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Additive Genetic Effects on Circulating Periostin Contribute to the Heritability of Bone Microstructure

N. Bonnet, E. Biver, C. Durosier, T. Chevalley, R. Rizzoli, and S. Ferrari

Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals & Faculty of Medicine, 1211 Geneva 14, Switzerland

Context: Genetic factors account for 60–80% of the areal bone mineral density (aBMD) variance, whereas the heritability of bone microstructure is not clearly established. aBMD and microstructure are under the control of osteocytes, which regulate bone formation through the expression of molecules such as sclerostin (SOST) and periostin (POSTN).

Objective: We hypothesized that additive genetic effects contribute to serum levels of SOST and POSTN and thereby to the individual variance of bone microstructure.

Subjects and Methods: In a retrospective analysis of 432 subjects from the Geneva Retiree Cohort age 64.9 ± 1.4 years and 96 of their offspring age 37.9 ± 5.7 years, we measured serum SOST (sSOST) and serum POSTN (sPOSTN), distal radius and tibia microstructure, hip and lumbar spine aBMD, and bone turnover markers, Heritability (h^2, %) was calculated as twice the slope of the regression (β) between parents and offspring.

Results: cPOSTN levels were significantly higher in men than women and in offspring than parents. h^2 values for bone microstructural traits ranged from 22–64% depending on the envelope (trabecular [Tb] or cortical [Ct]) and skeletal site (radius or tibia), whereas h^2 for sPOSTN and sSOST was 50% and 40%, respectively. sPOSTN was positively associated with Tb bone volume on total volume and Ct thickness, and negatively with Ct porosity. The associations for Ct parameters remain significant after adjustment for propetide of type-I procollagen, cross-linked telopeptide of type I collagen, femoral neck aBMD, sex or age. After adjustment of bone traits for sPOSTN, h^2 values decreased for several Tb and Ct bone parameters, but not for aBMD. In contrast, adjusting for sSOST did not alter h^2 values for bone traits.

Conclusions: Additive genetic effects account for a substantial proportion of the individual variance of bone microstructure, sPOSTN, and sSOST. sPOSTN is largely inherited as a sex-related trait and carries an important contribution to the heritability of bone microstructure, indicating that these traits are at least partly determined by common genetic effects. **(*J Clin Endocrinol Metab* 100: E1014–E1021, 2015)**

Areal bone mineral density (aBMD) is a predictor of fracture risk and highly heritable, with 60–90% of its variance explained by additive genetic effects (1, 2). However, half of incident fractures occur in subjects whose aBMD values are not in the osteoporosis range (3, 4), indicating the importance of other determinants of bone fragility. The contribution of aBMD-independent heritable factors on fracture risk is illustrated by the FRAX tool (FRAX), showing that the 10-year probability of a major fracture almost doubles in the presence of a parental history of hip fracture (5–7). Trabecular (Tb) and cortical (Ct) microstructure, as assessed by high-resolution peripheral quantitative computed tomography, are aBMD-independent determinants of fracture risk (8–10). Taken to-

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Abbreviations: aBMD, areal bone mineral density; BMD, bone mineral density; BMI, body mass index; BTM, bone turnover marker; Ct, cortical; Ct.Th, Ct thickness; CTX, cross-linked telopeptide of type I collagen; GERICO, Geneva Retired Workers cohort; MI, moment of inertia; P1NP, propetide of type-I procollagen; POSTN, periostin; SOST, sclerostin; sPOSTN, serum periostin; sSOST, serum sclerostin; Tb, trabecular; vBMD, volume BMD.

gether, these data suggest that the familial segregation of fracture risk could at least partly be carried by the heritability of bone microstructure. Bone turnover markers (BTMs) have also been shown to predict fracture risk independently of aBMD (11, 12). However, the contribution of the Tb and Ct bone loss to bone fragility varies with age (13) and BTMs do not allow to discriminate between these two compartments. Moreover the contribution of additive genetics factors to the level of BTMs is modest (<50%) (14).

Two new biochemical bone markers principally produced by osteocytes, serum sclerostin (sSOST), and serum periostin (sPOSTN), have been recently associated with microstructure. sSOST has been positively correlated with Tb and Ct microstructure (15, 16). sPOSTN is another potential bone marker unrelated to bone turnover and specifically related to Ct structure, at least in mice (17, 18). Periostin (POSTN) is a matricellular protein of 90 kD secreted by osteocytes and osteoblasts (19, 20). It is essential for the down-regulation of sclerostin (SOST) and plays an important role on bone formation (21) in response to mechanical loading and PTH (20, 22, 23). A specific POSTN immunoassay has been developed for rodents (24) and humans (25). Using this assay (17) we previously reported that sPOSTN levels in mice correlates with Ct structure parameters, independently of propetide of type-I procollagen (P1NP) and cross-linked telopeptide of type I collagen (CTX) (17). Very little is known about the relationship between sPOSTN, bone mass, microstructure, and strength in humans. However, a recent prospective study suggested that the highest quartile of sPOSTN was associated with an increased risk of incident fractures (26).

These observations led us to hypothesize that sSOST and sPOSTN levels, reflecting osteocytes number and/or activity, could be related to bone microstructure and these traits be influenced by shared genetic factors, thereby explaining some of the inheritance for bone fragility. The objectives of the present study were 1) to determine the heritability of bone microstructure, sSOST, and sPOSTN; 2) to assess the relationship between sSOST, sPOSTN, and bone microstructure; and 3) to investigate the contribution of sSOST and sPOSTN to the heritability of bone microstructure.

Subjects and Methods

Parent-offspring correlations

To establish parent-offspring correlations for the various bone and biochemical parameters we studied 84 subjects from the Geneva Retired Workers Cohort (GERICO), and 96 of their offspring. To confirm the relationship between BTMs, including sPOSTN and sSOST, and bone microstructure, we further extended the investigations to 432 randomly chosen subjects in GERICO (15), 310 healthy women and 122 men. Medical and fracture assessment are described in Supplemental Subjects and Methods.

Bone mineral density, microstructure, and bone markers measurement

aBMD at various skeletal sites were determined by dual-energy x-ray absorptiometry. Tb and Ct bone microstructure at the

Table 1. Bone Microstructure of Parents and Offspring

Microstructure	Offspring (n = 96)	Parents (n = 84)	*P* Value	*P* Value[a]
Distal radius				
vBMD total, mg HA/cm^3	346.2 ± 56.3	297.8 ± 55.7	**.001**	**.001**
Ct.vBMD, mg HA/cm^3	903.3 ± 43.2	865.7 ± 57.3	**.001**	**.001**
Tb.vBMD, mg HA/cm^3	173.9 ± 35.8	146.0 ± 37.1	**.001**	**.001**
Tb.N, 1/mm	2.02 ± 0.22	1.84 ± 0.30	**.001**	**.001**
Tb.Th, mm	0.072 ± 0.012	0.066 ± 0.012	**.001**	.05
Tb.Sp, mm	0.431 ± 0.064	0.497 ± 0.136	**.001**	**.001**
Ct area, mm^2	65.08 ± 14.83	54.00 ± 14.71	**.001**	**.001**
Ct.Th, mm	0.883 ± 0.166	0.735 ± 0.165	**.001**	**.001**
Ct.Porosity, %	1.04 ± 0.64	2.96 ± 1.60	**.001**	**.001**
Total polar MI, mm^4	5694.9 ± 2400.0	4971.1 ± 2223.1	**.003**	.30
Distal tibia				
vBMD total, mg HA/cm^3	321.18 ± 59.26	264.91 ± 50.48	**.001**	**.001**
Ct.vBMD, mg HA/cm^3	903.33 ± 43.18	865.65 ± 57.27	**.001**	**.001**
Tb.vBMD, mg HA/cm^3	173.88 ± 35.78	145.97 ± 37.06	**.002**	**.02**
Tb.N, 1/mm	1.9555 ± 0.29	1.8232 ± 0.33	**.004**	.15
Tb.Th, mm	0.072 ± 0.012	0.066 ± 0.012	**.001**	.98
Tb.Sp, mm	0.447 ± 0.081	0.496 ± 0.117	**.001**	.05
Ct area, mm^2	142.4 ± 35.9	107.5 ± 27.9	**.001**	**.001**
Ct.Th, mm	1.329 ± 0.299	0.984 ± 0.245	**.001**	**.001**
Ct.Porosity, %	3.66 ± 1.59	8.56 ± 2.93	**.001**	**.001**
Total polar MI, mm^4	24 803 ± 9214	23 348 ± 9841	**.01**	.15

[a] Adjusted for sex.

Bold indicates *P* value < .05.

nondominant distal radius and tibia were measured by high-resolution peripheral quantitative computed tomography as previously described (27). sSOST, sPOSTN, amino-terminal P1NP and β-carboxyterminal CTX were measured by ELISA. References of the kit and short summary of the procedure are provided in Supplemental Materials and Methods.

Statistical analysis

Statistical analyses were performed using MedCalc Statistical Software version 13.1.2 (MedCalc Software bvba). All data were reported as means ± SD. To take into account that not all variables were normally distributed, the differences were assessed by a Mann-Whitney *U* test. Correlations of sSOST and sPOSTN with bone parameters were analyzed by single and multivariate linear regression analyses. Heritability (h^2, %) was estimated as twice the slope of the regression (β) between parents and offspring for each serum and bone parameter separately (28). To evaluate the contribution of additive genetic factors to the covariance of sPOSTN, respectively sSOST, with microstructural traits, residuals of the linear regression between bone parameters and serum measurements were calculated within class (ie, in parents, respectively offspring), and these residuals then regressed between parents and offspring to estimate the remaining heritability of bone microstructural traits after adjusting for sPOSTN or sSOST (29). $P < .05$ was considered the level of statistical significance for regression coefficient, β values, and for heritability estimates.

Results

sPOSTN levels are age and sex dependent

We first analyzed data from 84 parents and 96 of their offspring. As expected, descendants exhibited lower body mass index (BMI), higher bone mineral density (BMD) at all measured skeletal sites, Tb bone volume, Ct area, and lower Ct.Porosity at both distal radius and tibia compared with their parents (Table 1 and Supplemental Table 1). sSOST was not different between parents and offspring but tended to be higher in men (625.5 ± 26.4 ng/L) than women (588.5 ± 19.6 ng/L; $P = .052$). sPOSTN levels

Table 2. Clinical, BMD, and Bone Microstructure Heritability Estimates in Parents and Offspring Cohort

Characteristic	B (CI)	h^2, %	h^2, %[e]	h^2, %[f]
Height, cm	**0.35 (0.12–0.57)**	**70**[a]	/	
Weight, kg	**0.36 (0.14–0.57)**	**72**[b]	/	
BMI, kg/m^2	**0.43 (0.25–0.62)**	**86**[c]	/	
LS BMD, g/cm^2	**0.21 (0.09–0.33)**	**42**[b]	**46**[b]	**38**[a]
FN BMD, g/cm^2	**0.46 (0.26–0.66)**	**92**[c]	**80**[c]	**72**[b]
Tot Hip BMD, g/cm^2	**0.39 (0.22–0.56)**	**78**[c]	**80**[c]	**70**[c]
P1NP, μg/L	0.04 (−0.20–0.27)	8	30	18
CTX, ng/L	0.12 (−0.12–0.37)	26	**48**[d]	26
sSOST, ng/L	**0.20 (0–0.39)**	**40**[d]	26	26
sPOSTN, ng/mL	**0.25 (0.06–0.56)**	**50**[d]	8	/
Distal radius				
vBMD total	**0.28 (0.05–0.43)**	**56**[d]	**48**[d]	22
Ct.vBMD, mg HA/cm3	**0.29 (0.07–0.45)**	**58**[a]	**54**[a]	23
Tb.vBMD, mg HA/cm3	**0.27 (0.02–0.40)**	**54**[a]	**50**[a]	18
Tb.N, 1/mm	0.22 (−0.05–0.26)	44	24	16
Tb.Th, mm	**0.32 (0.11–0.49)**	**64**[a]	**56**[a]	**50**[d]
Ct.Pm, mm	**0.23 (0.03–0.43)**	**46**[a]	**68**[a]	**41**[d]
Ct.Th, mm	0.09 (−0.12–0.30)	18	20	18
Ct.Porosity, %	**0.30 (0.10–0.42)**	**60**[b]	**22**[a]	12
Total polar MI, mm^4	0.13 (−0.07–0.38)	26	**86**[a]	**37**[d]
Distal tibia				
vBMD total	**0.28 (0.05–0.51)**	**56**[d]	**48**[d]	38
Ct.vBMD, mg HA/cm^3	**0.13 (0.01–0.26)**	**26**[d]	**44**[d]	28
Tb.vBMD, mg HA/cm^3	**0.20 (0.02–0.43)**	**40**[d]	**44**[d]	19
Tb.N, 1/mm	0.09 (−0.08–0.27)	18	**34**[d]	28
Tb.Th, mm	**0.31 (0.11–0.51)**	**62**[a]	**46**[d]	**26**[d]
Ct.Pm, mm	**0.29 (0.10–0.48)**	**58**[a]	**64**[b]	**47**[d]
Ct.Th, mm	**0.23 (0–0.48)**	**46**[d]	**70**[a]	**46**[d]
Ct.Porosity, %	**0.11 (0–0.22)**	**22**[d]	**16**[d]	6
Total polar MI, mm^4	**0.26 (0.02–0.50)**	**52**[d]	**53**[b]	**48**[a]

Abbreviations: Beta, coefficient of regression; CI, confidence interval; FN, femoral neck; LS, lumbar spine.

$h^2 = 2 \times \beta$, where β is the coefficient of the regression between parents (X) and offsprings (Y).

Bold indicates *P* value < .05.

Significant difference: [a] $P < .01$; [b] $P < .001$; [c] $P < .0001$; [d] $P < .05$.

[e] Adjusted for age, BMI, years of menopause, and sex.

[f] Adjusted for age, BMI, years of menopause, sex, and sPOSTN.

were higher in men vs women either in offspring (1078.9 ± 26.6 vs 916.1 ± 25.4 ng/mL; $P < .001$) and in parents (546.8 ± 37.6 vs 355.6 ± 22.4 ng/mL; $P < .001$), and 2.5-fold higher in offspring than parents (Supplemental Table 1). Adjustment for sex did not affect sPOSTN difference between offspring and parents.

Heritability of bone microstructure and sPOSTN

As expected, 70% of the variance for height and weight were explained by heritability (h^2). The h^2 for aBMD varied from 42–92% depending on the skeletal site. h^2 values for microstructural traits ranged from 22% (tibia Ct.Porosity) to 64% (radius Tb.Th) (Table 2). In general, both Tb and Ct parameters showed similar heritability at radius and tibia. However, h^2 was higher for Tb.Th than for Tb.N, whereas Ct bone perimeter, thickness, and total polar moment of inertia (MI) showed higher heritability estimates at tibia (ie, weight-bearing sites) than radius. Adjustment for age, BMI, years of menopause, and sex had little influence on heritability estimates (Table 2).

sPOSTN and sSOST were also heritable, $h^2 = 50\%$ and $h^2 = 40\%$, respectively (Table 2). h^2 values of sPOSTN and sSOST was unchanged after age, BMI, and years of menopause adjustment (data not shown) but decreased and became nonsignificant by adding sex.

Covariance of sPOSTN with microstructure influences bone traits heritability

sPOSTN was positively correlated with bone volume on total volume (BV/TV) and Ct thickness (Ct.Th), and negatively with Ct.Porosity at both the radius and tibia (Figure 1). Correlations with Ct.Th and Ct.Porosity remained significant after adjustment for P1NP, CTX, femoral neck aBMD, and sex or age. However, these correlations were no more significant after adjustment for both sex and age. sSOST was positively associated with spine and hip aBMD ($r^2 = 0.27$ and $r^2 = 0.20$, respectively; $P < .001$ and $P < .01$) and also with distal radius or tibia BV/TV ($r^2 = 0.25$; $P < .001$ and $r^2 = 0.26$; $P < .05$). However, no significant associations were observed with Ct parameters. Moreover, the positive association with Tb parameters disappeared after adjustment by sex.

After adjusting bone traits for sPOSTN (Subjects and Methods), the residual h^2 of microstructural parameters was not any more significant for total volume BMD (vBMD), Tb and Ct, vBMD, and Ct.Porosity at both sites; and for tibia, Tb.N. For radius, Ct.Pm and total polar MI and tibia Tb.Th, Ct.Pm, and Ct.Th h^2 also modestly decreased after adjustment for sPOSTN (Table 2). In contrast, adjustment for sPOSTN did not affect h^2 estimates for aBMD, further indicating that additive genetic effects on sPOSTN contribute to the heritability of bone microstructure at radius and tibia, but not necessarily of aBMD at other skeletal sites. In contrast adjusting for sSOST did not alter h^2 values for bone traits (data not shown).

Correlation of sPOSTN with bone microarchitecture in the extended retiree cohort

To confirm the association of sPOSTN with bone microstructure, we performed additional sPOSTN measure-

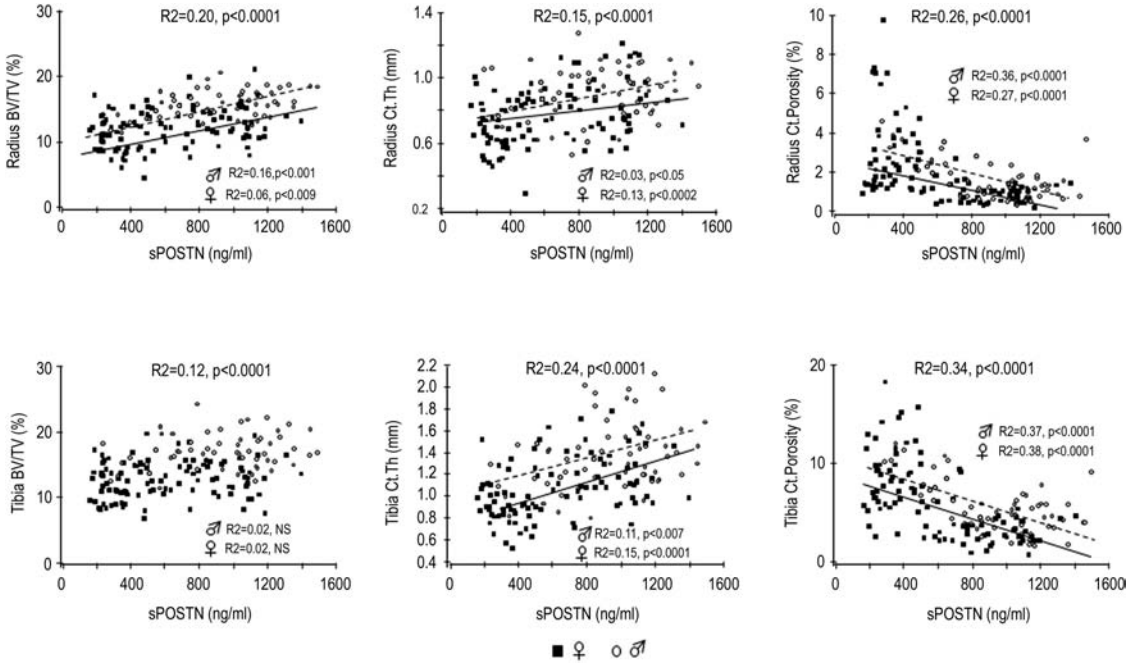

Figure 1. sPOSTN association with Tb BV/TV, Ct.Th, and Ct.Porosity in distal radius and tibia of offsprings (n = 96) and parents cohort (n = 84). In close symbols are illustrated the association in women, in open symbols the association in men.

Table 3. Association of sPOSTN with Bone Microstructure in Retired Workers from the GERICO Cohort

	Beta♀♂	Beta♀♂[d]	Beta♀[e]	Beta♂[f]
Distal radius				
vBMD total, mg HA/cm^3	**0.08**	0.05	**0.10**	0.003
Ct.vBMD, mg HA/cm^3	**0.10**[a]	0.02	0.04	0.01
Tb.vBMD, mg HA/cm^3	**0.10**[a]	0.02	0.02	0.004
BV/TV, %	**0.10**[a]	0.02	0.04	0.004
Tb.N, 1/mm	**0.11**[a]	0.04	0.04	0.01
Tb.Th, mm	0.04	0.01	0.02	0.02
Tb.Sp, mm	**−0.08**	−0.04	−0.06	−0.008
Ct area, mm^2	**0.13**[b]	0.04	0.06	**0.15**
Ct.Pm, mm	**0.16**[c]	0.03	0.05	0.03
Ct.Th, mm	0.07	0.002	**0.09**	**0.14**
Ct.Porosity, %	**−0.06**	**−0.11**[a]	**−0.14**[a]	−0.002
Total polar MI, mm^4	**0.17**[c]	0.06	0.03	0.09
Distal tibia				
vBMD total, mg HA/cm^3	0.05	−0.01	0.02	0.07
Ct.vBMD, mg HA/cm^3	0.06	−0.03	0.02	0.04
Tb.vBMD, mg HA/cm^3	0.06	0.03	0.02	0.05
BV/TV, %	0.07	0.03	0.02	0.05
Tb.N, 1/mm	0.06	0.04	0.03	0.05
Tb.Th, mm	0.03	0.01	0.01	0.01
Tb.Sp, mm	−0.05	−0.04	−0.03	−0.07
Ct area, mm^2	**0.14**[b]	0.03	0.02	0.03
Ct.Pm, mm	**0.16**[c]	0.01	0.01	0.07
Ct.Th, mm	**0.09**	0.03	0.01	0.05
Ct.Porosity, %	0.04	−0.04	−0.02	**−0.17**[a]
Total polar MI, mm^4	**0.20**[c]	0.001	0.03	0.05

In bold, regression with *P* between .10 and .05.

Significant difference: [a] $P < .05$; [b] $P < .01$; [c] $P < .001$.

[d] Coefficient of regression adjusted for age, BMI, years of menopause, and sex.

[e] Coefficient of regression adjusted for age, BMI, years of menopause.

[f] Coefficient of regression adjusted for age, BMI.

ment in an extended set of 432 subjects from the GERICO cohort. Demographic, densitometric, BTMs and microstructure parameters are reported in Supplemental Table 2. sPOSTN was not associated with BMI, aBMD, P1NP, CTX, PTH, SOST, or serum 25-hydroxy vitamin D (Supplemental Table 3). In contrast, positive correlations between sPOSTN and BV/TV at distal radius, Ct area, perimeter, and polar MI at distal radius and tibia were confirmed (Table 3). The correlation between sPOSTN and Ct.Porosity at distal radius remained significant after adjustment by age, BMI, years after menopause, and sex (Table 3), whereas sex-specific associations were found between sPOSTN and vBMD, Ct.Th and porosity at the radius in women, and with Ct.Porosity of the tibia in men. Similar trends were observed for Ct area, thickness, and perimeter. These data confirmed that sPOSTN is at least partly related to Ct bone parameters in aging men and women. However, sPOSTN was associated neither with clinical fractures nor with morphometric vertebral fractures (Supplemental Table 3). sSOST was positively correlated with spine, femoral neck, or total hip aBMD. This association remained significant after adjustment for age, BMI, years of menopause, and sex (Supplemental Table S). sSOST also correlated with distal radius and tibia Tb.N, but not with Tb thickness. However, no significant associations were observed with radius and tibia Ct.Pm and Ct.Porosity (Supplemental Table 4).

Discussion

By investigating the relationship of bone microstructure, sSOST, and sPOSTN between parents and their adult offspring, we have found that both serum markers of osteocytic number and/or activity and bone microstructure at distal radius and tibia are heritable and likely to share some common genetic determinants. Heritability of bone microstructure ranges from 48–62% for the Tb compartment, and 22–60% for the cortex. Despite the limitation of the sample size of parents and offspring, our data confirm and expend the recently published results from a twin study by showing similar range of Tb and Ct bone microstructure heritabilities (30).

Similarly, heritability was in the range of 40–50% for sSOST and sPOSTN. Heritability estimate for sPOSTN disappeared after sex adjustment, suggesting that additive

gene effect on sPOSTN is sex dependent. In contrast, P1NP and CTX did not exhibit significant heritability. The apparent lack of additive genetic effects on BTMs may partly result from the fact that parents were mainly women whereas half of the descendents were men, and should therefore be interpreted with caution. Twin studies in pre- or postmenopausal women have shown a range of heritabilities from 21–74% for BTMs such as osteocalcin, alkaline phosphatase, CTX, or urinary deoxypyridinoline (31–33). In accordance with the literature, 42–92% of aBMD variance in our cohort was explained by genetic factors (34). Adjustments of aBMD by POSTN covariance using residual regressions did not diminish the heritability of aBMD, indicating that genetic factors susceptible to influence sPOSTN did not have a major effect on aBMD. Actually, POSTN alleles have not been found to be associated with aBMD in large genome-wide association studies (35). In contrast, the heritability of Tb and Ct vBMD at distal radius and tibia was reduced by adjustment for sPOSTN and additional effects of sPOSTN were observed on the h^2 for Ct.Pm and Ct.Porosity, arguing that part of the heritability for microstructure is carried by genes that regulate sPOSTN.

Future studies might therefore examine genetic variations associated with both sPOSTN and microstructure in large populations. An association between Postn genotypes and vertebral fractures has previously been suggested (36), however it was not shown whether this polymorphism influences sPOSTN levels nor bone microstructure. Besides Postn alleles, estrogen receptor alleles, which are associated with prevalent fractures (35), could be common determinants of sPOSTN and microstructure, given that estrogen receptor has been shown to influence the bone mechanical response to loading (37). For comparison, residual genetic heritability of sSOST was 39% in Afro-Caribbean (38), which is close to the level found in our study ($h^2 = 40\%$). In this case, a single-tag nucleotide polymorphism accounted for 7.8% of the phenotypic variation in sSOST (38). SOST alleles were associated with fracture risk in GWAS meta-analysis (35).

In agreement with the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH), which investigated hormonal and clinical sex differences in heart failure, sPOSTN levels in our study were higher in men than women (39). We also found that sPOSTN was higher in offspring than in parents. In accordance with two previous studies, sPOSTN were not associated with aBMD nor BTMs (25, 26). Consistent with the role of POSTN in the bone mechanostatic signaling provided by osteocytes, we noticed an association of sPOSTN with Ct.Th and Ct.Porosity in weight-bearing bone tibia but not in nonweight-bearing bone radius. Interestingly, Ct.Porosity, which results from bone resorption on the endocortical surface and on the surfaces of the Haversian canals, has been shown to be a significant predictor of bone's mechanical strength (40–43). Moreover, Ct.Porosity has been shown to be more discriminant than aBMD for fractures prediction in women with osteopenia (44). These observations support a rationale for validating the clinical relevance of a simple biological marker of the Ct compartment and/or osteocyte functions (18). The sPOSTN assay is promising in this regard, although sPOSTN levels also correlated with Tb parameters to some extent and the associations of sPOSTN with microstructure were weak after adjustment for both age and sex.

In the extended retired workers cohort, as previously published sSOST correlated positively with aBMD and Tb.vBMD, Tb.N at the tibia and radius, but not with Ct.Porosity or perimeter (15). This absence of association can be due to the immunoassay specificity (ie, the epitope recognized by the antibody of the ELISA test) as previously highlighted (15). We also did not confirm an association between sPOSTN and prevalent fracture previously found in the OFELY cohort. However, our analysis of fracture was retrospective. Moreover, sPOSTN measured with this assay is not specific to bone tissue (45–47). This could attenuate the correlation with bone parameters. Hence, attempts must be made to develop a serum assay for sPOSTN isoforms and/or fragments that would be more specific for POSTN from bone origin.

In conclusions, additive genetic effects account for a substantial proportion of the individual variance of bone microstructure, sPOSTN, and sSOST. Moreover, sPOSTN is largely inherited as a sex-related trait and carries an important contribution to the heritability of bone microstructure, particularly vBMD and Ct.Porosity. Future identification of these genetic markers may provide further insights into the inherited mechanisms of bone fragility.

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Address all correspondence and requests for reprints to: Nicolas Bonnet, Division of Bone Diseases, 64 Avenue de la

Roseraie, 1205 Geneva CH-14, Switzerland. E-mail: nicolas.bonnet@unige.ch.

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