

SCIENTIFIC  
SECTION

# Effect of inbreeding and endogamy on occlusal traits in human isolates

T Lauc, and P Rudan

Institute for Anthropological Research, Zagreb, Croatia

I Rudan,\* † and H Campbell†

\*University Medical School, Zagreb, Croatia, and †University of Edinburgh Medical School, Edinburgh, UK

## Abstract

*Objective:* To discuss the genetic basis of occlusal traits through analysis of the effects of inbreeding in a subdivided isolated community.

*Subjects and methods:* The sample comprised dental casts of 224 children, aged 7–14 years, from 15 villages of the Island of Hvar, Croatia.

*Main outcome measures:* Studied traits were Angle class, overjet, vertical bite, overbite, and crowding/spacing.

*Design:* Children with complete grandparental endogamy (all four grandparents born in the village of residence of the examinee) were compared to children with incomplete grandparental endogamy. In addition, children resident in the group of villages with a high prevalence of inbreeding were compared to children resident in the groups of villages with moderate and low prevalence of inbreeding.

*Results:* In both designs, inbreeding seemed to increase the mean values of overjet, overbite, and vertical bite, while it had little or no effect on crowding/spacing. Angle classes were correlated to inbreeding at the individual level, but this was not supported at the population level. The effects were stronger in the subsample with bilaterally concordant Angle classes.

*Conclusion:* The observed inbreeding effects imply that the genetic basis of some occlusal traits is polygenic and, in considerable part, influenced by rare and recessive genetic variants.

## Index words:

Endogamy, genetics, inbreeding, isolate populations, occlusal traits, overbite, overjet.

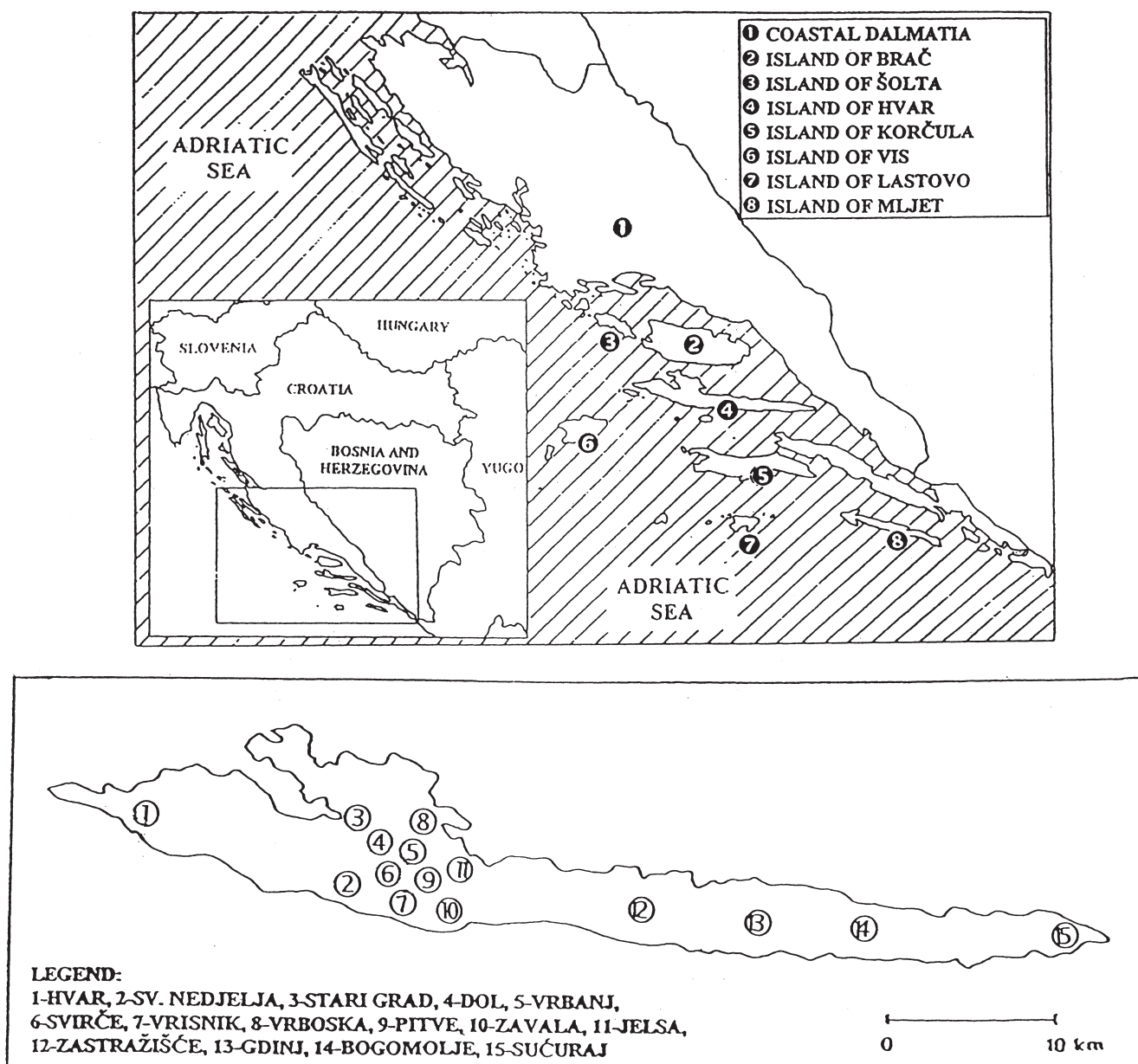
Received 13 August 2002; accepted 12 March 2003

## Introduction

A number of studies have confirmed the importance of both environmental and genetic determinants of occlusal traits in humans and experimental animals. Occlusal traits are generally dependent upon a combination of variation in tooth position and skeletal development. The former is generally thought to be more environmentally and the latter more genetically influenced. One of the best examples for the importance of environmental factors was reported by Weiland *et al.*,<sup>1</sup> who showed secular changes in malocclusion in Austrian men within the last century that corresponded to changes in dietary habits. In another study, Corruccini and Lee<sup>2</sup> reported occlusal deterioration in Chinese children born and bred in the United Kingdom in comparison to their immigrant parents of Chinese upbringing. Furthermore, a change to

a less tough diet has been shown to increase occlusal variation in laboratory rats,<sup>3</sup> macaques,<sup>4</sup> and squirrel monkeys,<sup>5</sup> probably due to exertion of less force on the jaws in chewing.

Genetic factors are also significant in the development of malocclusion. Studies of heritability in monozygotic and dizygotic twins and in large samples of families from different populations reveal strong evidence of a genetic component for overjet, arch size, cross-bite, and individual tooth displacement.<sup>6–11</sup> The genetic component, however, seems to be considerably smaller for overbite, and very low for molar relationships, crowding and rotations. The importance of hereditary factors generally increases with the severity of malocclusions.<sup>8,12</sup> Importantly, none of these studies could find support for simple Mendelian inheritance, even in the most apparent familial clustering of severe malocclusions. This led to the



**Fig. 1** Geographic location of Hvar island, Croatia, with position of 15 studies villages.

hypothesis of polygenic transmission of these traits that depends on a threshold beyond which persons are at risk,<sup>8</sup> although that hypothesis is quite difficult to prove.

In polygenic inheritance, the interaction of a number of genes at different loci that may interact with environmental factors determine phenotypic variation of the trait. Various genes have different contribution to phenotypic variation—an 'additive' effect on some trait. It is hypothesized that the large majority of genetic variants involved in polygenic inheritance model would have

small additive effects, and only several of the variants would exhibit intermediate or even a large effect on the phenotypic variation. Polygenic inheritance is mostly associated with the type of variation along a continuous scale, which is complicated if individuals with some trait are characterized in a qualitative way as 'affected' or 'unaffected' individuals. Such characterization should be used only in the specific conditions, when the liability exceeds a critical threshold value and the greater the level of liability beyond the threshold, the more severe the

disease.<sup>13</sup> In contrast to simple Mendelian inheritance, polygenic inheritance of the more extreme expression of the trait implies a greater frequency of affected relatives than a weak expression. The frequency of affected relatives rises with the number of relatives<sup>14</sup> and, therefore, populations characterized with higher inbreeding coefficients can be used as a model of a large family. Sharing the common gene pool, inbred populations tend to have different genetic structures than the large outbred population. The mechanisms of polygenic transmission and the theory of components of phenotypic variance are described in detail in recent papers.<sup>15,16</sup>

In this paper, we present an approach that could provide empirical support for the polygenic determination of several occlusal traits in humans. Our hypothesis was that if a modest increase in sharing of genes identical by descent (e.g. an increase in inbreeding coefficient from 0 to 3%) leads to significant changes in characteristics of occlusal traits, this is consistent only with a large number of genomic loci influencing the trait. We further considered that it would be advantageous to explore this hypothesis in a population in which the variation in dental care and nutrition habits is minimal.<sup>10</sup>

We therefore investigated the hypothesis in a genetic isolate population. The studied population included schoolchildren from the island of Hvar, Croatia, a population ethnohistorically,<sup>17</sup> anthropologically,<sup>18–20</sup> and genetically<sup>21–24</sup> well characterized through long-term multidisciplinary research. This paper also builds up on the previous research on dental and occlusal traits in the Hvar population.<sup>25,26</sup>

## Materials and methods

### Studied population

The sample for this study comprised 224 dental casts of children aged 7–14 years from all elementary schools on the island of Hvar, Croatia (Figure 1). The study was approved by the ethics committee of the Zagreb University Medical School. Informed consent was obtained from children's parents. Probability matching was employed to yield a 20% sample that reflected the age and sex distribution of the total elementary school population of the island. Eighteen children had orthodontic treatment and their data were registered from the medical records.

The pupils' parents provided complete two-generation genealogical data for each examined child (including parents and grandparents with the place of residence in each case). Table 1 presents the distribution of the

sample according to gender, age, place of residence (at birth) within the Island of Hvar, and the grandparental endogamy.

The main characteristic of Hvar island population that makes it very suitable for this study is its subdivision into 15 villages that present a range of average population inbreeding coefficients, while sharing very similar environmental impacts. This has been documented in papers by Rudan *et al.*<sup>18,19,27</sup> and Waddle *et al.*<sup>20</sup>

### Studied occlusal traits

Upper and lower alginate impressions were taken and poured into dental stone. Six occlusal variables were selected for study as described below:

**Table 1** The distribution of the sample according to gender, age, place of residence within the Island of Hvar, and the grandparental endogamy

	Total
Gender of the examinees	
Males	126 (56.3%)
Females	98 (43.7%)
Age	
7	27 (12.0%)
8	34 (15.2%)
9	28 (12.5%)
10	21 (9.4%)
11	26 (11.6%)
12	27 (12.1%)
13	28 (12.5%)
14	33 (14.7%)
Village of residence*	
Hvar (1)	32 (14.3%)
Sveta Nedjelja (2)	6 (2.7%)
Stari Grad (3)	39 (17.4%)
Dol (4)	10 (4.5%)
Vrbanj (5)	25 (11.1%)
Svirce (6)	30 (13.4%)
Vrisnik (7)	10 (4.5%)
Vrboska (8)	7 (3.1%)
Pitve (9)	2 (0.9%)
Zavala (10)	6 (2.7%)
Jelsa (11)	30 (13.4%)
Zastrazisce (12)	11 (4.9%)
Gdinj (13)	6 (2.7%)
Bogomolje (14)	3 (1.3%)
Sucuraj (15)	7 (3.1%)
Grandparental endogamy	
Four grandparents from the same village	47 (21.0%)
Three grandparents from the same village	27 (12.1%)
Two grandparents from the same village	148 (66.1%)
All grandparents from different villages	2 (0.9%)

\*At birth, as some children have moved after reaching school age.

1. Buccal relationship was classified as Angle's Class I, II, or III. Half unit Class II or half unit Class III were considered Class II or Class III, respectively.
2. The effects of inbreeding were investigated separately in examinees bilaterally concordant for Angle class (it is hypothesized that they could reflect better the genetic influence, while the lack of bilateral symmetry could reflect environmental effects).
3. Overjet was evaluated to the nearest 0.5 mm; normal range was determined at 0.5–4.0 mm.
4. Vertical bite was categorized as normal (<3.5 mm), deep (3.6–6.5 mm), and very deep (>6.5 mm).
5. Overbite was measured directly, as a quantitative trait. The categorization resembled that of the vertical bite. Overbite measurements included edge-to-edge and open bites.
6. Intra-arch relationships (normal, crowding, or spacing) were categorized as follows: no crowding/no spacing (including crowding = <0.5 mm and spacing = <0.5 mm); crowding (>0.5 mm); and spacing (>0.5 mm).<sup>28</sup> Both maxilla and mandible were assessed together.

Values of overjet, overbite, and midline shifts were measured using caliper (Digimatic, Mitutoyo Corp., Japan) with digital output to the nearest 0.01 mm.

### Study design

Two different analytic approaches were adapted. The first design attempted to roughly evaluate the effect of inbreeding on occlusal traits at the individual level, irrespective of the village of residence of the examinee, using the benefit of reduced variance in environmental factors across studied villages, which has been demonstrated previously.<sup>19</sup> This compared all the children with complete grandparental endogamy (all four grandparents were born in the village of residence of the examinee) with the children with incomplete grandparental endogamy. Several previous studies in Hvar island population showed that complete grandparental endogamy is a very reliable indicator of inbreeding in these small villages, as most (if not all) individuals will eventually be related at some point in history.<sup>29,30</sup> The degree of inbreeding in offspring of such consanguineous unions can be measured by the genetic term 'inbreeding coefficient' ( $F$ ), which indicates the proportion of autosomal genome which is expected to be homozygous through inheritance of identical genes from common ancestors [i.e. proportion of alleles identical by descent

(IBD) or 'autozygosity']. The  $F$  value is calculated from genealogical information, and it amounts to about 6% in the offspring of first cousin parents and 25% in the offspring of incestuous unions of first-degree relatives. The apparent risk in individuals with a considerable proportion of their genes homozygous for identical allelic variants is the occurrence of 'Mendelian' (monogenic) diseases caused by rare and recessive deleterious autosomal mutations. However, the effect on the polygenic traits should also be notable if they are determined by numerous, rare, and predominantly recessive genetic variants—a phenomenon known in the literature as 'inbreeding depression' and proven for a large number of plant, animal, and human quantitative traits.<sup>31,32</sup>

Thus, complete endogamy in these populations will be related to a greater expected coefficient of inbreeding in the studied individuals and will (at least in some instances) carry even greater potential to discriminate inbred from non-inbred individuals than the actual genealogical reconstruction, as the latter tends to underestimate the remote component of inbreeding.<sup>33,34</sup>

The second approach was ecological and it was conducted at the level of villages, rather than individual examinees. Due to different political and socio-cultural reasons, discussed in-depth elsewhere,<sup>18</sup> these villages present a range of inbreeding coefficients characteristic of their population while sharing very similar environments. The inbreeding coefficients ( $F$ ) were already assessed on representative population samples (20–30% of inhabitants) using genealogical information,<sup>27</sup> isonymy methods,<sup>22</sup> serogenetic polymorphisms,<sup>21</sup> and STR and VNTR polymorphisms.<sup>23,35</sup> The estimates were generally concordant and they allowed the classification of the villages from this study into three large groups according to the average inbreeding coefficient in each village (Table 2). The first group included the villages on the coastline that became popular tourist resorts during last several decades, and in which the average inbreeding coefficient does not reach the value expected in offspring of third-cousin mating ( $F = 0.0039$ ). The second group included the villages that are small and relatively isolated, but the mating patterns resulted in average inbreeding coefficients ranging between the values expected in offspring of third-cousin mating ( $F = 0.0039$ ) and second cousin mating ( $F = 0.0156$ ). Finally, the third group included very small and isolated villages in which the average inbreeding coefficient was equal to or greater than 0.0156. This design simply compared the frequencies and mean values of measured occlusal traits between examinees affiliated to different village groups. The statistical

**Table 2** Distribution of the examined villages of Hvar island according to median inbreeding coefficient ( $F$ ) determined from genealogies, isonymy, serogenetic polymorphisms, and STR and VNTR polymorphisms. The cut-off values correspond to offspring of third-cousin mating ( $F = 0.0039$ ) and second cousin mating ( $F = 0.0156$ )

Group I ( $F < 0.0039$ )*	Group II ( $0.0039 = F < 0.0156$ )*	Group III ( $F \geq 0.0156$ )*
Hvar (1)	Sv. Nedjelja (2)	Vrisnik (7)
Stari Grad (3)	Dol (4)	Zastrazisce (12)
Jelsa (11)	Vrbanj (5)	Gdinj (13)
	Svirce (6)	Bogomolje (14)
	Vrboska (8)	
	Pitve (9)	
	Zavala (10)	
	Sucuraj (15)	

\*Median inbreeding coefficient ( $F$ ) determined from genealogies, isonymy, serogenetic polymorphisms, and STR and VNTR polymorphisms.

significance of the differences in frequencies was compared using  $\chi^2$ -test. The mean values were compared between samples using Student's  $t$ -test for independent samples.

## Results

Table 3 presents the results of the study at the individual level. Patients with complete grandparental endogamy seemed to exhibit irregular molar relationships (Angle Class II or III) significantly more frequently than the controls, especially in the subsample of examinees with bilaterally concordant Angle Class ( $P < 0.05$ ). Mean values for overjet and overbite were about 15–20% greater among completely endogamous examinees. Accordingly, deep and very deep bite was more frequent among completely endogamous examinees. No significant differences were noted between the two groups with respect to crowding/spacing.

Table 4 presents the results at the level of village groups. The hypothesis was that if the effects of inbreeding were real, then the children from villages that are more inbred would generally show similar trends to the children who were completely endogamous irrespective of the village in previous analysis. There was little support for that hypothesis in the analysis of distribution of frequencies of Angle classes, which showed no consistent effect of inbreeding. The exception is again the subsample of examinees with bilaterally concordant Angle class, where the predicted effects were observed. The results for overjet, overbite, and vertical bite generally confirmed the

**Table 3** Frequencies, mean values, standard deviations and observed ranges for Angle classes (all examinees and bilaterally concordant only), overjet, vertical bite, overbite, and intra-arch relations in examinees with incomplete and complete grandparental endogamy

	Grandparental endogamy	
	Incomplete	Complete
<b>Angle class (n), all measurements</b>	<b>173</b>	<b>46</b>
I	86 (49.7%)	20 (43.5%)
II	77 (44.5%)	24 (52.2%)
III	10 (4.6%)	2 (4.3%)
<b>Angle class (n), bilaterally concordant only</b>	<b>118</b>	<b>33</b>
I	82 (69.5%)	16 (48.5%)*
II	35 (29.6%)	16 (48.5%)*
III	1 (0.9%)	1 (3.0%)
<b>Overjet (n)</b>	<b>177</b>	<b>47</b>
Mean	3.40 mm	4.00 mm*
SD	1.52 mm	2.09 mm
Range	0.0–8.7 mm	0.0–9.6 mm
<b>Vertical bite (n)</b>	<b>166</b>	<b>45</b>
Normal (<3.5mm)	83 (50.0%)	12 (26.7%)*
Deep (3.6–6.5mm)	80 (48.2%)	30 (66.7%)*
Very deep (>6.5mm)	3 (1.8%)	3 (6.7%)
<b>Overbite (n)</b>	<b>177</b>	<b>47</b>
Mean	3.36 mm	4.00 mm*
SD	1.60 mm	1.66 mm
Range	0–7.2 mm	0.0–7.6 mm
<b>Intra-arch relationships</b>	<b>177</b>	<b>47</b>
Normal	63 (35.6%)	15 (31.9%)
Crowding	98 (55.4%)	30 (63.8%)
Spacing	16 (9.0%)	2 (4.3%)

\* $P < 0.05$ .

Note: some examinees were excluded from the analysis of some specific variables due to missing teeth or unilateral asymmetry.

findings obtained at the individual level, while no notable effect was confirmed for crowding/spacing.

## Discussion

It has been previously suggested that inbreeding could enhance the occurrence of malocclusion. Direct evidence in humans was provided by Schull and Neel in Japan,<sup>36</sup> and Maatouk *et al.* in Tunisia.<sup>37</sup> Evidence in animals (Papio hamadryas) has also been reported.<sup>38</sup> Indirect evidence for the effect of inbreeding on occlusal traits in humans can be found in studies reporting high prevalence of malocclusion in small isolate consanguineous communities such as Yanomami Indians of Brazil,<sup>39</sup> Kwaio people of Solomon Islands,<sup>40</sup> and Ashkenazi Jews.<sup>41</sup> However, it is unclear why inbreeding should increase mean values of some quantitative occlusal traits. If

**Table 4** Frequencies, mean values, standard deviations and observed ranges for Angle classes (all examinees and bilaterally concordant only), overjet, vertical bite, overbite, and intra-arch relations in examinees from villages with low, intermediate, and high inbreeding

	Village group (see Table 2)		
	Group I (low F)	Group II (intermediate F)	Group III (high F)
<b>Angle class (n), all measurements</b>	<b>98</b>	<b>91</b>	<b>30</b>
I	41 (41.8%)	51 (56.0%)	14 (46.7%)
II	53 (54.1%)	34 (37.4%)	14 (46.7%)
III	4 (4.1%)	6 (6.6%)	2 (6.7%)
<b>Angle class (n), bilaterally concordant only</b>	<b>62</b>	<b>66</b>	<b>23</b>
I	42 (66.7%)	43 (65.6%)	13 (56.5%)
II	19 (30.6%)	22 (33.3%)*	10 (43.5%)*
III	1 (1.6%)	1 (1.5%)	0 (0.0%)
<b>Overjet (n)</b>	<b>101</b>	<b>93</b>	<b>30</b>
Mean	3.31	3.48	3.91
SD	1.83	1.69	1.67
Range	0–8.7	0–9.6	0–7.5
<b>Vertical bite (n)</b>	<b>94</b>	<b>88</b>	<b>29</b>
Normal bite (<3.5 mm)	39 (41.5%)	46 (52.3%)	10 (34.5%)
Deep bite (3.6–6.5 mm)	53 (56.4%)	40 (45.5%)	17 (58.6%)
Very deep bite (>6.5 mm)	2 (2.1%)	2 (2.3%)	2 (6.9%)
<b>Overbite (n)</b>	<b>101</b>	<b>93</b>	<b>30</b>
Mean	3.48	3.31	4.00
SD	1.59	1.66	1.74
Range	0–6.7	0–7.6	0–7.3
<b>Intra-arch relations</b>	<b>101</b>	<b>93</b>	<b>30</b>
Normal	35 (34.7%)	34 (36.6%)	9 (30.0%)
Crowding	57 (56.4%)	50 (53.8%)	21 (70.0%)
Spacing	9 (8.9%)	9 (9.7%)	0 (0.0%)

\* $P < 0.05$ .

Note: some examinees were excluded from the analysis of some specific variables due to missing teeth or unilateral asymmetry.

additive variance is the main component of total genetic variance in occlusal traits, then inbreeding should have quadratic effect on the values without necessarily changing the mean (as it should equally increase high values and decrease low values). A change in mean value of quantitative occlusal traits with inbreeding is predicted as a consequence of recessive or partially recessive variants (i.e. the dominance variance) with the direction of change towards the value of the more recessive alleles.<sup>42</sup> Physiological homeostasis may act to support a directional change, for example, through selection against variants tending to reduce values of overjet and overbite. Another possible explanation is that differences in environmental exposures due to cultural and socio-

logical peculiarities of human isolates predispose those populations in some way to malocclusion. However, in this particular study this is unlikely to be the case, given the reduced environmental and cultural variation in the 15 different small populations living on the same island.<sup>18,20</sup> We can only conclude that the consistency of results obtained through two different designs (individual and population-based) and the observed dose-response effect over the three village groups for some traits indeed suggests that inbreeding could predispose humans to malocclusion, especially to the increase in overjet, overbite, and vertical bite.

In support of this conclusion, the inbreeding effect was not observed on all measured traits, but rather on those already considered to show a significant genetic basis in previous heritability studies. For example, the effect was quite apparent for overjet, a trait that demonstrated a considerable heritability, while it was negligible for crowding, a trait considered to have little genetic basis.<sup>6–11</sup> Further support for this conclusion comes from the separate analysis of the subsample of examinees with bilaterally concordant Angle class, which are thought to be under greater genetic influence. Although more weight should be given to the results of individual over the population-based analysis, both support the general conclusion that inbreeding could have an effect at least on some occlusal traits, especially those with greater reported heritability.

If we accept the conclusion that an increase in inbreeding of about 2–3% (from  $F = 0.005–0.03$ ) could be responsible for the observed 15–20% increase in mean value of some quantitative occlusal traits, the central question becomes what does it tell us about the genetic basis of those traits. The data are consistent with a genetic component mediated through the recessive genetic variants. The underlying variants are also likely to be rare, since if they were common in the population, the inbreeding would not be expected to have a notable influence on the results. In addition, if we accept that the total number of human genes is between 30,000 and 40,000,<sup>42</sup> then an increase in inbreeding of 3% would correspond to having about 1000 random genes across the genome identical by descent. If this unrecombined homozygosity in only 1000 genes (3% of the total) could lead to a notable effect on a mean value of a quantitative trait, there are two main mechanisms that could explain it:

- this brings together rare major effect genes in a simple Mendelian fashion;

- the genes controlling this trait are of small effect but extremely numerous, scattered across the entire genome.

The design of this study provides strong arguments against the first explanation. Major effect genes arise after mutations that are considered to be extremely rare, as the probability of random mutation causing small effect is much greater. Therefore, even if such mutations were present in some of the studied villages, it is extremely unlikely that similar effects of inbreeding would be observed across all of the villages, as our results indicate. In addition, under such an assumption, the differences between inbred and outbred individuals would normally be much larger than it was the case in this study. It is more likely that the occlusal traits in humans are therefore partly controlled by a large number of genes, partially recessive.

## Conclusion

This study attempts to explore the genetic basis of occlusal traits through an analysis of results of an inbreeding study in a subdivided isolated community. The data support a conclusion that there are differences in the heritability of different occlusal traits, and that the basis of many of them is polygenically determined, largely through rare and recessive genetic variants.

## Acknowledgements

This work was supported by the Croatian Ministry of Science and Technology grants No. 0196001 to NS-N., No 0196005 to PR and 0108330 to IR, and the Wellcome Trust (IRDA) grant to HC and IR. IR was supported by funds from the UK Medical Research Council, the University of Edinburgh, and the Overseas Research Scheme.

## References

- Weiland FJ, Jonke E, Bantleon HP. Secular trends in malocclusion in Austrian men. *Eur J Orthod* 1997; **19**: 355–9.
- Corruccini RS, Lee GTR. Occlusal variation in Chinese immigrants to the United Kingdom and their offspring. *Arch Oral Biol* 1984; **29**: 779–82.
- Beecher RM, Corruccini RS. Effects of dietary consistency on craniofacial and occlusal development in rat. *Angle Orthod* 1981; **51**: 61–9.
- Beecher RM, Corruccini RS. Effects of dietary consistency on maxillary arch breadth in macaques. *J Dent Res* 1981; **60**: 68–72.
- Corruccini RS; Beecher RM. Occlusal variation related to soft diet in a non human primate. *Science* 1982; **218**: 74–6.
- Lundstrom A. *Tooth Size and Occlusion in Twins*. Basel, S. Krager, 1948.
- Iwagaki H. Hereditary influence of malocclusion. *Am J Orthod* 1938; **24**: 328–36.
- Litton SF, Ackermann LV, Isaacson RJ, Shapiro BL. A genetic study of Class III malocclusion. *Am J Orthod* 1970; **58**: 565–77.
- Stein KF, Kelley T, Wood E. Influence of heredity on the etiology of malocclusion. *Am J Orthod* 1956; **42**: 125–41.
- Harris EF, Smith RJ. A study of occlusion and arch widths in families. *Am J Orthod* 1980; **78**: 155–63.
- Corruccini RS, Potter RHY. Genetic analysis of occlusal variation in twins. *Am J Orthod* 1980; **78**: 140–54.
- Lundstrom A. The significance of genetic and nongenetic factors in the profile of the facial skeleton. *Am J Orthod* 1955; **41**: 910–16.
- Mossey PA. The heritability of malocclusion: Part 1—Genetics, principles and terminology. *Br J Orthod* 1999; **26**: 103–13.
- Stern C. *Principles of Human Genetics*. San Francisco, W.H. Freeman, 1973.
- Wright A, Charlesworth B, Rudan I, Carothers A, Campbell H. A polygenic basis for late-onset disease. *Trends Genet* 2003; **19**: 97–106.
- Barton NH, Keightley PD. Understanding quantitative genetic variation. *Nat Rev Genet* 2002; **3**: 11–21.
- Rudan P, Sujoldžić A, Šimić D, Bennett LA, Roberts DF. Population structure in the eastern Adriatic: the influence of historical processes, migration patterns, isolation and ecological pressures, and their interaction. In: Roberts DF, Fujiki N, Torizuka K. (eds), *Isolation, Migration and Health*. Cambridge, Cambridge University Press 1992, **33**: 204–18.
- Rudan P, Šimić D, Smolej-Narančić N, Bennett LA, Janičijević B, Jovanović V, Lethbridge MF, Miličić J, Roberts DF, Sujoldžić A, Szirovicza L. Isolation by distance in Middle Dalmatia, Yugoslavia. *Am J Phys Anthropol* 1987; **74**: 417–26.
- Rudan I, Campbell H, Rudan P. Genetic epidemiological studies of Eastern Adriatic Island isolates, Croatia: objectives and strategies. *Coll Antropol* 1999; **23**: 531–46.
- Waddle DM, Sokal R, Rudan P. Factors affecting population variation in Eastern Adriatic isolates, Croatia. *Hum Biol* 1998; **70**: 845–64.
- Janičijević B, Bakran M, Papiha SS, Chaventre A, Roberts DF. Serogenetic analysis in the study of population structure of the Eastern Adriatic (Croatia). *Hum Biol* 1994; **66**: 991–1003.
- Roguljić D, Rudan I, Rudan P. Estimation of inbreeding, kinship, genetic distances and population structure from surnames: example from the island of Hvar, Croatia. *Am J Hum Biol* 1997; **9**: 595–608.
- Martinović I, Barać L, Furač I, Janičijević B, Kubat M, Peričić M, Vidović B, Rudan, P. STR polymorphisms in the population of the island of Hvar. *Hum Biol* 1999; **71**: 341–52.

24. Tolk HV, Peričić M, Barać L, Martinović Klarić I, Jančićević B, Rudan I, Parik J, Villems R, Rudan P. mtDNA haplogroups in the populations of Croatian Adriatic islands. *Coll Antropol* 2000; **24**: 267–79.
25. Lauc T, Schäfer K, Prossinger H, Šlaj M. Orofacial analysis of the Adriatic islands: 1. The island of Hvar as a model for odontogenetic researches. *Coll Antropol* 2000; **24(Suppl)**: 63–9.
26. Lauc T. Orofacial analysis on the Adriatic islands: an epidemiological study of malocclusions on Hvar island. *Eur J Orthod* 2003; **25(3)**: 273–8.
27. Rudan I, Padovan M, Rudan D, Campbell H, Biloglav Z, Jančićević B, Smolej-Narančić N, Rudan P. Inbreeding and nephrolithiasis in Croatian Island isolates. *Coll Antropol* 2002; **26**: 11–21.
28. Ben-Bassat Y, Harari D, Brin I. Occlusal traits in a group of school children in an isolated society in Jerusalem. *Br J Orthod* 1997; **24**: 229–35.
29. Rudan I, Rudan P. Comparison between coefficients of inbreeding computed from deficit of heterozygotes for codominant autosomal genetic polymorphisms and from isonymy data: a study of Hvar island isolates, Croatia. In: Susanne C, Bodszar EB. (eds), *Human population genetics in Europe*. Biennial Book of European Anthropological Association, Budapest 2000; **1**: 117–28.
30. Smolej-Narančić N, Rudan I. Endogamy and blood pressure variation in Croatian island isolates. *J Physiol Anthropol Appl Hum Sci* 2001; **20**: 85–94.
31. Rudan I, Smolej-Narančić N, Campbell H, Carothers A, Wright A, Jančićević B, Rudan P. Inbreeding and the genetic complexity of human hypertension. *Genetics* 2003; **163**: 1011–21.
32. Charlesworth B, Charlesworth D. The genetic basis of inbreeding depression. *Genet Res* 1999; **74**: 329–40.
33. Broman KW, Weber JL. Long homozygous chromosomal segments in reference families from the centre d'Etude du polymorphisme humain. *Am J Hum Genet* 1999; **65**: 1493–500.
34. Shifman S, Darvasi A. The value of isolated populations. *Nat Genet* 2001; **28**: 309–10.
35. Martinović I, Mastana S, Jančićević B, Jovanović V, Papiha SS, Roberts DF, Rudan P. VNTR DNA variation in the population of the island of Hvar, Croatia. *Ann Hum Biol* 1998; **25**: 489–99.
36. Schull W, Neel J. *The Effect of Inbreeding on Japanese Children*. New York, Harper and Row, 1965.
37. Maatouk F, Laamiri D, Argoubi K, Ghedira H. Dental manifestations of inbreeding. *J Clin Pediat Dent* 1995; **19**: 305–6.
38. Baume RM, Lapin BA. Inbreeding effects on dental morphometrics in Papio Hamadryas. *Am J Physical Anthropol* 1983; **62**: 129–35.
39. Periera CB, Evans H. Occlusion and attrition of the primitive Yanomami indians of Brasil. *Dent Clin North Am* 1975; **19**: 485–98.
40. Lombardi VA, Bailit H. Malocclusion in the Kwaio, a Melanesian group on Malaita, Solomon Islands. *Am J Phys Anthropol* 1972; **36**: 283–94.
41. Falconer DS, Mackay TFC. *Introduction to Quantitative Genetics*, 4th edn. Harlow, Longman, 1996.
42. Subramanian G, Adams MD, Venter JC, Broder S. Implications of the human genome for understanding human biology and medicine. *J Am Med Ass* 2001; **286**: 2296–307.