Original Research Article
Correlation of long bone length and number of nutrient foramina – importance in everyday clinical practice

.

ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Aims: Nutrient artery is the principal source of nutrition to the long bones. The topography of nutrient foramina on long bones is well known, but it has not yet been established whether the number of nutritive foramina (NF) is related to total bone length. The objective of the present study was to study the correlation of total number of nutrient foramina and long bone length of upper and lower limb to provide detailed data on such features.

Study design:A cross-sectional, descriptive study

Place and Duration of Study: Department of anatomy, Medical Faculty University of Sarajevo

Methodology: In the present study, 300 adult human long bones of the upper (50 humeri, 50 radii, 50 ulnae) and lower (50 femora, 50 tibiae, 50 fibulae) limbs were investigated to determine the number of their nutrient foramina. The nutrient foramina were identified analysed macroscopically and total number of nutrient foramina for each bone was recorded.Total length of each bone within a group was recorded.Statistical analysis was performed to determine correlation between total bone length and number of nutrient foramina.

Results:A statistically significant negative correlations between the left humerus length and the number of NF was found. A positive correlations between the length of the right radius and the number of NF, the left ulna length and the number of NF, the right ulna length and the number of NF were found. A negative correlations between the length of the left radius and the number of NF and between right humerus length and number of NF were found. A positive correlation between the length of the right and left femur and the number of NF were found. A negative correlation between the length of left tibia and the number of NF was found, as well as negative correlation between the length of right and left fibula and number of NF.
Conclusion: Total bone length is not related to the number of nutrient foramina. The number of nutrient foramina does not depend on the total length of the bone, which is important when assessing the success of grafts for transplantation on long bones in taller people.

Keywords: nutritive foramina, long bones, morphology, number

1. INTRODUCTION

Numerous developmental factors, both genotypic and phenotypic, can influence the development of skeletons and soft tissues, and lead to minor or major deviations from the most common anatomical features called variations [1]. Accurate knowledge of the variables in the structure of the human body is important to improve diagnostic and therapeutic effects, especially in the field of modern imaging diagnostic techniques such as echocardiography, magnetic resonance imaging, computed tomography, endoscopy and laparoscopy.

Adequate blood supply is the basis of bone vitality and growth, resistance to infection and the ability to heal fractures [2]. Apart from the importance of nutrient arteries in fracture healing, some other conditions of bones, such as developmental abnormalities and hematogenic osteomyelitis, are also dependent on the vascular system of bones [3].

Long bones have three different vascular systems that are interconnected. These are the metaphysical complex, the nutritional system and the periosteal capillary system. The nutritional system is the largest, supplying blood to the bone marrow and the inner two-thirds of the bone cortex [4]. Nutrient foramina (NF) are the largest openings in the trunk of long bones through which nutritional arteries pass. Each long bone has its own nutritional artery, and some bones often have more. They are usually the collateral blood vessels of the limb arteries.

Many scholars have studied the NF of long bones [5, 6, 7]. Most of these studies were performed many years ago, and mainly focused on the number, location, and direction of the nutrient foramina.

The position and the direction of the NF are known to vary in human long bones. The blood supply of the femur has been described in detail by Lexer, Kuliga and Turk [8]. Nutrient foramina of the femur and humerus have been investigated by Lutken [9], Laing [10, 11] and Carroll [12]. Nutrient foramina on the radius and ulna have been studied by Shulman [13]. Hughes [14] has formulated an interesting explanation for the normal and abnormal direction of the NF and has stated that anomalous canals are frequent in the femur, but rarely occur in the radius and seldom in the other bones. None of the above workers has studied all the long bones together and it was thought worth while to reinvestigate the problem in all the long bones. Few studies were specific to correlation of number of NF and length of the long bones in upper and lower extremities [15].

Given the significance of NF in clinical and morphological fields, it is of paramount importance that the characteristics of NF are studied on an ongoing basis in order to validate the findings from literature and to explore and discover new findings that can play a critical role in the field of medical science. In this study, we systematically observed the number of NF and their relation to the length of the specific bones.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY

The research was conducted at the Department of Human Anatomy, Faculty of Medicine, University of Sarajevo. It is a cross-sectional, descriptive study, in which we analyzed and interpreted the results obtained by observation on bone material. The material for this study consisted of a total of 300 macerated and degreased adults, long bones of the upper and lower extremities (50 humerus, 50, radius, 50 ulna, 50 femur, 50 tibia, 50 fibula). All selected bones were anatomically preserved, with no noticeable pathological changes. Bones with noticeable damage were not included in the study. The age and gender of the people from whom the bones originate were not known. The following parameters were analyzed on the bones of each group: total number of NF and bone length.

On each bone, within each group, the total number of macroscopically observed NF on the diaphyses was recorded. A probe was passed through each hole to confirm the existence of the foramina. Nutritive foramina were observed only on the diaphyses of long bones. They were observed macroscopically, using a 6x hand magnifier. On the diaphyses, the NF were

observed by a slightly raised edge of the foramina and by a shallow groove existing proximally from the NF.
Determination of total bone length was done individually for each bone within each group, according to the following:

1. Humerus: distance between the top of the head of the humerus and the superior point of the trochlea
2. Radius: distance between the proximal point of the radius head and the top of the styloid process
3. Ulna: distance between the proximal point of the olecranon and the apex of the styloid process
4. Femur: distance between the proximal point of the head and the most distal lying point on the medial condyle
5. Tibia: distance between the proximal point of the medial condyle and the tip of the medial malleolus
6. Fibula: distance between the top of the head and the top of the lateral malleolus

2.1. Statistical analysis

Categorical data were expressed in frequencies and relevant percentage. The existence of a relationship between categorical variables was tested by the Chi-square test. The Kolmogorov-Smirnov or Shapiro-Wilk test, depending on the sample size, was used to assess the normality of the distribution of continuous variables. Mean and standard deviation (SD) were determined for the independent continuous variables that follow the normal distribution. The significance of the difference for the continuous independent variables that accompany the normal distribution was tested by Student t-test. Values of $p < 0.05$ were considered statistically significant. The statistical program SPSS version 17.0 for Windows was used for the above descriptions and analyzes.

2.1 Statistical analysis

Categorical data were expressed in frequencies and relevant percentage. The existence of a relationship between categorical variables was tested by the Chi-square test. The Kolmogorov-Smirnov or Shapiro-Wilk test, depending on the sample size, was used to assess the normality of the distribution of continuous variables. Mean and standard deviation (SD) were determined for the independent continuous variables that follow the normal distribution. The significance of the difference for the continuous independent variables that accompany the normal distribution was tested by Student t-test. Values of $p < 0.05$ were considered statistically significant. The statistical program SPSS version 17.0 for Windows was used for the above descriptions and analyzes.

3. RESULTS AND DISCUSSION

An average length for right humerus was 31.21 ± 2.27 cm, and 31.30 ± 2.51 cm for left humerus, with no statistically significant differences between the length of humerus from right and left extremity ($p = 0.902$; $p > 0.05$). The right radius had an average length of 23.41 ± 1.51 cm, while left radius had an average length of 22.86 ± 1.53 cm. The determined difference between the average radius length of the right and left extremities was not statistically significant ($p = 0.204$; $p > 0.05$). An average length for right ulna was 25.27 ± 2.02 cm, and 24.85 ± 1.82 cm for left one, with no statistically significant differences between the length of right and left ulna ($p = 0.44$; $p > 0.05$).

Table 1. Length of humerus, radius and ulna(cm) on right and left extremity

	Humerus		**Radius**		**Ulna**	
Length (cm)	Right (n=20)	Left (n=30)	Right (n=24)	Left (n=26)	Right (n=27)	Left (n=23)
	31.21±2.27	31.30±2.51	23.41±1.51	22.86±1.53	25.27±2.02	24.85±1.82

	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
	26.3	35.1	25.7	35.8	20.5	26.0	20.2	25.9	22.2	30.4	21.5	27.8

One NF was observed in 13 (72.2%) right humerus and 18 (60.0%) left humerus, in 22 (91.7%) right and 21 (91.3%) left radius, and in 19 (70.4%) right and 19 (82.6%) left ulna. Two NF were recored in 5 (27.8%) right and 9 (30.0%) left humerus, in 2 (8.3%) right and in 2 (8.7%) left radius, and in 7 (25.9%) right and 4 (17.4%) left ulna. Three NF were found on 3 (10.0%) left humerus and 1 (3.7%) right ulna (Table 2).

Table 2. Representation of number NF on the humerus, radius and ulna

Number of NF	**Humerus**				**Radius**				**Ulna**			
	Right		Left		Right		Left		Right		Left	
	n	%	n	%	n	%	n	%	N	%	n	%
1	13	72.2	18	60.0	22	91.7	21	91.3	19	70.4	19	**%**
2	5	27.8	9	30.0	2	8.3	2	8.7	7	25.9	4	82.6
3	0	0.0	3	10.0	0	0.0	0	0.0	1	3.7	0	17.4
Total	18	100.0	30	100.0	24	100.0	23	100.0	27	100.0	23	100.0

A statistically significant negative correlations between the left humerus length and the number of NF was found. A positive correlations between the length of the right radius and the number of NF, the left ulna length and the number of NF, the right ulna length and the number of NF were found. A negative correlations between the length of the left radius and the number of NF and between right humerus length and number of NF were found. The identified correlations were not statistically significant (Table 3.).

Table 3. Correlation between the length of the humerus, radius and ulna with number of NF

Variable		**Number of NF**
Humerus	Right	r = - 0.143
	Left	r = **- 0.438***
Radius	Right	r = 0.059
	Left	r = - 0.208
Ulna	Right	r = 0.110
	Left	r = 0.020

r – correlation coefficient
* – *p < 0,05*

An average length of right femur, tibia and fibula were 44.30 ± 2.4 cm, 35.73 ± 2.33 cm and 35.20 ± 2.7 cm, respectively, while an average length of left femur, tibia and fibula were 44.38 ± 2.7 cm, 36.26 ± 1.85 cm and 35.52 ± 2.1 cm, respectively. There were no statistically significant differences between right and left femur (p = 0.915; p> 0.05), tibia (p = 0.403; p> 0.05) and fibula (p = 0.645; p> 0.05) (Table 4).

Table 4. Length of femur, tibia and fibula on right and left extremity

Leng	**Femur**	**Tibia**	**Fibula**

	Right (n=29)		Left (n=21)		Right (n=31)		Left (n=19)		Right (n=25)		Left (n=25)	
	44,30±2,4		44,38±2,7		35.73±2.33		36.26±1.85		35.20±2.7		35.52±2.1	
	Min.	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**
	38,0	48,5	39,2	49,0	31.5	39.9	33.3	40.0	29.6	39.5	30.3	39.9

One NF was recorded in 1 (32.1%) right and 10 (52.6%) left femur, in 31 (100.0%) right and 16 (84.2%) left tibia and in 19 (90.5%) right and 21 (100.0%) left fibula. Two NF were recorded in 16 (57.1%) right and 8 (42.1%) left femur, in 3 (15.8%) left tibia and in 2 (9.5%) right fibula. Three NF were recorded in 3 (10.7%) right and in 1 (5.3%) left femur (Table 5).

Table 5. Representation of number NF on the femur, tibia and fibula

Number of NF	**Femur**				**Tibia**				**Fibula**			
	Right		Left		Right		Left		Right		Left	
	n	%	n	%	n	%	n	%	N	%	n	%
1	9	32.1	10	52.6	31	100.0	16	84.2	19	90.5	21	100.0
2	16	57.1	8	42.1	0	0.0	3	15.8	2	9.5	0	0.0
3	3	10.7	1	5.3	0	0.0	0	0.0	0	0.0	0	0.0
Total	28	100.0	19	100.0	31	100.0	19	100.0	21	100.0	21	100.0

A positive correlation between the length of the right and left femur and the number of NF were found. The found correlations were not statistically significant. A negative correlation between the length of left tibia and the number of NF was found, as well as negative correlation between the length of right and left fibula and number of NF. The found correlations were not statistically significant. Due to the size of the sample, we were not able to examine the correlation between the length of the right tibia and the number of NF (Table 6).

Table 6. Correlation between the length of the femur, tibia and fibula with number of NF

Variable		**Number of NF**
Femur	Right	r = 0.219
	Left	r = 0.260
Tibia	Right	/
	Left	r = - 0.030
Fibula	Right	r = - 0.164
	Left	r = - 0.138

The knowledge about the location of the NF is highly important because of the increased chances of damage to the nutrient artery during open or closed surgical procedures. The arrangement of the diaphyseal NF in the long bones usually follows a defined pattern in which the foramina are located on the flexor surface of the bones (anterior in the upper limbs and posterior in the lower) [16, 17, 18].

Most of the studies done so far on NF of long bones of upper and lower limb have examined NF position, number, and direction of the nutritional canal. But so far, no systematic studies have been done to examine whether the number of NF is correlated with bone length. Most of the long bones in our study had one NF, which is in agreement with the results of other authors [19, 20, 21].

Knowing the position of the NF is useful not only during bone surgeries, but also has forensic significance. In forensic medicine, it is possible to estimate the total length of the bone if the ratio between the total length of the bone and the distance of the NF from both ends of the bone is known. This is especially important because bones broken at one or both ends are sometimes sent for examination [22]. In our study, a statistically significant negative correlation was found between the length of the left humerus and the number of NF (r = -0.438).

Houssaye et al. [23] revealed a trend for nutrient canals to be generally more numerous and relatively thinner in less elongated bones. As for the canal diameter, the diameters taken at mid-length or at the periphery co-vary. These parameters are also the only one to co-vary between the humeri and the femora. This shows that the diameter of the canals is rather constrained. Seymour et al. [24] suggested a link between blood vessel circumference and metabolic rates (larger blood vessels to service higher flow rates) and thus that the diameter of the nutrient canals would be linked to the physiology of the organisms. The femur is the longest bone in the human body and in our study the largest number of bones with two NF was found in this group, which is confirmed by positive correlations between the length of the femur and the number of NF. Only 15.8% of left tibia had two NF in our study, while the study of Haidara et al. [25] where they found more double foramina in tibia**.** That might be explained by the superiority of CT scan used in his study, in comparison to utilizing the naked eye and magnifying lenses in our study.

In our study we found more frequent double NF in long bones of lower extremity, in compering to upper extremity long bones. Long bones of lower extremity are longer, but in our study there was not statistically significant correlation between length of femur, tibia or fibula with number of NF. Larger number of NF in femur, tibia and fibula can be due to the higher force and stress transmitted to the lower limbs than to the upper limbs in view of the weight bearing and locomotive functions of the lower limbs and the relatively finer functions of the upper limbs, thereby warranting a more robust blood supply for the lower limb bones, resulting in a larger numer of the NF. This finding however has to be confirmed by more extensive studies and with a larger sample size. Neil J. [26]found found that the dominant NF occurred more frequently in the lower limbs than in the upper limbs, and the secondary foramina were more common in the upper limbs, which were statistically significant. In cases with many NF, although the fracture may damage some blood vessels, the residual intact blood vessels may still be able to provide the required blood supply to the bone. Although NF number has not been linked to age, multivariate logistic analysis revealed a significant interaction between the effects of gender and sidedness on foramen number ($p < 0.01$) in a study of NF within the human femoral diaphysis [27]. Patake [15] and Mysorekar [28] opined that the number of foramina does not seem to have any significant relation to the length of the bone. Also, according to several other studies (29, 30, 31) the distribution of the NF within the long bone shaft of upper and lower limb is not related to the length of the shaft. Zhiquan et al. [32] found the mean total bone length for humerus was 305.12±16.29 mm. They analyzed the relationship between foramen size and humerus length and found no correlation (r=0.094, p=0.552). This suggests that clinicians cannot estimate the size of nutrient arteries by their patients body size.

Larger prospective studies are needed, therefore, to provide clinical data regarding gender and sidedness and also to explore the effect of shaft length on the number of NF within the shaft. These results are in agreement with our results, where we did not found statistically significant correlation with bone length and number of NF. The absence of NF in long bones is well known [28, 33]. It was reported that in instances where the nutrient foramen is absent, the bone is likely to be supplied by periosteal arteries [15].

In the setting of reconstructive surgery, the use of vascularized allografts has been proven effective albeit challenging [34, 35]. Vascularized bone and joint allograft survival is strongly contingent upon preservation of periosteal and intraosseous blood supply [35]. Hence, graft preservation methods as well as surgical techniques depend upon a thorough understanding of vascular anatomy. The results of our study showed that there is no statistically significant association between bone length and the number of NF, except in humerus. The correlation

between length in human long bones and number of NF has been reported in only a few papers. Because there have been no reference data on the long bones to date, the results reported here are novel data. This should of use to surgeons. In case the graft should be taken from a very tall person, it is considered that there will be no disruption of the vascular integrity of the long bone, because regardless of the length of the bone itself, other nutritional arteries can supply bone. In bone grafts, the nutrient blood supply is crucial and it should be preserved in order to promote the fracture healing hence a sound knowledge of the topography and morphometry of nutrient foramina is of importance to orthopaedic surgeons and oncologists.
This study has some limitations. These include age and gender differences which were not considered as we were not able to estimate the age and gender of the bones studied. These differences might alter the results as the anatomy of foramina might differ in males and females. In old ages, some foramina might also get ossified. So it is better to consult a forensic expert to segregate the bones and analyse them based on a specific age group and gender. Since the NF of the long bones may alter during growth, the sample long bones should be confined in a specific age group.

4. CONCLUSION

Knowledge of the number of NF is crucial for many procedures performed in everyday clinical practice. The number of NF is not related to the total length of long bones. This allows freer access to surgeons without fear of damaging the vascular integrity of the bone regardless of its size.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

[1]Moore KL. Meaning of „normal". Clin Anat, 1989; 2: 235- 239.
[2] Skawina A, Litwin JA, Gorzyca J, Miodonski AJ. The vascular system of human fetal long bones: A scanning electron microscope study of corrosion casts. J. Anat, 1994; 185: 369-367.
[3] Zahra SU, Kervancioğlu P, Bahşi İ. Morphological and Topographical Anatomy of Nutrient Foramen in the Lower Limb Long Bones. Eur J Ther 2018; 24: 36-43
[4] Vinay G, Kumar A. A study of nutrient foramina in long bones od upper limb. Anatomica Karnataka, 2011; 5(3):53-56.
[5] Gűműsburun E, Yűcel F, Ozkan Y, Akgűn Z. A study of the nutrient foramina of lower limb long bones. Surg Radiol Anat, 1994; 16(4): 409- 412.
[6] Longia GS, Ajmani ML, Saxna SK, Thomas RJ. Study of diaphyseal nutrient foramina in human long bones. Acta Anat, 1980; 107: 399-406.

[7] Sandemir E, Cimen A. Nutrient foramina in the shafts of lower limb long bones: situation and number. Surg Radiol Anat, 1991; 13:105-108.
[8] Lwxer, Kuliga, Turk (1904). Quoted by Laing, P. G. J. Bone Pt Surg. A. 1956;38: 1105-1116.
[9] Lutken P . Investigation into the position of the nutrient foramina and the direction of the vessel canals in the shafts of the humerus and femur in man. Acta anat.1950; 9. 57-68.
[10] Laing PG. The blood supply of the femoral shaft: An anatomical study. J. Bone Jt Surg. B. 1953; 35: 462-466.
[11] Laing PG. The arterial supply of the adult humerus. J. Bone Pt Surg. 1956; A 38: 1105-1116.
[12] Carroll SE. A study of the nutrient foramina of the humeral diaphysis. J. Bone Jt Surg. 1963; B 45: 176-181.
[13] Shulman S. Observations on the nutrient foramina of the human radius and ulna. Anat. Rec. 1959;134: 685-697.
[14] Hughes H. The factors determining the direction of the canal for the nutrient artery in the long bones of mammals and birds. Acta anat. 1952;15: 261-280.
[15] Patake SM, Mysorekar VR. Diaphysial nutrient foramina in human metacarpals and metatarsals. J Anat 1977; 124:299- 304.
[16] Hemang J, Bhavik D, Ojaswini M. A Study of The Nutrient Foramina Of The Humeral Diaphysis. NJIRM. 2011; 2(2): 14-17.
[17] Sharma M, Prashar R, Sharma T, Wadhwa A. Morphological variations of nutrient foramina in upper limb long bones. IJMDS. 2013; 2(2): 177-181.
[18] Gopalakrishna K, Sreekala MA, Rathna BS. A study on the incidence and direction of nutrient foramina in South Indian humeral diaphysis and their clinical importance. RRJMHS. 2014; 3(1): 71-76.
[19] Collipal E, Vargas R, Parra X, Silva H, Del Sol M. Diaphyseal nutrient foramina in the femur, tibia and fibula bones. Int J Morphol, 2007; 25(2): 305-308.
[20] Solanke KS, Bhatnagar R, Rokhrel R. Number and position of nutrient foramina in humerus, radius and ulna of human dry bones of Indian origin with clinical correlation. OA Anatomy, 2014; 2(1): 4.
[21] Yaseen S, Nitya W, Ravinder M. Morphological and topographical study of nutrient foramina in adult humerii. International Journal of Innovative Research & Development, 2014; 3(4): 7-10.
[22] Gandhi S, Singla RK, Suri RK, Mehta V. Diaphyseal nutrient foramina of adult human tibia - its positional anatomy and clinical implications. Rev Arg de Anat Clin, 2013; 5(3): 222-228.
[23] Houssaye, Jocerand Prévoteau. What about limb long bone nutrient canal(s)? - A 3D investigation in mammals. Journal of Anatomy, Wiley. 2020; 236 (3), pp.510-521.
[24] Seymour RS, Smith SL, White CR, Henderson DM, Schwarz-Wings D. Blood flow 491 to long bones indicates activity metabolism in mammals reptiles and dinosaurs. Proc R Soc 492 B: Biol Sci 2011; 279: 451–456.
[25] Haidara A , Eleftherios A, Marie KR, Konstantin N, Springer F. The Anatomy of the Tibial Nutrient Artery Canal—An Investigation of 106 Patients Using Multi-Detector Computed Tomography . J. Clin. Med. 2020; 9: 1135.
[26] Neil James E. A study of nutriet foramina in teh shaft of long bones of upper and lower limbs at Sree Mokambika institute of medical sciences. Sree Mookambika Institute of Medical Sciences, Kulasekharam.
[27] Bridgeman G, Brookes M. Blood supply to the human femoral diaphysis in youth and senescence. J Anat. 1996; 188(Pt 3):611–621.
[28] Mysorekar VR. Diaphysial nutrient foramina in human long bones. J Anat. 1967; 101:813-822.

[29] Murlimanju B, Prashanth K, Prabhu LV, Chettiar GK, Pai MM, Dhananjaya K. Morphological and topographical anatomy of nutrient foramina in the lower limb long bones and its clinical importance. Australas Med J. 2011; 4(10):530–537.
[30] Murlimanju BV, Prashanth KU, Prabhu LV, Saralaya VV, Pai MM, Rai R Morphological and topographical anatomy of nutrient foramina in human upper limb long bones and their surgical importance. Rom J Morphol Embryol. 2011; 52(3):859–862.
[31] Kizilkanat E, Boyan N, Ozsahin ET, Soames R, Oguz O. Location, number and clinical significance of nutrient foramina in human long bones. Ann Anat. 2007; 189(1):87–95.
[32] Zichao X, Haoliang D, Chuanzhen HB, Haitao XAG, Zhiquan A. Anatomical Study of the Nutrient Foramina of the Human Humeral Diaphysis. Med Sci Monit, 2016; 22: 1637-1645.
[33] Lutken P. Investigation into the position of the nutrient foramina and the direction of the vessel canals in the shafts of the humerus and femur in man. Acta Anat (Basel) 1950; 9:57-68.
[34] Sendemir E, Cimen A. Nutrient foramina in the shafts of lower limb long bones: Situation and number. Surg. Radiol. Anat. 1991; 13: 105–108.
[35] Kirschner MH Menck J, Hennerbichler A, Gaber O, Hofmann GO. Importance of arterial blood supply to the femur and tibia for transplantation of vascularized femoral diaphyses and knee joints. World J. Surg. 1998; 22: 845–852.