INFLUENCE OF INBREEDING ON THE CARABELLI TRAIT IN A HUMAN ISOLATE

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ABSTRACT The purpose of this study is to evaluate the influence of increased homozygosity due to inbreeding on the phenotypic distribution of the Carabelli trait. The sample consisted of 224 dental casts representing 20.2% of the total children aged 7 to 14 years from the endogamous, inbred population of the Island of Hvar, Croatia. Inbreeding analysis compared the children with different rates of grandparental endogamy relative to the expression of Carabelli's trait. The design evaluated the effect of inbreeding on Carabelli trait on the maxillary permanent first molar within a natural setting of reduced variability of environmental factors.

Very high frequency of the Carabelli trait was observed for the permanent first molar on both sides of the arcade (84% and 86% on left and right sides). Significant difference among the groups who have different degrees of inbreeding was found when Carabelli trait was divided into absent, negative features, and a positive cusp using Dahlberg's grading system.

It seems that Carabelli's trait is strongly genetically determined, and present findings imply it may be controlled byrecessive alleles. If heterogeneous polygenic developmental modules are responsible for the diversity of Carabelli's trait, they stay relatively stable after initiation of the developmental process when it appears that other environmental factors have no measurable effect. *Dental Anthropology* 2003;16(3):65-72.

The Carabelli trait is a well-known morphological feature positioned at the mesiolingual surface of maxillary molars and the trait is expressed along a continuum of a wide range of pits, crescents, grooves and cusps. Carabelli's trait is most commonly observed in European populations where frequencies vary from 50% to 90% (Laatikanen and Ranta, 1996).

Kiesser and van der Merwe (1984) evaluated the classificatory reliability of four grading systems that have been described in the literature, showing Dahlberg's eight-grade classification to be the most confidently applied. In general, Carabelli traits can be divided into two main groups: positive features (protuberance and cusp-form structures) and negative features (furrow and pit-form structures), with few morphological variations in both groups (Alvesalo *et al.*, 1975; Townsend and Brown, 1981; Laatikanen and Ranta, 1996). This classification commonly has been used in interpopulation analyses (Alvesalo et al., 1975).

Although most authors agree that the Carabelli trait is genetically determined, the basis of inheritance is still not clear. Some twins studies suggest that the heritability of the trait is low (Biggerstaff, 1973; Alvesallo *et al.*, 1975; Scott and Potter, 1984), whereas other results suggest high heritability (Škrinjarić, 1985; Townsend and Martin, 1992). Early studies proposed a single-gene, autosomal dominant genetic model (Dietz, 1944) and an intermediate two-allele mode of inheritance (Kraus, 1951). A polygenetic model was suggested after phenotypes were compared with the expected Hardy-Weinberg distribution (Goose and Lee, 1971).

The trait occurs mostly bilaterally with symmetrically expressed grades (Alvesalo et al., 1975; Thomas et al., 1986; Laatikainen and Ranta, 1996), and, in asymmetric situations, no directional asymmetry has been detected (Townsend and Martin, 1992). These same authors suggest a genetic basis for the fluctuating trait asymmetry as a

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consequence of developmental instability, namely the degree of individuals' heterozygosity in the population (Townsend and Martin, 1992). Hence, it should be of interest to analyze a population with high homozygosity and to compare the phenotypic trait distributions and the degree of trait symmetry among its subpopulations defined by degree of homozygosity.

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TABLE 1. Age distribution of the sample

Age (years)	Total children		Sample		Sampled proportion of the total children
	n	%	n	%	%
7	129	11.6	27	12.0	20.9
8	153	13.8	34	15.2	22.2
9	125	11.3	28	12.5	22.4
10	117	10.6	21	9.4	17.9
11	143	12.9	26	11.6	18.2
12	136	12.3	27	12.1	19.9
13	168	15.1	28	12.5	16.7
14	138	12.4	33	14.7	23.9
Total	1109	100.0	224	100.0	20.2

An appropriate data set for such analysis is a well-investigated population divided into subpopulations that share similar environmental conditions. During 30 years of continuous interdisciplinary investigation of the rural population of the Adriatic island of Hvar different biomedical, sociocultural, biocultural, genetic and orofacial traits have been studied (Rudan, 1972; Rudan *et al.*, 1982a,b, 1986; Roguljić *et al.*, 1997; Janićijević, 1994; Smolej, 1987; Sujoldžić, 1997; Šimić and Rudan, 1990; Šimić *et al.*, 1992; Martinović *et al.*, 1998; Waddle et al., 1998). Population structure studies (Roguljić *et al.*, 1997; Rudan *et al.* 1990) indicate notably high levels of inbreeding, endogamy, and isonymous marriages (marriages between individuals sharing the same surname) on this island, thus identifying the population of Hvar as one of the last genetic isolates in Europe. Such a population is an interesting model for orofacial genetic analyses because the main genetic consequence of inbreeding is to increase the proportion of homozygotes in the population (Bodmer and Cavalli-Sforza, 1976). If some recessive genes are responsible for phenotypic trait expression, prevalence of such expression is expected to be higher in an inbred than in the general population. Therefore, the aim of this study was to evaluate the influence of elevated homozygosity on the phenotypic distribution of Carabelli's trait on the permanent first molar.

MATERIALS AND METHODS

The material for this investigation consisted of 224 dental casts of children aged 7 to 14 years from all elementary schools on the island of Hvar, Croatia (Tables 1 and 2). The sample was targeted, matched for age and sex distribution to the total elementary school population of the island, and the sample covered 20.2% of the total cohort. The pupils' parents provided complete two-generation genealogical data for each examined child (*i.e.*, parents and grandparents with the place of residence of each individual). Table 1 presents the distribution of the sample according to sex, age, birthplace, and grandparental endogamy.

Dahlberg's classification was used with the following gradations: (0) smooth mesiobuccal crown surface; (1) small vertical ridge and groove; (2) small pit with minor grooves diverging from depression; (3) double vertical ridges or slight and incomplete cusp outline; (4) Y-form (*i.e.*, moderate grooves curving occlusally in opposite directions); (5) small tubercle; (6) broad cusp outline with a moderate tubercle, and (7) large tubercle with a free apex (Kieser and van der Merwe, 1984). In Dahlberg's classification, four grades (1 through 4) can be termed negative and three grades (5 through 7) positive trait forms. Asymmetry was expressed in terms of the proportion of individuals showing differences be-

TABLE 2. Sex and demographic distribution[1]

	Inhabitances on island under 15 years of age					Sample Size			
Location	Males	Females	Total			Males	Females	Total	
Towns	766	711	1477	69.6%		86	68	154	68.8%
Villages	339	305	644	30.4%		40	30	70	31.2%
Total	1105	1016	2121			126	98	224	
	52.1	47.9%				56.3%	43.7%		

[1]There are three towns on the island of Hvar: Hvar, Starigrad and Jelsa. These towns are administrative centers for a number of villages around the island, and the majority of inhabitants on the island live in these centers.

TABLE 3. Distribution of left Carabelli trait according to Dahlberg's classification

| | Grade of Carabelli's Trait | | | | | | | | |
	0	1	2	3	4	5	6	7	Total
Outbred									
Number	5	1	6	0	0	2	0	0	14
Percent	35.7	7.1	42.9	0.0	0.0	14.3	0.0	0.0	
Low inbreeding									
Number	19	14	17	9	34	23	9	1	126
Percent	15.1	11.1	13.5	7.1	27.0	18.3	7.1	0.8	
High inbreeding									
Number	4	5	12	3	14	16	5	2	61
Percent	6.6	8.2	19.7	4.9	23.0	26.2	8.2	3.3	
Total									
Number	28	20	35	12	48	41	14	3	201
Prcent	13.9	10.0	17.4	6.0	23.9	20.4	7.0	1.5	

tween sides as described by Kieser (1984).

Inbreeding analysis compared the children based on three rates of grandparental endogamy (i.e., grandparents born in the same settlement). One, an outbred group (some grandparents were not from the island). Two, a group with "low inbreeding" (one or two grandparents born in the same village). Three, a group with "high inbreeding" (all four grandparents born in the same village). This was done across all studied villages. Several previous studies in Hvar showed that complete grandparental endogamy is a reliable indicator of inbreeding in these small villages, as most (if not all) individuals will eventually be related at some point in history (Rudan and Rudan, 2000; Smolej-Narančić and Rudan, 2001). Thus, complete endogamy in these

populations in some instances carries greater potential to discriminate inbred from non-inbred individuals than the actual genealogical reconstruction, because the latter tends to underestimate the remote component of inbreeding (Broman and Weber, 1999; Shifman and Darvasi, 2001). The present study design was to evaluate the effect of inbreeding on Carabelli's trait at the individual level. The study has the benefit of reduced environmental variance across studied villages, a feature that has been documented previously (Rudan *et al.*, 1999).

The statistical significance of the differences in frequencies was evaluated using a chi-square test, and symmetry was evaluated using the Wilcoxon test with alpha level set at 0.10 and at 0.05. Pearson chi-square value, likelihood ratio and linear-by-linear association

TABLE 4. Distribution of right Carabelli trait according to Dahlberg's classification

| | Grade of Carabelli's Trait | | | | | | | | |
	0	1	2	3	4	5	6	7	Total
Outbred									
Number	5	1	5	1	0	2	0	0	14
Percent	35.7	7.1	35.7	7.1	0.0	14.3	0.0	0.0	
Low inbreeding									
Number	19	14	13	16	34	17	10	1	124
Percent	15.3	11.3	10.5	12.9	27.4	13.7	8.1	0.8	
High inbreeding									
Number	7	4	10	4	12	14	7	1	59
Percent	11.9	6.8	16.9	6.8	20.3	23.7	11.9	1.7	
Total									
Number	31	19	28	21	46	33	17	2	197
Prcent	15.7	9.6	14.2	10.7	23.4	16.8	8.6	1.0	

TABLE 5. Statistical tests for data from the left side

Statistic	Value	df	P
Chi-Square	23.944*	14	0.047
Likelihood Ratio	26.689	14	0.021
Mantel-Haentzel	9.662	1	0.002

*12 cells (50.0%) have expected counts less than 5. The minimum expected count is 0.21.

were presented after testing inter-group differences. Likelihood ratio is a goodness-of-fit statistic similar to Pearson's chi-square and equivalent to it in large sample sizes—with the advantage that it can be subdivided into interpretable parts that add up to the total. Linear-by-linear association (*i.e.*, the Mantel-Haenszel chi-square test) is a measure of linear association between the row and column variables.

RESULTS
Trait expression

Tables 3 and 4 show the distributions of Carabelli's trait on the left and right first molars in the outbred sample, and the samples with low and high inbreeding. All distributions varied significantly in frequency between groups ($P < 0.05$) for each side of the arch (Tables 5 and 6). In the outbred group, grade 0 on the right side and 0 and 2 on the left side occurred most frequently. In the sample with inbreeding, grade 4 (group with low inbreeding) and 5 (group with high inbreeding) were most common.

Chi-square tests (Tables 5 and 6) disclosed statistically significant differences among the groups ($P < 0.05$ for left side and $0.10 > P > 0.05$ for right side) with different degrees of inbreeding when Carabelli's trait was divided into absent, negative, and positive expressions. Positive trait expression was observed in 14% of the individuals in the outbred group, 23-26% with low inbreeding, and 37-38% with high inbreeding. Absence of the trait was observed in 36% of the outbred individuals but only 7-12% of individuals with high inbreeding.

Trait symmetry

The distribution of the grades in 197 individuals is shown in Table 7. Significant correlation ($P < 0.001$) was observed between the sides of the jaw (Table 8). No individual showed a positive cusp on one side and absence of the character on the other. However, twelve individu-

TABLE 6. Statistical tests for data from the right side

Statistic	Value	df	P
Chi-Square	21.988*	14	0.079
Likelihood Ratio	24.312	14	0.042
Mantel-Haentzel	7.138	1	0.008

*10 cells (41.7%) have expected counts less than 5. The minimum expected count is 0.14.

als (5%) showed a negative expression unilaterally, with no trait on the other side.

Table 9 shows the distribution of Carabelli's trait according to Dahlberg's classification, and Table 10 shows the left-right concordance according to the negative and positive expressions among the individuals with different inbreeding levels. No significant difference was found among the groups (Table 11). Using Dahlberg's classification, inbred individuals were more symmetric than those from the outbred group. The opposite finding was observed when comparing a negative and a positive expression, namely more asymmetric expressions occurred in inbred groups.

DISCUSSION

The highly endogamous population of Hvar is characterized by a very high frequency of Carabelli's trait. The overall frequency was 84% on the right side and 86% on the left side. This is approximately the same as the highest frequency of the trait reported by Kirveskari (1974) among Skolt Lapps (90%). A positive cusp was observed in 29% of individuals on the left side and 26% on the right side, which is somewhat higher than the value observed among Skolt Lapps (20%) and is almost equal to findings by Townsend and Martin (1992) in a sample of Caucasian twins and to the frequency in the German population (30%) reported by Reiners-Karsch (1964). A higher frequency of the cusp has only been reported by Keene (1968) among north-American military recruits (38%).

The literature illustrates that inbreeding can affect orofacial traits. Direct evidence for the influence of inbreeding on orofacial traits and on syndromes has, for example, been provided by Schull and Neel (1965), Maatouk et al. (1995), and Zlotoroga (1997) on humans and by Baume and Lapin (1983) on *Papio hamadryas*. Indirect evidence for the effect of inbreeding on orofacial traits in humans can be found in studies reporting higher prevalence of various orofacial traits in small isolated consanguineous communities such as Yanomami Indians of Brazil (Pereira and Evans, 1975), the Kwaio of the Solomon Islands (Lombardi and Bailit, 1972), and Ashkenazi Jews (Ben-Bassat *et al.*, 1997). However, the Carabelli trait has not previously been the focus of inbreeding investigations.

The biologically isolated population of Hvar Island was divided into three groups in this study. First, there was a group with some grandparents who moved to the island from abroad, carrying new genes into the island's gene pool (the outbred group). This group consists of just 14 children, but this represents the actual proportion of incomers. The second and the third groups are individuals whose ancestors were born on the island. In the second group are individuals with up to two grandparents from the same village, whose inbreeding scores range from 0.0039 to 0.0156. The third group consists of individuals with three or four grandparents from the

TABLE 7. Distribution of Carabelli trait according to negative-positive dichotomy

	Left-Hand Side				Right Hand Side			
	Absent	Negative	Positive	Total	Absent	Negative	Positive	Total
Outbred								
Number	5	7	2	14	5	7	2	14
Percent	35.7	50.0	14.3		35.7	50.0	14.3	
Low inbreeding								
Number	19	74	33	126	19	77	28	124
Percent	15.1	58.7	26.2		15.3	62.1	22.6	
High inbreeding								
Number	4	34	23	61	7	30	22	59
Percent	6.6	55.7	37.7		11.9	50.8	37.3	
Total								
Number	28	115	58	201	31	114	52	197
Percent	13.9	57.2	28.9		15.7	57.9	26.4	

same village, mostly villages with an inbreeding score over 0.0156, which is representative of an extremely isolated group. Using Dahlberg's classification, absence of Carabelli's trait was the modal finding in the outbred group, while grade 4 was most common in the low-inbreeding group, and grade 5 was most common in the high-inbreeding group. Of note, there was an obvious and statistically significant *dose-response relationship* for the expression of Carabelli's cusp (Dahlberg's grade 5, 6 and 7) with the degree of inbreeding.

This association between inbreeding and trait frequency implies that the trait may be modulated by recessive genes. Rudan (2002) has noted that an increase in inbreeding of 5% corresponds to having about 1750 random genes across the genome identical by descent if the total number of human genes is between 30,000 and 40,000 (Subramanian et al., 2001). If this unrecombined homozygosity has a notable effect on Carabelli's

TABLE 8. Statistical tests for data from the sides after dichotomizing the data into negative and positive trait expressions

Statistic	Value	df	P
	Right Side		
Chi-Square	10.466[a]	4	0.033
Likelihood Ratio	9.701	4	0.046
Mantel-Haentzel	8.606	1	0.003
	Left Side		
Chi-Square	9.275[b]	4	0.055
Likelihood Ratio	8.288	4	0.082
Mantel-Haentzel	6.745	1	0.009

[a]2 cells (22.2%) have expected counts less than 5. The minimum expected count is 1.95.
[b]2 cells (22.2%) have expected counts less than 5. The minimum expected count is 2.20.

trait frequency, two mechanisms could explain it, (1) homozygosity brings together rare major genes or (2) the genes controlling this trait are of small effect but are incredibly numerous, scattered across the genome. Genes with major effects arise after mutations that are considered to be extremely rare, because the probability of a random mutation that causes a small effect is much greater. Even if such mutations are present in some individuals, it is extremely unlikely that similar effects of inbreeding, as the high significance of linear-by-linear association indicated, would be observed in the whole group with high inbreeding and across all of the villages. It is more likely that the Carabelli trait is therefore a polygenetic trait. Moreover, as results from this study indicate, it seems that the trait is caused by a rare allelic variant rather then a common one because if the trait were caused by common allelic variants, inbreeding could not increase the frequency in the homozygotes. A large number of genes involved in the model of trait expression can be explained as a product of a dynamic developmental program manifested in the activation of the developmental modules. As Jernvall and Jung (2000) suggest, a cascade model of molar trait development includes a number of stages and can be used to explain the variation of properties of dental characters and character states related to cusp initiation. A portion of a number of genes involved in such a complex developmental model can be recognized in different and tissue-related homeobox gene expression (transcription factors responsible for activation of primary genes and direct the differentiation of whole body parts (Gilbert *et al.*, 1996)).

Despite our expectation of significant difference of bilateral symmetry among the groups, all groups had similar distributions of bilateral asymmetry. Increased fluctuating asymmetry in the inbred group had been

*TABLE 9. Occurrence of Carabelli trait on the maxillary first molar on the two sides of the dental arcade**

Class	Right-hand side 0	1	2	3	4	5	6	7	Total
0	23	1	3						32
1	4	9	1	5					18
2	3	4	20		3	2	1		26
3		3		8		1			19
4	1	1	1	2	35	4	1		45
5			1	3	7	23	6		34
6				1		4	8	1	17
7							1	1	2
Total	28	19	33	12	45	40	14	2	193

Left Side labels rows 0–7.

*Kendall's tau = -0.735.

anticipated because individuals with reduced genetic heterogeneity are more sensitive to environmental stress during ontogeny (e.g., Bailit *et al.*, 1970; Thornhill and Moller, 1997).

Results of left-right concordance when using Dahlberg's eight grades differ from those that lump the expressions into a positive-negative dichotomy. Dahlberg's classification is more precise and only virtually-identical expressions are recognized as bilaterally symmetric, whereas different grades of positive and negative expressions will be pooled together in the second, dichotomous classification. However, a similar symmetry distribution was observed with both classifications, rejecting the hypothesis about influence of inbreeding on fluctuating asymmetry of Carabelli's trait. If inbreeding increases the symmetry of a trait, one explanation is that different genes with recessive variants are responsible for trait expression on the left and right sides of the arcade. This explanation can be rejected here because the repeated activation of the de-velopmental modules during tooth development suggests that homologous cusps and crests are not coded as such into the genome, but that the whole cusp pattern is a product of a dynamic program (Jernvall, 2000; Zhao et al., 2000). Obviously, high bilateral symmetry of the trait in various investigations implies that a multitude of other environmental factors during the development of the trait have no significant effect. It seems that this trait is almost completely genetically determined with a predominant genetic variance and that most of factors during odontogenesis are not environmental. Those factors, as Jernvall and Jung (2000) commented on for primate molar shapes, "do not reflect just a static genetic code readable deep inside the genome, but rather, it is a readout of the information stored in the dynamic cusp-making program." Therefore, polygenic developmental module responsible for the diversity of Carabelli trait could be variable, but it stays relatively stable after initiation of the developmental process.

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TABLE 10. Left-right symmetry of trait expression

Group	Dahlberg's Eight-Grade Scale Symmetric	Asymmetric	Total	Dichotomized Trait Expressions Symmetric	Asymmetic	Total
Outbred						
Number	3	11	14	12	1	13
Percent	21.4	78.6		92.3	7.7	
Low inbreeding						
Number	42	78	420	100	17	117
Percent	35.0	65.0		85.5	14.5	
High inbreeding						
Number	20	37	57	46	7	53
Percent	35.1	64.9		86.8	13.2	
Total						
Number	65	126	191	158	25	183
Percent	34.0	66.0		86.3	13.7	

TABLE 11. Statistical tests for left-right symmetry of trait expression

Statistic	Value	df	P
Eight-Grade Scale			
Chi-Square	1.069[a]	2	0.586
Likelihood Ratio	1.149	2	0.563
Mantel-Haentzel	0.405	1	0.525
Dichotomized Expression			
Chi-Square	0.477[b]	2	0.788
Likelihood Ratio	0.539	2	0.764
Mantel-Haentzel	0.042	1	0.837

[a] 1 cell (16.7%) has expected counts less than 5. The minimum expected count is 4.76.

[b] 1 cell (16.7%) has expected counts less than 5. The minimum expected count is 1.78.

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Laboratory Name Change

Ebba During reports that theArchaeoosteological Research Laboratory, Royal Castle Ulriksdal, S-17079 Solna, Sweden, has undergone a name change to a "less lumbering" title. The new name is **Osteoarchaeological Research Laboratory**. The address remains the same.

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