threshold of the BAER to the click stimuli used was $\leqslant$54 dB SPL peak equivalent. This value was determined from non-white cats with normal hearing, that were examined by the same testing methods as described above. These animals were housed as control population for the hearing experiments at the Institute of Physiology III, University of Frankfurt. Cats with bilaterally absent responses up 120 dB SPL were classified as deaf. Animals with partial hearing in one or both ears (detectable BAER threshold between 55 and 119 dB SPL) or with unilateral deafness and impaired hearing on the other ear were classified as partial hearing. To exclude the possibility of a pathologic process in the external ear canal or the tympanum, each cat was examined otoscopically.

2.1. Segregation analysis

Deafness and eye colour were measured as an ordered categorical trait, but assuming an underlying continuous liability, where thresholds determine the hearing or the colour status (Falconer and Mackay, 1996). Complex segregation analyses were conducted to find out the most probable mode of inheritance using the unified version of the mixed model (Elston and Stewart, 1971; Lalouel et al., 1983; Morton and MacLean, 1974) as implemented in the Pedigree Analysis Package (PAP) (Hasstedt, 2002). Calculations were performed by maximum likelihood, where the likelihoods were maximised with NPSOL (Gill et al., 1986).

The model for a joint segregation analysis of hearing status and blue eyes included the independent and additive contribution of a single gene with pleiotropic effect on hearing and eye colour, additive genetic effects for a number of independent genes affecting both traits and a genetic correlation between these genes as well as an individual-specific environmental effects on both traits with the corresponding environmental correlation. The single major gene was assumed to consist of two alleles (A: hearing and pigmented eye colour, a: deaf and blue eye colour). The parameter dominance (d) and displacement (t) characterise the distribution of the traits within the three genotypes. The dominance was defined such that $d = 0$ corresponds to a recessive gene, $d = 1$ to a dominant gene and $0 < d < 1$ to an intermediate gene. The displacement refers to the mean difference between homozygous genotypes (AA and aa). Within each genotype of the two traits, the proportion of the variance due to polygenic effect is characterized by the heritability (h^2) and the relationship between the common genes, other than the pleiotropic single gene, as well as between the common environmental effects of both traits measured by the genetic and environmental correlation, respectively. Univariate analyses for hearing status and eye colour were adapted accordingly.

We used four models to analyse the data: (1) the environmental model, which assumed no genetic effect; (2) the mixed inheritance model, which assumed Mendelian segregation of the major gene and additional polygenic effect; (3) the major gene model, which assumed the segregation of the major gene only; and (4) the polygenic model, which assumed the effect of a number genes only. The likelihood ratio test (LRT) was used to test hypotheses.

Descriptive and test statistics were performed using the software package SAS (Release 8.01, SAS Institute Inc., 2002). Because some of the cells in the contingency tables had low expected frequencies only Fisher's-Exact Tests were applied to examine associations (SAS procedure PROC FREQ).

3. Results

3.1. Prevalence

The prevalence of deafness (Table 1) in the experimental colony reached 67% and the one of partial hearing 29%.

Table 1
Frequency in percent of hearing status and eye colour in the experimental colony

Hearing status (N = 104)	%
Hearing	4
Partial hearing	29
Deaf	67
Eye colour (N = 85)	
Pigmented	35
Odd	9
Blue	55

The range of the partial hearing ears lies between 57 dB and 115 dB SPL peak equivalent. One of the cats was unilaterally deaf and had normal hearing on the fellow ear. More than half of the cats (55%) had blue eyes and 9% possessed heterochromia irides. Eight percent of the offspring wore a pigmented coat indicating that a few founders were heterozygote for the W-locus (1 sire and 2 dams). All cats with a pigmented coat were partially hearing. No significant differences between the prevalence of deafness and sexes were observed. No progression of hearing loss was detected in partial hearing cats over several years of observation (Heid et al., 1998).

In the experimental colony, the hearing status of 99 progeny of parents with known phenotypes was recorded. The percentage of normal hearing, partial hearing and deaf offspring from matings of deaf sires with partial hearing dams ($n = 72$) were 4%, 22% and 46%, respectively. Deaf × deaf matings ($n = 27$) resulted in 0%, 19% and 81% deaf offspring, respectively. The results of these two matings did not differ significantly ($P = 0.219$). Only one of the six partial hearing dams had a normal hearing ear, the others were partial hearing with thresholds ranging from 65 dB to 90 dB SPL peak equivalent. The coefficient of inbreeding F was larger in the mating group deaf × deaf ($F = 0.19$) than in the one deaf × partial hearing ($F = 0.09$).

3.2. Segregation analyses

The comparison between the mixed inheritance and the environmental model of the predisposition to deafness and eye colour indicated clearly that genetic components play a highly significant role in both traits as well as in the univariate (figures not shown) as in the bivariate analyses ($P \leqslant 0.001$, LRT mixed inheritance vs. environmental; Table 2). Based upon the highest maximum likelihood, the mixed inheritance model fitted the data best. The univariate segregation analysis of the eye colour showed significant effects of the major gene as well as for the polygenic effect ($P \leqslant 0.001$). In the univariate analysis of the hearing status these effects could not be demonstrated. When the major gene was removed from the mixed inheritance model (polygenic model) in the bivariate analysis then the maximum likelihood became significant lower ($P \leqslant 0.01$, Table 2). The deletion of the polygenic effect from the mixed inheritance model reduced the maximum likelihood significantly too ($P \leqslant 0.001$). This indicates that a common single gene as well as polygenic effect played an important role in the expression of both traits. The estimated frequency of the pleiotropic allele of the major gene was 0.15. The mode of inheritance of this allele was recessive for the predisposition to deafness ($d = 0.00$) but intermediate for the blue eye colour ($d = 0.31$). The displacement for hearing status was very large ($t = 98.8$) but the one for blue eye colour moderate only ($t = 1.6$). The heritability in the mixed inheritance model reached a value of 0.55 for the predisposition to deafness and 0.75 for blue eyes (Table 2). The genetic correlation attained a

Table 2
Results of the bivariate segregation analysis of hearing status and eye colour in the experimental colony (LRT, likelihood ratio test)

Model	Trait	Allele frequency[a]	Dominance	Displacement	Heritability	Genetic correlation	Environmental correlation	−2ln Likelihood
Environmental	Hearing status							592.85
	Eye colour							
Mixed inheritance	Hearing status	0.15	0.00	98.8	0.55	0.28	0.02	266.47
	Eye colour		0.31	1.6	0.75			
Major gene	Hearing status	0.04	0.00	7.3			−0.16	291.21
	Eye colour		0.51	4.6				
Polygenic	Hearing status				0.57	0.44	0.22	285.56
	Eye colour				0.79			

LRT mixed inheritance vs. environmental: 326.38 (6 df) $P < 0.001$ H_0: no genetic effects; LRT mixed inheritance vs. major gene: 24.74 (3 df) $P < 0.001$ H_0: no polygenic component; LRT mixed inheritance vs. polygenic: 19.09 (3 df) $P = 0.002$ H_0: no major locus component.
[a] Frequency of the allele with predisposition to deafness and blue eye.

value of 0.28, and no correlation between common environmental effects was found (0.02).

4. Discussion

The results obtained from the experimental colony should be extended with care to other breeding populations of cats because in complexes traits different major genes can induce the same phenotype and a major gene may not have the same role in other cat populations. However, since this study is focusing on a pleiotropic major gene that affect the hearing status and eye colour in white cats where the W gene is segregating, these results are useful for those white cat breeds.

The prevalence of completely deaf individuals in the experimental colony (67%) is similar to figures given in the review of Bosher and Hallpike (1965) and by Mair (1973) (68% and 52%, respectively) for comparable mating schemes. Bergsma and Brown (1971) obtained a lower prevalence of 43% for matings between deaf parents and deaf × unilateral deaf parents. Although not significant, matings between deaf sires with partial hearing dams showed, however, less deaf progeny (46%) than deaf × deaf matings (81%). The increased prevalence of deaf offspring out of deaf × deaf matings could also be due because they were higher inbred. One of us (K.D.) collected, among others, data of the hearing status of registered cats: Norwegian Forest ($n = 329$), Maine Coon ($n = 134$) and Turkish Angora ($n = 474$). These data were delivered from registered breeders from all over the world. The applied method for testing hearing function was not uniform: some cats were BAER-tested others were diagnosed by means of clinical observation of their reactions to noisy stimuli. The prevalence of deafness was 18%, 17% and 11%, respectively. The large differences between the results of the experimental colony and the registered breeds are mainly due to the different mating policies. Whereas in registered breeds one tries to avoid matings that could lead to cats with hearing disorders, the purpose in the experimental colony was just the reverse.

Evaluation of partial hearing in cats is not well defined because an internationally standardized classification is lacking. In this study, partial hearing was assessed with BAER by determination of hearing threshold and measurement of amplitude height. As various technical factors and anatomic properties of the animal may influence amplitude height, this method does not represent the gold standard for assessment of hearing remnants. However, the cats in this colony were homogeneous with respect to their anatomy and BAER testing was standardized so that erroneous results could be excluded with the greatest certainty. In agreement with the findings of Rebillard et al. (1981a,b) we feel that it is correct to classify deaf white cats as ''partial hearing'' and not to restrict the disease symptoms to ''hearing'' and ''deaf''. This differentiation in several severity classes will improve inference of genetic epidemiological studies.

The fact that predisposition to deafness and eye colour is genetically controlled has been known for many decades (Darwin, 1859; Bosher and Hallpike, 1965; Bergsma and Brown, 1971; Gebhardt et al., 1979; Delack, 1984). However, our approach to treat these two traits as ordered categorical traits by analysing them assuming an underlying continuous liability and demonstrating the presence of pleiotropic effects of a major gene as well as polygenic effect, has not been performed before. Our results do not allow us to propose that the pleiotropic major gene is the only gene with a large effect determining deafness and blue eyes. The high estimated heritabilities in both traits suggest that there are probably other major genes affecting this phenotype. At least a part of this polygenic effect has a moderate effect on both traits measured by the positive genetic correlation. The importance of the other involved genes is not unexpected when we consider that the congenital hearing ability is not an all-or-none trait but has several intermediate severity conditions. For statistical reasons, we had to pool all cats that were not deaf or had normal hearing in one group as partial hearing. However, more intermediate severity conditions would fit the data better.

Another reason why the mode of inheritance of sensorineural deafness is complex is also due to the two different forms of pathology that are associated with deafness: degeneration of the Scheibe type and epithelial overgrowth

(Ryugo et al., 2003). In addition, the variety of histological damage within the two forms renders a clear histopathological differentiation difficult. Thus, the various pathological forms might be coded by different genes. The limited sample size of this study allows only provisional inferences of genetic hypotheses. These have to be confirmed by additional independent studies.

Although the molecular basis for hearing problems in deaf white cats is not known, it has often been suggested that the disorder is a feline homologue of the human Waardenburg syndrome (Bergsma and Brown, 1971; Delack, 1984; Mair, 1973; Rebillard et al., 1976, 1981a,b; Schwartz and Higa, 1982; West and Harrison, 1973). In humans, the causal mutation for this disorder was identified in the Pax 3 gene (DeStefano et al., 1998), which is also a candidate for deafness in mice (Steel and Brown, 1996). Comparing DNA sequences of the canine PAX 3 gene of healthy and deaf Dalmatian dogs (Brenig et al., 2003), no causative mutations in the analyzed coding regions were found. In the experimental colony, the Pax 3 gene was checked with Southern Blotting and no major rearrangement could be detected in this gene (R. Balling, personal communication). This finding does not rule out point mutations, therefore the PAX 3 gene cannot be definitively excluded as a cause of congenital sensorineural deafness in cats.

Another possible candidate gene that could have an effect on hearing capacities and eye colour is the W-locus. As found in mice, this gene encodes for a growth factor receptor known as the c-kit, which is involved in the formation, migration, proliferation and/or differentiation of germ cells, haemopoietic tissues, and melanoblasts (Chabot et al., 1988; Geissler et al., 1988). It encodes a transmembrane protein tyrosine kinase receptor that is structurally similar to the receptors for colony stimulating factor-1 (CSF-1) and platelet derived growth factor. However, skit has been excluded as the cause of deafness in Dalmatians (Tsai et al., 2003). A study on melanoblasts development suggests that it is primarily the survival of melanoblasts that is affected by defects in the W gene (Chabot et al., 1988). In humans, many other recessive candidate genes are known to be related to non-syndromic deafness e.g. "The Hereditary Hearing loss Homepage" at http://webhost.ua.ac.be/hhh/.

5. Conclusion

Recommendations on how to breed cats with the dominant white gene avoiding as much as possible deaf offspring have been published by feline breeding organisations that take care of cats were the W-locus is segregating (summarized in Vella et al., 1999). To date, detection of genetic mutations or linked genetic markers to select against the disorder seems to be still far away. As long as the responsible genes are not known and marker tests are not available, mating and selection programs using BAER recordings remain the only alternative to reduce genetic hearing disorders. Prerequisites are, however, reliable and complete records of cat families in the whole breeding population.

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