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ANIMAL GENETICS

# Polymorphism of Dental Formula and Segregation of Its Variants in a Pedigree of Kerry Blue Terrier Dogs

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**Abstract**—Polymorphism of the dental formula was analyzed in a complex pedigree of Kerry Blue Terrier. A lack of one or more lower premolars was observed in some dogs. Two different patterns of missing teeth were identified. One pattern consisted in agenesis of a second premolar, often in combination with agenesis of neighbor teeth, including the fourth premolar. In the second pattern, agenesis of a fourth premolar was expressed as an isolated abnormality. It was shown previously that the first pattern is inherited as a recessive trait with near complete penetrance. In this work, the major-gene control was demonstrated for the second pattern. This abnormality develops in 70–80% of mutant homozygotes and in no more than 20% of heterozygotes and wild-type homozygotes. It was shown that the two dentition abnormalities are controlled by different genes, which were designated *LPA2* and *LPA4* (Lower Premolar Agenesis).

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## INTRODUCTION

The dental formula is highly conserved within species, genera, and even order and, consequently, is used as one of the main characteristics in mammalian taxonomy. The stability of the dental formula is most probably determined by natural selection. When the selection pressure is weakened, the dental formula becomes polymorphic, as is the case with humans and domestic animals.

A lack or underdevelopment of some teeth is the most common deviation from the species-specific dental formula. This abnormality is widespread in humans, and its genetic basis is well studied. Tooth agenesis occurs as a manifestation of many hereditary syndromes and as a separate abnormality [1]. Several genes have been identified as determining tooth agenesis. Of these, the *MSX1* and *PAX9* genes have been studied most extensively. Mutations of the *PAX9* gene often cause agenesis of molars [2–5], while mutations of the *MSX1* gene usually lead to maldevelopment of second premolars and third molars [6–8]. Families with dentition abnormalities are often polymorphic for the number and type of missing teeth [9, 10].

The genetics of hypodontia and oligodontia has been thoroughly studied in mice. More than two hundred genes have been found to play a role in tooth development. Mutations of some of these genes lead to tooth agenesis [11]. Most mutations responsible for agenesis affect homeobox genes. Mutations of different genes cause maldevelopment of different groups of teeth both in humans and in mice [12].

The genetic control of tooth development in other mammals is far more poorly understood, although various forms of hypodontia and oligodontia have been observed in several species. Domestic dog provides an interesting and convenient model for studying the genetic control of tooth development. The dog standard dental formula, describing the character of teeth in each half of a jaw, is I3/3, C1/1, P4/4, M2/3 = 42, where I are the incisors, C are the canines, P are the premolars, and M are the molars. Deviations from this formula have been observed in many breeds [13–15]. In some breeds, such deviations are subject to negative selection. In some others, for instance, in Kerry Blue Terrier, deviations from the standard dental formula arise regularly, but are disregarded during expert evaluation of dogs and are not eliminated by selection.

We have previously described a large pedigree of Kerry Blue Terrier dogs with agenesis of lower premolars [16]. Complex segregation analysis has shown that hypodontia is determined genetically by several genes [17]. A hypothesis has been advanced that agenesis of different teeth is genetically heterogeneous. To verify, we have considered separately agenesis of the second and the fourth premolars and have shown that agenesis of the second lower premolars is controlled by a major gene. Agenesis of the fourth premolars has shown a more complex inheritance, details of which have not been elucidated [17].

It is well known that the results of segregation analysis strongly depend on the definition of phenotypes. We have used a phenomenological approach in our previous work: dogs with at least one particular premolar missing have been assigned to the abnormal group and those having both premolars, to a normal group. A lack of other teeth has been disregarded. In this work, complex segregation analysis was performed with the same pedigree but with another definition of the phenotype: polymorphism for missing tooth patterns, rather for individual missing teeth, was analyzed in members of the pedigree.

## MATERIALS AND METHODS

The pedigree under study was described in detail previously [16, 17]. The pedigree included 911 dogs of ten generations and was structurally complex, containing many inbreeding and outbreeding loops. The dental formula was determined in 598 dogs.

Tooth agenesis patterns observed in sib groups were described using the *RMF* (relative morphogenetic fields) index according to Line [18]. *RMF* was calculated for each lower premolar as $RMF = P/(P + M)$, where $M$ the number of missing teeth and $P$ is the number of present teeth in all relatives with abnormal dentition.

Complex segregation analysis was carried out according to Elston and Stewart [19]. A major-gene control was assumed to be due to a diallelic autosomal locus with alleles $A$ and $a$, the latter being associated with an abnormality.

Our model of inheritance implied that the probability of an abnormality depends on the genotype and the sex of the dog. To describe this model, we used six penetrance parameters $w_{g,s}$, which were determined for each sex (s) and each genotype (g). The probabilities of an abnormal and the normal phenotype for a dog of a particular sex and a known genotype were determined as $Pr(\text{abnormal}|g, s) = w_{g,s}$ and $Pr(\text{normal}|g, s) = 1 - w_{g,s}$.

A priori probability $Pr(g)$ was determined for each genotype g of the pedigree founders, i.e., dogs whose parents were not included in the pedigree. In the case of the Hardy–Weinberg equilibrium, $Pr(g)$ is described by the parameter $q$ defined as the frequency of allele $A$: $Pr(AA) = q^2$, $Pr(Aa) = 2q(1 - q)$, and $Pr(aa) = (1 - q)^2$. The assumption of the Hardy–Weinberg equilibrium seems justified for our sample, because the dental formula has been disregarded during breeding Kerry Blue Terrier dogs. Moreover, even a bias of the equilibrium does not considerably affect the results of segregation analysis of an extended pedigree [20].

The distribution of $Pr(g|g_m g_f)$ describes the probability of parents with genotypes $g_m$ and $g_f$ having a offspring with genotype g. In the case of a major-gene diallelic model, the distribution is determined by three transmission probabilities $\tau_g$, which are the probabilities of transmitting allele $A$ from the parents with genotypes $AA$, $Aa$, or $aa$. If the inheritance is Mendelian, $\tau_g = 1.0$, 0.5, and 0 for genotypes $AA$, $Aa$, and $aa$, respectively.

Thus, the most general model of inheritance is described by the following ten parameters: $q$, which is the frequency of allele $A$; $w_{AA,1}$, $w_{Aa,1}$, $w_{aa,1}$, $w_{AA,2}$, $w_{Aa,2}$, and $w_{aa,2}$, which are the six parameters of penetrance; and $\tau_{AA}$, $\tau_{Aa}$, and $\tau_{aa}$ which are the three transmission probabilities.

The likelihood ($LH$) function for a pedigree including $n$ dogs is defined as

$$LH = \sum_{g_1 \in G} \cdots \sum_{g_n \in G} \left[ \prod_i Pr(x_i|g_i, s_i) \times \prod_j Pr(g_j) \prod_k Pr(g_k|g_{m_k}, g_{f_k}) \right],$$

where $G = \{AA, Aa, aa\}$, i relates to dogs with known $x_i$ genotypes, j relates to the founders, and k relates to the progeny.

To check the major-gene hypothesis, we compared the Mendelian model ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, and $\tau_{aa} = 0$) with the most general unrestricted model ($0 \le \tau_g \le 1$). In addition, the unrestricted model was compared with the environmental one, which implies that $\tau_{AA} = \tau_{Aa} = \tau_{aa} = q$. The major-gene hypothesis is accepted when the Mendelian model does not differ significantly from the unrestricted model and the environmental model describes the data significantly more poorly than the unrestricted model [21]. The hypotheses were compared by the likelihood ratio test [22].

The pedigree under study included multiple loops. To calculate the likelihood function for this pedigree, we used an algorithm cutting the loops by copying particular individuals [23, 24].

Analysis was performed using the PED_LOOP and MAN-A1 programs, which were developed in our laboratory and are available at ftp://mga.bionet.nsc.ru.

## RESULTS

### *Patterns of Tooth Agenesis*

Agenesis of one to six lower premolars was observed in 163 out of the 598 dogs examined. The first (5 dogs), the second (21 dogs), or the fourth (151 dogs) premolar was missing.

Small families are usually analyzed to study the clustering of missing tooth patterns [12]. In our study, all 910 dogs belonged to one large pedigree. To reduce the genetic heterogeneity of the trait in the pedigree, the patterns of missing teeth were analyzed in groups of close relatives. Groups of relatives with a high probability of agenesis of the second premolars are shown in Fig. 1a. RMF for the second premolars varied from 0 to 0.5 in these groups (Fig. 2a). Abnormalities of other

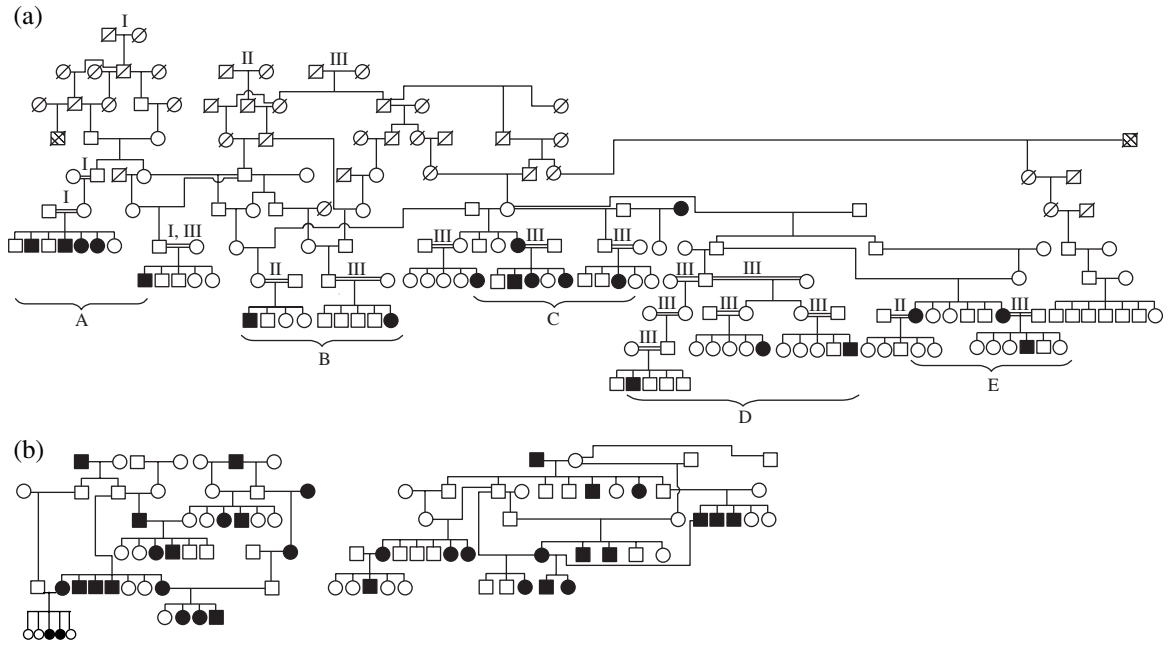


**Fig. 1.** Pedigree fragments including (a) all dogs with agenesis of the second premolars and (b) dogs displaying the lack of the fourth premolars as the only deviation from the normal dental formula. Circles and squares show females and males, respectively. Black symbols, dogs with a changed dental formula; crossed symbols, dogs with unknown phenotypes. Double lines show inbred matings; common ancestors are indicated with Roman numerals. Two crosshatched symbols correspond to one dog. Groups of relatives whose patterns of missing teeth are shown in Fig. 2a are indicated with capital letters.

teeth were rare, and the between-group differences were greater than within-group differences. For instance, agenesis of the first premolars was detected in only one out of five groups. The greatest between-group difference was observed for the fourth premolar. The fourth premolars were present in all dogs of one group and were missing in all dogs of another group. In the remaining three groups, RMF varied from 0.4 to 0.7; i.e., these groups included dogs with a varying number of the fourth premolars (from 0 to 2).

Almost all other dogs with agenesis of the lower premolars had the same pattern of missing teeth (Fig. 2b): one or both lower fourth premolars were missing (RMF = 0.16), while all other teeth were present. This pattern substantially differed in the most frequently missing tooth and the variability of the dental formula from the patterns observed in the above five groups (Fig. 1a).

We assumed that it is the pattern of missing teeth, rather than particular elements of the dental formula, that is controlled genetically.

The first pattern was characterized by the invariant lack of one or two second premolars and was often associated with agenesis of other premolars. To analyze its inheritance, we considered all dogs with this pattern as expressing the abnormal phenotype and all other dogs, as expressing the wild-type phenotype. In essence, this definition of the phenotypes coincides with the definition used previously to analyze agenesis of the second premolars [17].

The second pattern was characterized by a lack of one or two fourth premolars with all other teeth being present. In the analysis of its inheritance, the abnormal phenotype was ascribed only to the dogs that displayed agenesis of the fourth premolars and had all other teeth. The wild-type phenotype was ascribed to dogs with the unchanged dental formula; agenesis of other premolars; or agenesis of not only the fourth premolars, but also of other teeth. Complex segregation analysis of the trait defined as above was performed in this work.

### *Segregation Analysis*

All dogs having all teeth but one or both lower fourth premolars were considered expressing the abnormal phenotype. In ten dogs of our pedigree, agenesis of the fourth premolars was accompanied by agenesis of some other teeth. This phenotype could be due to a mutation causing agenesis of the second premolars or by its combination with another mutation causing agenesis of the fourth premolars. Since it was impossible to decide between these possibilities, the dogs were excluded from the analysis and their phenotypes were considered unknown. The group of 141 abnormal dogs included 59 males and 82 females. Because the segregation by sex significantly differed from the expected ratio 1 : 1 ($\chi^2 = 3.75$, $df = 1$, $P \approx 0.05$), the effect of the sex was included in the model of inheritance.

The results of segregation analysis are summarized in the table. The unrestricted hypothesis significantly

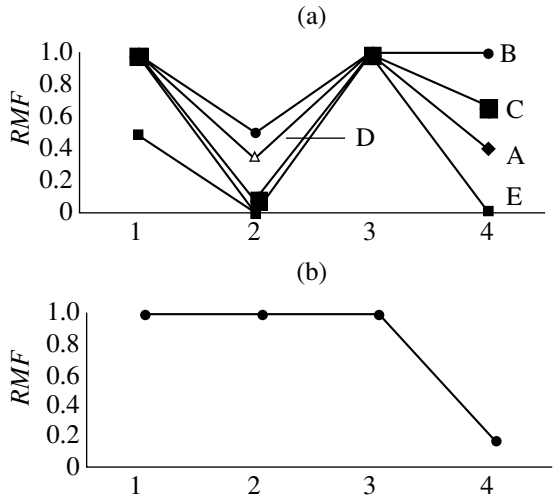


**Fig. 2.** Patterns of tooth agenesis in (a) groups of related dogs shown in Fig. 1a and (b) in all other abnormal dogs. Abscissa, lower premolar.

differed from the environmental hypothesis ($\chi^2 = 70.58$, $df = 3$, $P < 0.001$), testifying again to the genetic determination of the trait in question. No significant difference was observed between the Mendelian and unrestricted hypotheses ($\chi^2 = 6.08$, $df = 3$, $P > 0.1$). This result provides evidence in favor of a major-gene inheritance of the trait. As seen from the table, the effect of the sex was significant ($\chi^2 = 17.52$, $df = 6$, $P < 0.01$). We attempted to simplify the major-gene model, but both dominant ($\chi^2 = 25.72$, $df = 5$, $P < 0.001$) and recessive ($\chi^2 = 14.48$, $df = 5$, $P < 0.025$) models proved to be inferior to the codominant model with a sex effect. According to this model, the abnormal phenotype is determined by an allele occurring in the population at a frequency of 0.33. Approximately 75% of mutant homozygotes express the abnormal phenotype. For the other genotypes, the risk is no more than 20%. This pattern of penetrance distribution among the genotypes is close to the pattern expected in the case of a recessive inheritance.

## DISCUSSION

Our results showed that the inheritance of agenesis of the fourth premolars in Kerry Blue Terrier dogs is described by a major-gene model. A similar major-gene inheritance was earlier demonstrated for agenesis of the second premolars in the same pedigree [17]. Several factors suggest that the genes involved are different.

First, the major-gene model was rejected when all dogs with agenesis of the second and the fourth lower premolars were pooled in one group expressing the abnormal phenotype [17].

Second, the inheritance of agenesis of the second premolars is described by a recessive model without a sex effect, while a codominant model with a sex effect is the best in the case of agenesis of the fourth premolars.

Third, the models of inheritance of the two patterns of tooth agenesis differ in some parameters. According to our model, agenesis of the second premolars is determined by a rare mutant allele (frequency 0.14) with almost complete penetrance. The frequency of the allele responsible for agenesis of the fourth premolars is 0.33, and the genotypes each show incomplete penetrance.

With the high frequency of the mutant allele and incomplete penetrance of the genotypes, which characterize the inheritance of agenesis of the fourth premolars, it can be expected, first, that abnormal puppies can be produced in various matings, rather than occurring preferentially in progenies of phenotypically normal dogs, and, second, that most normal dogs producing abnormal puppies are close relatives. The pedigree fragments (Fig. 1b) support these predictions. Dogs with agenesis of the fourth premolars were produced in all three types of matings: abnormality × abnormality, norm × abnormality, and norm × norm. Normal parents producing abnormal puppies are often involved in inbred loops.

The above facts suggest that the two patterns of agenesis of lower premolars are determined by different major genes in Kerry Blue Terrier. The gene controlling agenesis of the fourth premolars was termed *LPA4* (Lower Premolar Agenesis). We propose that the gene previously found to control agenesis of the second premolars is termed *LPA2*.

Interestingly, the *LPA2* gene controls the development of the second premolar and some neighbor teeth (including the fourth premolar), while the *LPA4* gene is responsible for the formation of only one tooth (the lower fourth premolar). The difference in gene effect can be explained on the basis of current views of tooth development, assuming that segmentation of dental fields is determined by genes acting on specific subregions within a field [25].

Expression of the homeobox *MSX1* gene and the pair-box *PAX9* gene plays the crucial role in development of oligodontia and hypodontia in mouse and human. Mutations of these genes are associated with agenesis of particular teeth. For instance, a missense mutation of the *MSX1* gene leads to agenesis of the third molars and second premolars in humans [6]. Several other mutations of this gene are associated with a lack of premolars and other teeth [7, 8, 26]. It is noteworthy that mutations of the *MSX1* gene cause agenesis not only of the second premolars, but also of neighboring teeth (the first molars and the first premolars) in some patients and often lead to a lack of the third molars (wisdom teeth) [6, 7, 26]. This effect is similar to that of the *LPA2* gene in dogs.

Mutations of the *PAX9* gene cause agenesis of distal teeth in humans. Molars are affected most frequently and distal premolars, in fewer cases. Agenesis of the

Results of segregation analysis of agenesis of the fourth premolars in Kerry Blue Terrier dogs

| Parameter | Hypothesis | | | | | |
|---|---|---|---|---|---|---|
| | unrestricted | environmental | codominant | without sex effect | recessive | dominant |
| $q$ | 0.828 | 0.575 | 0.673 | 0.584 | 0.605 | 0.879 |
| $\tau_{AA}$ | 1.0 | 0.575[b] | 1[a] | 1[a] | 1[a] | 1[a] |
| $\tau_{Aa}$ | 0.363 | 0.575[b] | 0.5[a] | 0.5[a] | 0.5[a] | 0.5[a] |
| $\tau_{aa}$ | 0.216 | 0.575[b] | 0[a] | 0[a] | 0[a] | 0[a] |
| $w_{AA,1}$ | 0.156 | 0.112 | 0.162 | 0.098 | 0.060 | 0.065 |
| $w_{Aa,1}$ | 0.0 | 0.099 | 0.0 | 0.048 | 0.060[b] | 0.538 |
| $w_{aa,1}$ | 1.0 | 0.650 | 0.720 | 0.668 | 0.635 | 0.538[b] |
| $w_{Aa,2}$ | 0.0 | 0.226 | 0.0 | | 0.100 | 0.151 |
| $w_{Aa,2}$ | 0.254 | 0.101 | 0.205 | | 0.100[b] | 0.573 |
| $w_{aa,2}$ | 1.0 | 0.831 | 0.801 | | 0.748 | 0.573[b] |
| $LH$ | –287.85 | –322.14 | –290.93 | –296.61 | –295.09 | –300.71 |
| $\chi^2$ ($df$)[c] | | 70.58(3) | 6.08(3) | 17.52(6) | 14.48(5) | 25.72(5) |
| $P$ | | $\ll$0.001 | >0.1 | <0.01 | <0.025 | <0.001 |

Notes: [a] The parameter values were constant.
[b] The parameter value is equal to the previous one and is not estimated in the model in question.
[c] The likelihood ratio test ($\chi^2$) was performed for comparisons with the unrestricted hypothesis.

third premolars is so frequent in human populations that it is not considered to be abnormal. This deviation from the complete dental formula is especially frequent in families with mutations causing hypodontia or oligodontia. The fact suggests that the development of the most distal teeth is extremely unstable and is sensitive to various genetic and environmental factors distorting odontogenesis.

The fourth premolars are the most distal premolars in dogs, and their agenesis is the most frequent dental abnormality in Kerry Blue Terrier. We believe that this abnormality arises as a primary effect of an *LPA4* mutation or a pleiotropic effect of an *LPA2* mutation. In addition, agenesis of the fourth premolar may arise spontaneously in heterozygotes and wild-type homozygotes as a result of odontogenesis disturbances caused by stochastic and/or environmental factors. Agenesis of distal premolars in Kerry Blue Terrier is similar in this respect to defects of the wisdom teeth in humans.

It is of interest that premolar agenesis is recessive in dogs, while most of the above abnormalities of the human dental formula are inherited as autosomal dominant traits with incomplete penetrance and varying expressiveness [8–10, 26]. However, several cases where dentition abnormalities are inherited as a recessive trait have been described for inbred human families [27, 28].

The pedigree under study had a high degree of inbreeding. This feature is characteristic of many dog pedigrees. Recent molecular phylogenetic investigations make it possible to assume that the founder and bottleneck effects played an important role in the genetic history of many dog breeds [29]. In addition, breeding often employs a few males with excellent show results (the effect of a male's popularity), which also contributes to the high degree of inbreeding. Several autosomal recessive abnormalities have been revealed in dogs owing to inbreeding; about half of these abnormalities have been observed only in one or a few breeds [30]. Note in this connection that our conclusions about the genetic control of premolar agenesis apply only to Kerry Blue Terrier and should be verified in the case of other dog breeds.

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