Lance canines are associated with small body size and genetic variants on chromosome 9

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A rostrally-displaced maxillary canine tooth, more commonly known as a lance canine, is an upper canine tooth that points forward toward the nose (**Figure 1A**), instead of downward (**Figure 1B**). A lance canine tooth sits closer to the upper third incisor and is located in front of, instead of behind, the lower canine tooth. One or both upper canines may be affected. Lance canines may prevent the mouth from closing properly, can rub against the upper lip which can lead to ulceration, and can cause tartar buildup between the affected canine and upper third incisor which can lead to periodontal disease. Treatment of lance canines involves extraction or orthodontic repositioning (braces). This condition is rarely reported outside of the Shetland sheepdog and is suspected to have an underlying genetic cause.

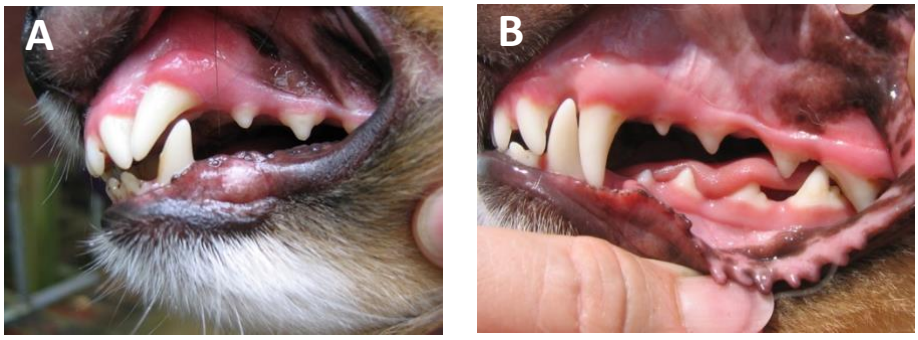

Figure 1. (A) The upper canine tooth of an affected dog compared to (B) a Sheltie with normal dentition.

We searched genome-wide for genetic variants that are associated with lance canines and identified a region on chromosome 9. Within this region, we found two variants in two different genes. One of the genes is necessary for normal body growth, so we decided to compare the heights and weights of affected dogs to those of dogs with normal canine teeth. We discovered that dogs having lance canines are, on average, one inch shorter and 6 pounds lighter than unaffected Shetland sheepdogs.

The most significantly associated variant was in *FTSJ3* on chromosome 9. Another variant near *IGF1* was previously determined to play a role in body size in Shetland sheepdogs. In **Table 1** we show how genotypes at these two genes correlate with body weight and lance canine. For example, a dog having two wt (wild-type, or non-risk) alleles at both genes weighs, on average, 26.5 pounds and is highly unlikely to have a lance canine (in our study, no dogs with this genotype were affected). Conversely, a dog having two mut (mutant, or risk) alleles at both genes weighs, on average, 13.4 pounds and is at

high risk for having a lance canine (in our study, 88% of dogs with this genotype were affected).

	***IGF1* (chr15)**		
***FTSJ3* (chr9)**	wt/wt	wt/mut	mut/mut
wt/wt	26.5 (0)	23.4 (10)	26.4 (0)
wt/mut	21.7 (17)	21.2 (24)	18.1 (64)
mut/mut	16.5 (67)	14.7 (78)	13.4 (88)
	Average weight (% affected)		

Table 1. Risk alleles (denoted as mut) in the genes *FTSJ3*, on chromosome 9, and *IGF1*, on chromosome 15, are associated with lance canines and reduced body size in 65 cases and 100 controls. The average weight in pounds and the percentage of dogs with the genotype that were affected are reported for each genotypic combination.

The chromosome 9 variants were present in toy breeds, such as the Yorkshire Terrier, Chihuahua, and Pomeranian, but were never observed in larger breeds, supporting a role for the variants in reducing body size. It is interesting that of the breeds having the chromosome 9 variants, lance canines only occur in Shelties. This may relate to the Shetland sheepdog's elongated skull shape, which is not a feature of any other breeds having the variants. Because there are many other genetic factors that contribute to body growth and skull formation, some Shelties are homozygous for the risk variants but do not have a lance canine.

In our study, the average affected Sheltie was 13.97 inches tall and weighed 16.2 pounds, while the average control was 14.93 inches and 21.97 pounds. About 60% of cases were 14.2 inches or shorter and 75% were 18 pounds or lighter. Only 25% of controls were 14.2 inches or shorter and 20% were 18 pounds or lighter. To reduce the incidence of lance canine, breeders may choose to simply avoid mate pairs that are likely to produce very small Shelties. Some breeders may prefer to use a genetic test to determine which dogs possess a chromosome 9 risk allele and then select mate pairs that will not result in individuals homozygous for the risk alleles, as 67 to 88% of these individuals will have a lance canine. Punnett squares showing the possible offspring for each *FTSJ3* breeding combination are included on the following pages.

FTSJ3 Punnett Squares

The predicted outcome for each potential *FTSJ3* mate pair. The *FTSJ3* alleles are denoted as wt (wild-type, or non-risk) and mut (mutant, or risk). The expected proportion of offspring with each possible genotype and the percentage of dogs in our study with the genotype that were affected are shown beneath each breeding scenario. The percentage of affected dogs of each genotype varies because there are alleles of other genes that affect body size in Shetland sheepdogs. The chromosome 9 allele is the major factor impacting body growth and lance canine risk, but there are other "size" alleles that can make a Sheltie larger or smaller, which alters their risk for developing lance canines. Testing for the *FTSJ3* variant can be useful to select breeding pairs that will not produce mut/mut offspring, but even these matings can result in affected pups if the pups are smaller in size. Shelties having one copy of the chromosome 9 risk allele have the most variability in their likelihood of developing a lance canine because they are the most influenced by other size alleles.

		wt/wt	
		wt	wt
wt/wt	wt	wt/wt	wt/wt
	wt	wt/wt	wt/wt

All wt/wt (0-10% affected)

		wt/wt	
		wt	wt
wt/mut	wt	wt/wt	wt/wt
	mut	wt/mut	wt/mut

½ wt/wt (0-10% affected)
½ wt/mut (17-64% affected)

wt/mut	wt	mut
wt	wt/wt	wt/mut
mut	wt/mut	mut/mut

¼ wt/wt (0-10% affected)
½ wt/mut (17-64% affected)
¼ mut/mut (67-88% affected)

mut/mut	wt	mut
mut	wt/mut	mut/mut
mut	wt/mut	mut/mut

½ wt/mut (17-64% affected)
½ mut/mut (67-88% affected)

mut/mut	mut	mut
mut	mut/mut	mut/mut
mut	mut/mut	mut/mut

All mut/mut (67-88% affected)

Related Links

The link to the scientific paper, which was published in the journal PNAS, is: https://doi.org/10.1073/pnas.2009500117

This work was also featured on the cover of PNAS, and the link to the cover art and caption is: https://www.pnas.org/content/117/40.cover-expansion

Clemson University published a news article on this research, which can be found at: https://newsstand.clemson.edu/mediarelations/national-academy-of-sciences-features-undergraduate-research-that-identifies-new-genetic-factors-contributing-to-small-body-size-in-dogs/