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Enhancement of Absolute Fracture Risk Prognosis with Genetic Marker: The Collagen I Alpha 1 Gene

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Abstract An important objective of genetic research in osteoporosis is to translate genotype data into the prognosis of fracture. The present study sought to develop a prognostic model for predicting osteoporotic fracture by using information from a genetic marker and clinical risk factors. It was designed as a prospective epidemiological study which involved 894 women of Caucasian background aged 60+ years who had been followed for a median of 9 years (from 1989 and 2008, range 0.2–18 years). During the follow-up period, fragility fracture was ascertained by X-ray reports for all women. Bone mineral density (BMD) at the femoral neck was measured by dual-energy X-ray absorptiometry. Genotypes of the Sp1 binding site in the first intron of the collagen I alpha 1 (*COLIA1*) gene polymorphism were determined by polymerase chain reaction, digestion with BalI restriction enzyme, and agarose gel electrophoresis. The relationship between *COL1A1* genotype and fracture was assessed by the Cox proportional hazards model, from which nomograms were developed for individualizing the risk of fracture. The distribution of *COL1A1* genotypes was consistent with the Hardy-Weinberg equilibrium law: *GG* (63.8%), *GT* (32.6%), and *TT* (3.6%). During the follow-up period, there were 322 fractures, including 77 hip and 127 vertebral fractures. There was an overrepresentation of the *TT* genotype in the fracture group (6.2%) compared with the nonfracture group (2.3%). Compared with carriers of *GT* and *GG*, women carrying the *TT* genotype had increased risk of any fracture (relative risk [RR] = 1.91, 95% CI 1.21–3.00), hip fracture (RR = 3.67, 95% CI 1.69–8.00), and vertebral fracture (RR = 3.36, 95% CI 1.81–6.24). The incorporation of *COL1A1* genotypes improved the risk reclassification by 2% for any fragility fracture, 4% for hip fracture, and 5% for vertebral fracture, beyond age, BMD, prior fracture, and fall. Three nomograms were constructed for predicting fracture risk in an individual woman based on age, BMD, and COLIA1 genotypes. These data suggest that the *COLIA1* Sp1 polymorphism is associated with the risk of fragility fracture in Caucasian women and that the polymorphism could enhance the predictive accuracy of fracture prognosis. The nonograms presented here can be useful for individualizing the short- and intermediate-term prognosis of fracture risk and help identify high-risk individuals for intervention for appropriate management of osteoporosis.

Keywords *COL1A1* gene · Genetic association · Osteoporosis · Bone mineral density · Fracture

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Introduction

From the age of 60, the lifetime risk of fracture for women is 44% [1]. The lifetime risk of hip fracture for a white woman (1/6) is higher than the lifetime risk of developing breast cancer (1/9) [2]. A preexisting fracture confers a substantially increased risk of subsequent fracture [3, 4] and premature mortality [5], which in turn incurs significant heath-care costs [6, 7]. Currently, fewer than one-third of patients who sustain a fragility fracture are properly

diagnosed and treated [8]. Therefore, one of the major priorities in osteoporosis research is to develop valid models for identifying individuals at high risk of fracture for allocating appropriate medical intervention [9].

Accumulated research evidence during the past three decades has suggested that advancing age, low bone mineral density (BMD) [10], low body mass index [11], smoking [12], corticosteroid use [13], and prior fractures [3, 4] are major independent predictors of fracture in women. Using these clinical risk factors, a number of prognostic models have recently been developed for predicting fracture risk [14–18]. The discriminatory value of these prognostic models is moderate to good, with areas under the receiver operating characteristic curve ranging 0.7–0.8 [17, 18]. However, there is still room for improving the predictive accuracy of these prognostic models by incorporating information from nonclinical risk factors.

Fracture liability is partially determined by genetic factors [19]. Twin studies suggest that approximately 48% of the liability to hip fracture is genetically related [20]. Among the genes that have been implicated in the regulation of fracture risk, the collagen I alpha 1 (*COL1A1*) gene has been consistently associated with fracture risk [21–28]. If the effect of *COL1A1* on fracture risk is independent of clinical risk factors, then the incorporation of *COL1A1* genotype could improve the prognosis of fracture.

A nomogram is a prognostic model that combines several risk factors to provide an accessible assessment tool to clinicians and patients. We have recently developed simple prognostic models for individualizing the risk of fracture [17] based on simple clinical risk factors. It is hypothesized that the incorporation of *COL1A1* genotypes would improve the predictive accuracy of the nomogram. The present study was designed to test that hypothesis by developing a prognostic model for predicting fracture risk, taking into account *COL1A1* genotype.

Materials and Methods

Study Design

The present study was part of the ongoing Dubbo Osteoporosis Epidemiology Study, which was designed as a prospective population-based investigation, in which women aged 60+ years in 1989 were invited to participate. The study details and protocol have been described elsewhere [1]. Briefly, Dubbo is a city located approximately 400 km from Sydney, with a population of 32,000 people. It was selected for the study due to its stable population and geographic isolation, which allow total ascertainment of fracture incidence. This study was approved by the St. Vincent's Ethics Committee, and written informed consent was obtained from each participant.

Measurements and Fracture Ascertainment

The original study population included 888 men and 1,402 women progressively recruited from 1989 and 1994. However, in this study, clinical history and anthropometric data from 915 women, who had provided blood samples for genetic analysis, were analyzed. Each woman was interviewed by a nurse coordinator at initial and subsequent visits at approximately 2-year intervals. At each visit a structured questionnaire was administered to collect data, including lifestyle factors (i.e., smoking habits, dietary calcium intake) and anthropometric variables (including weight and height) were measured. In addition, any history of falls in the preceding 12 months and any history of fractures after the age of 50 were recorded.

BMD (g/cm^2) was measured at the lumbar spine (LSBMD) and the femoral neck (FNBMD) by dual-energy X-ray absorptiometry with a LUNAR DPX-L densitometer (GE Lunar, Madison, WI). The precision of BMD measurements in normal subjects at our institution is 1.3% at the lumbar spine and 3.5% at the femoral neck [29]. In this study, FNBMD was used in the development of the prognostic model because it is less susceptible to age-related degenerative changes than LSBMD.

Fractures were recorded from radiology centers servicing the Dubbo area, and the circumstances surrounding the fractures were determined by personal interview. All fractures included in the study were low-trauma fractures caused by a fall from standing height or less. Vertebral fractures were clinically diagnosed. There was no systemic X-ray screening before the study to identify prevalent or asymptomatic vertebral fractures. Incidentally found, i.e., asymptomatic, vertebral fractures were included, provided that there was no known malignancy or metabolic bone disease. Morphometric vertebral fractures were not considered in the analysis.

Genotyping

Blood samples were collected at baseline and in each subsequent visit for genetic and biochemical analyses, and DNA was extracted from leukocytes. The polymorphism of *G* to *T* in the first intron of the *COL1A1* gene was genotyped by the restriction fragment length polymorphism method with *Msc*I (New England Biolabs, Beverly, MA) and an isoschizomer of *Bal*I. Digestions were analyzed by 3% agarose gel electrophoresis. Genotypes for this restriction site were denoted as *GG*, *GT*, and *TT*, with *T* being the minor allele. To validate the accuracy of

genotyping, 30 subjects were randomly regenotyped with 100% consistency.

Data Analysis

The association between clinical risk factors and *COL1A1* genotype and fracture was analyzed by the Cox proportional hazards model. In this model, the time from entry to fracture was considered an end point. Based on estimated parameters of the optimal model, nomograms with the inclusion of *COL1A1*, age, FNBMD, prior fracture, and fall were constructed using the Design library within the R system [30, 31]. In order to assess the incremental prognostic value attributable to *COL1A1* genotypes, a reclassification analysis [32] was performed. Two specific models were considered: model I, with age and BMD, prior fracture, and fall, and model II, with age, BMD, prior fracture, fall, and *COL1A1* genotypes. The area under the receiver operating characteristic curve [33] was not used because it is too insensitive to change [34]. In this reclassification analysis, the 10-year probability of fracture was estimated by each model and then classified into three risk groups: <10%, 10–20%, and >20%. The proportion of women who would be reclassified into three risk groups between the model without *COL1A1* genotypes and the model with *COL1A1* genotypes was calculated, and this proportion is regarded as the net improvement in prediction.

Results

During the follow-up period (median 9 years, range 0.2–18), 332 women had sustained at least one fragility fracture, including 77 hip and 127 clinical vertebral fractures. Women with fracture were older and had lower body weight, shorter stature, and lower BMD than women without fracture (Table 1). The differences were more pronounced in patients with hip fracture, in which FNBMD was approximately 1 standard deviation (SD) lower than in women without fracture. However, there were no significant differences in smoking habit, alcohol consumption, and dietary calcium intake between the fracture and nonfracture groups.

COL1A1 Genotypes and Fracture Risk

The Sp1 binding genotypes of the *COL1A1* gene were successfully determined in 894 women. The distribution of *COL1A1* genotypes was consistent with the expected frequencies by the Hardy–Weinberg equilibrium law: *GG* (63.8%), *GT* (32.6%), and *TT* (3.6%). There were no statistically significant differences in age, weight, and BMD among the genotypes (Table 2). However, carriers of the *TT* genotype had significantly greater height than those with the *GG* genotype. Women homozygous for the *T* allele had a greater dietary calcium intake than those without the allele ($P = 0.02$).

Table 1 Baseline clinical and anthropometric characteristics of participants stratified by fracture statures

Variable	Nonfracture ($n = 583$)	Any fracture ($n = 332$)	Hip fracture ($n = 77$)	Vertebral fracture ($n = 127$)
Age (years)	69.4 ± 6.8	71.5 ± 7.3*	75.5 ± 7.4*	71.6 ± 6.8*
Weight (kg)	65.8 ± 11.8	63.9 ± 12.5	57.5 ± 12.2*	63.4 ± 12.5*
Height (cm)	160.1 ± 6.2	159.7 ± 6.6	157.34 ± 7.0*	159.7 ± 6.5
FNBMD (g/cm^2)	0.81 ± 0.13	0.73 ± 0.12*	0.66 ± 0.1*	0.74 ± 0.12*
LSBMD (g/cm^2)	1.05 ± 0.18	0.97 ± 0.19*	0.94 ± 0.2*	0.94 ± 0.19*
Physical activity index score (METs/day)	30.7 ± 3.0	30.6 ± 3.4	29.6 ± 3.8*	30.6 ± 2.7
Dietary calcium intake (mg/day)	636 ± 318	650 ± 381	649 ± 371	711 ± 417
Quadriceps strength (kg)	21.1 ± 7.5	18.9 ± 7.8*	15.6 ± 7.3*	18.9 ± 7.9*
Current smoker†	178 (30.5)	98 (29.5)	22 (28.6)	45 (35.4)
Current alcohol consumption†	225 (38.6)	131 (39.5)	25 (32.5)	52 (40.9)
Prior fracture after age 50†	39 (6.7)	125 (38.8)*	33 (44.0)*	36 (29.2)*
Fall in the last 12 months†	124 (21.7)	98 (30.3)*	34 (45.3)*	31 (25.2)
COL1A1 genotype†				
GG	370 (64.9)	200 (61.7)	40 (53.3)	67 (54.5)
GT	187 (32.8)	104 (32.1)	28 (37.3)	45 (36.6)
TT	13 (2.3)	20 (6.2)*	7 (9.4)*	11 (8.9)*

Values are mean ± SD, unless otherwise specified; †, *n* (%)

* Significantly different at $P < 0.05$ compared to nonfracture group

METs, metabolic equivalent tasks

Table 2 Baseline clinical and anthropometric characteristics of participants stratified by *COL1A1* genotype

Factors	GG ($n = 570$)	GT ($n = 291$)	TT ($n = 33$)	*P*
Age (years)	70 ± 7	71 ± 7	69 ± 6	0.12
Weight (kg)	65 ± 12	64 ± 12	65 ± 13	0.40
Height (cm)	159.6 ± 6.3	160.3 ± 6.3	161.8 ± 6.7	0.07
FNBMD (g/cm^2)	0.79 ± 0.13	0.77 ± 0.14	0.78 ± 0.11	0.35
LSBMD (g/cm^2)	1.03 ± 0.19	1.01 ± 0.19	1.00 ± 0.20	0.40
Physical activity index score (METs/day)	30.7 ± 3.0	30.5 ± 3.4	30.9 ± 3.0	0.41
Dietary calcium intake (mg/day)	636 ± 326	630 ± 358	809 ± 448	0.02
Quadriceps strength (kg)	20.4 ± 7.7	20.1 ± 7.8	18.6 ± 5.9	0.37
Current smokers (*n*, %)	170 (42.5)	92 (46.5)	8 (32)	0.82
Current alcohol consumption (*n*, %)	231 (36.7)	108 (37.1)	9 (27.3%)	0.56

Values are mean ± SD, unless otherwise specified; *n* (%)
METs, metabolic equivalent tasks

Among the fracture group, 6.2% ($n = 20$) of fracture cases were carriers of the *TT* genotype; this proportion was significantly higher than that in the nonfracture group (2.3%, $P = 0.03$) (Table 1). In addition, the frequency of this homozygote was more prevalent in the hip fracture group (9.4%) and the vertebral fracture group (8.9%) compared with the nonfracture group. Furthermore, women with the *TT* genotype had a greater cumulative probability of fracture than those with the *GG* or *GT* genotype (Fig. 1)

Risk Factors for Fracture

Advancing age, weight loss, shorter stature, lower BMD at the femoral neck or lumbar spine, and a history of fractures and falls were associated with high risk of any fracture, hip or vertebral (Table 3). In hip fracture, the magnitude of association was more pronounced in which every 5 years of advancing age or 10 kg of lower weight had a double risk of hip fracture (Table 3). Similarly, women who were 5 cm shorter had a 50% risk of sustaining a hip fracture, but the magnitude of effect was reduced in non-hip fractures (Table 3).

BMD at both the femoral neck and lumbar spine was consistently associated with the risk of all types of fracture. Indeed, FNBMD was the most consistent predictor of hip fracture with a 3.35-fold (95% confidence interval [CI] 2.67–4.19) increase in hip fracture risk for every SD lower in BMD, while each SD lower in LSBMD was associated with a double risk of vertebral fracture (Table 3). The same relationship was observed for other fracture types, albeit with lesser effect size. There was no significant association between a history of falls and vertebral fracture risk.

Women carrying the *TT* genotype had an increased risk of any fracture (relative risk [RR] = 1.91, 95% CI 1.21–3.04), hip (RR = 4.21, 95% CI 1.88–9.45), and vertebral (RR = 3.57, 95% CI 1.89–6.77) fracture compared to

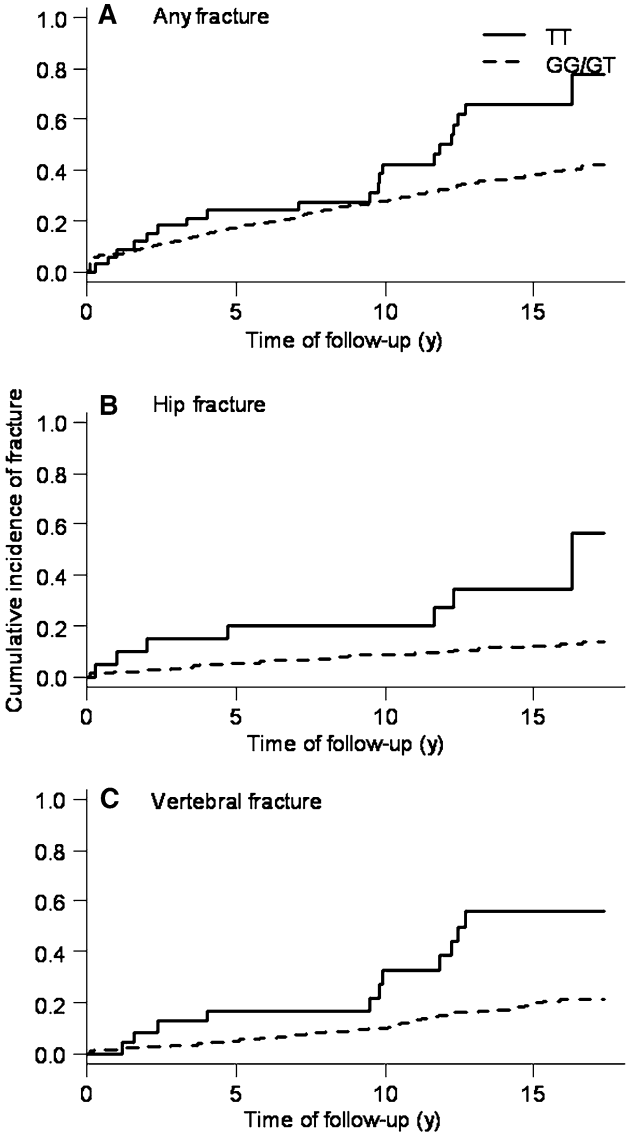

Fig. 1 Cumulative probability of any fracture (**a**), hip fracture (**b**), and clinical vertebral fracture (**c**), stratified by *COL1A1* genotype

Table 3 Association between clinical and genetic risk factors and fracture: univariate analysis

Risk factor	Comparison unit	Hazard ratio (95% CI)		
		Any fracture	Hip fracture	Clinical vertebral fracture
Age (years)	+5 years	1.38 (1.28–1.49)	2.04 (1.74–2.39)	1.51 (1.33–1.72)
Weight (kg)	−10 kg	1.18 (1.07–1.30)	2.16 (1.70–2.75)	1.26 (1.07–1.48)
Height (cm)	−5 cm	1.14 (1.05–1.25)	1.54 (1.28–1.84)	1.17 (1.01–1.35)
FNBMD	−0.12 g/cm^2	1.80 (1.61–2.01)	3.35 (2.67–4.19)	1.99 (1.66–2.38)
LSBMD	−0.18 g/cm^2	1.53 (1.36–1.72)	1.98 (1.55–2.52)	1.99 (1.62–2.41)
Prior fracture after age 50 years	+1	2.71 (2.41–3.05)	3.22 (2.58–4.02)	2.70 (2.20–3.30)
Fall in last 12 months	+1	1.24 (1.08–1.43)	1.81 (1.26–2.04)	1.46 (0.97–2.20)
COL1A1 genotype vs. *GG*				
GT		0.99 (0.78–1.26)	1.35 (0.83–2.20)	1.21 (0.83–1.77)
TT		1.91 (1.21–3.04)	4.21 (1.88–9.45)	3.57 (1.89–6.77)

Table 4 Independent risk factors of fracture: multivariable analysis

Risk factor	Comparison unit	Hazard ratio (95% CI)		
		Any fracture	Hip fracture	Clinical vertebral fracture
Age (years)	+5 years	1.38 (1.28–1.49)	1.43 (1.17–1.74)	1.39 (1.21–1.60)
FNBMD	−0.12 g/cm^2	1.80 (1.61–2.01)	2.44 (3.17–1.88)	1.51 (1.84–1.23)
Prior fracture after age 50 years	+1	2.72 (2.42–3.05)	2.01 (1.55–2.60)	2.44 (1.93–3.07)
Fall in last 12 months	+1	1.24 (1.07–1.42)	1.30 (1.00–1.74)	1.04 (0.80–1.34)
COL1A1 genotype	*TT* vs. *GG/GT*	1.91 (1.21–3.00)	6.42 (2.83–14.54)	4.38 (2.30–8.36)

women with the *GG* genotype. There were no statistically significant associations between the *GT* and *GG* genotypes for any type of fractures (Table 3). Therefore, in multivariable analysis, participants with *GT* and *GG* genotypes were combined into one group and compared with those with the *TT* genotype. This was in agreement with a previous study [25]. When age, FNBMD, and a history of fractures and falls were adjusted in a multivariable Cox proportional hazards model, the strength of association between *TT* genotype and risk of all fractures did not change or was even stronger (Table 4).

Reclassification Analysis

For any fracture, approximately 13% of women were reclassified into higher or lower risk categories in the model containing *COL1A1* genotypes (Table 5). This reclassification was 30% for hip fracture and 33% for clinical vertebral fracture (Table 5). On further analysis by fracture status to account for the "correct" movement into risk categories (higher risk for women in whom fracture had occurred and lower risk for women free of fracture), the inclusion of *COL1A1* genotypes mainly improved the classification of nonfracture rather than fracture cases. For example, in 561 women who had not sustained a fragility fracture, the model with *COL1A1* genotypes reclassified 17 down and eight up, a net improvement of nine (or ∼2%). On the other hand, among 317 women who sustained a fracture, the model with *COL1A1* genotypes was tied with the model without *COLIA1* genotypes. The overall net reclassification improvement was 4% for hip fracture and 5% for clinical vertebral fracture.

Multivariable models including the three independent predictive factors age, FNBMD and *COL1A1* genotype were developed for the risk of any, hip, or vertebral fracture. The areas under the curve of these models were 0.76, 0.88, and 0.72 for predictive models of any, hip, and vertebral fracture, respectively. Based on parameters obtained from multiple Cox proportional hazards models, nomograms were developed for prediction of any fracture (Fig. 2a), hip fracture (Fig. 2b), and clinical vertebral fracture (Fig. 2c).

Clinical Applications of the Nomogram

Patient 1

Patient 1 was a 75-year-old woman with an FNBMD T score of –2.5 (osteoporosis), one prior fracture, one fall in the last 12 month, and *GG* genotype. Her age (Fig. 2b)

Table 5 Comparison of 10-year predicted risk of any fracture, hip fracture, and clinical vertebral fracture in models including age and BMD T score with and without *COL1A1* genotype

Model I (age, BMD, prior fracture, and fall)	*n*	Model II (age, BMD, prior fracture, fall, and *COLIA1* genotypes)			Reclassified, *n* (%)
		<10%	10–20%	>20%	
Any fracture					
All women					
<10%	52	50	2	0	2 (3.8)
10–20%	331	6	312	13	19 (5.7)
>20%	495	0	18	477	18 (3.6)
Women without fracture					
<10%	44	43	1	0	1 (2.3)
10–20%	272	5	260	7	12 (4.4)
>20%	245	0	12	233	12 (4.9)
Women with fracture					
<10%	8	7	1	0	1 (12.5)
10–20%	59	1	52	6	7 (11.5)
>20%	250	0	6	244	6 (2.4)
Hip fracture					
All women					
<10%	574	466	4	4	8 (1.4)
10–20%	75	13	58	4	17 (22.7)
>20%	85	0	5	80	5 (5.9)
Women without fracture					
<10%	455	449	3	3	6 (1.3)
10–20%	60	11	48	1	12 (20.0)
>20%	46	0	4	42	4 (8.9)
Women with fracture					
<10%	19	17	1	1	2 (10.52)
10–20%	15	2	10	3	5 (20.0)
>20%	73	19	12	42	31 (42.5)
Clinical vertebral fracture					
All women					
<10%	437	422	9	6	15 (3.4)
10–20%	149	25	118	6	31 (20.8)
>20%	98	0	9	89	9 (9.1)
Women without fracture					
<10%	388	378	8	2	10 (2.6)
10–20%	114	21	91	2	23 (20.2)
>20%	59	0	7	52	7 (11.9)
Women with fracture					
<10%	49	44	1	4	5 (10.2)
10–20%	35	4	27	4	8 (22.9)
>20%	39	0	2	37	2 (5.1)

scored 18 points, T score 60 points, prior fracture 9 points, fall 3 points, and *GG* genotype 0 points. Therefore, the total points for the woman were 90 on the "Total Points" axis, giving an estimated 5-year average risk of hip fracture of $\sim$10%.

Patient 2

Patient 2 was a 60-year-old woman with an FNBMD T score of –2 (osteopenia), one prior fracture, one fall in the last 12 months, and *TT* genotype. Her age (Fig. 2b) scored

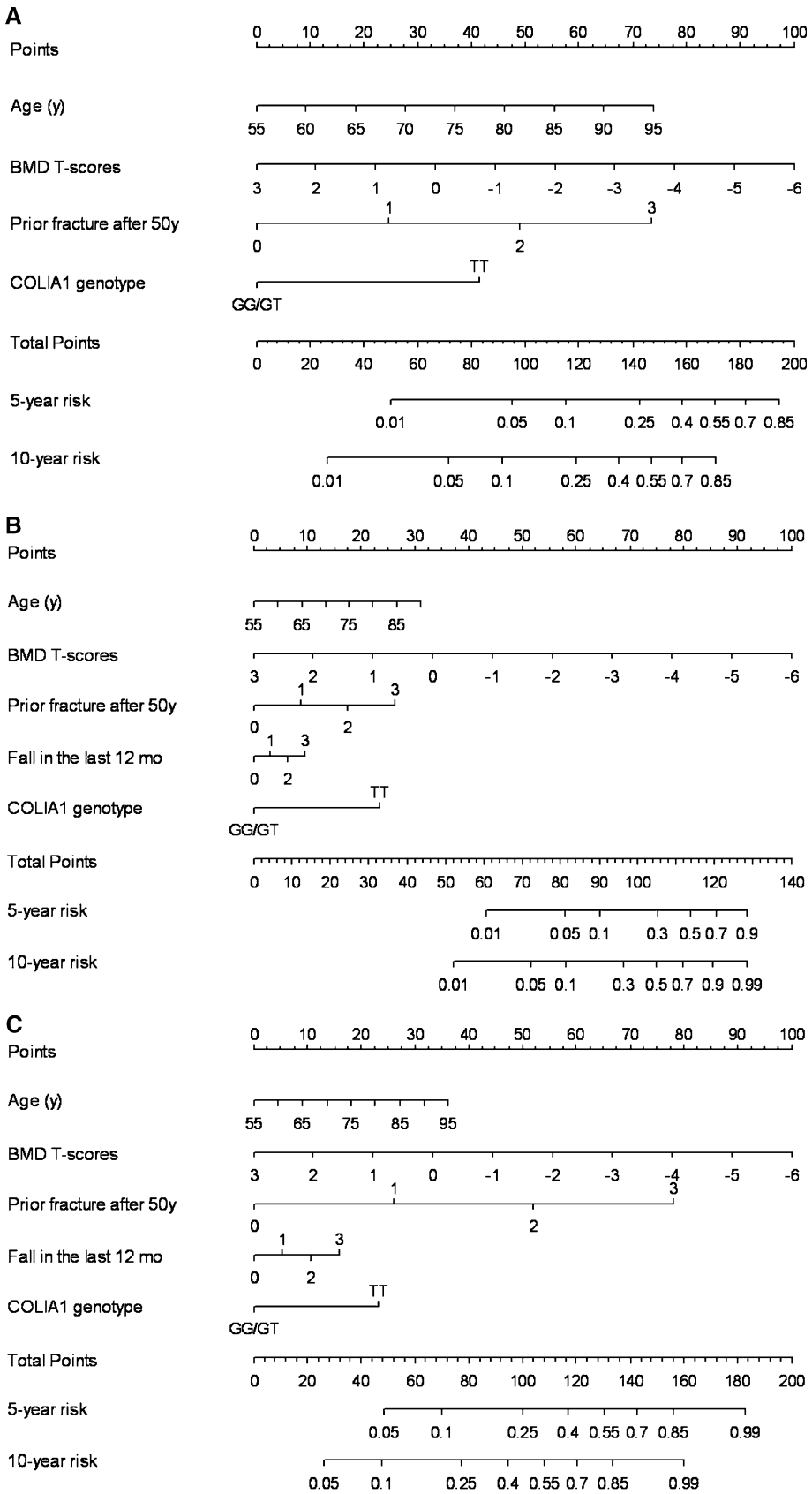

Fig. 2 Prognostic nomograms for predicting the probability of sustaining any fragility fracture (**a**), hip fracture (**b**), and vertebral fracture (**c**) based on age, FNBMD T score, history of fractures and falls, and genotype. *Instruction for usage*: Draw a vertical line from "Age" to the "Total Points" axis to determine the score for age. Repeat the process for the other risk factors to obtain total points, and from the "Total Points" axis draw a vertical line to the 5-year and 10-year risk axes to estimate the probability of sustaining a fracture in the next 5 and 10 years, respectively

5 points, T score 55 points, prior fracture 9 points, fall 3 points, and *TT* genotype 23 points. Therefore, the total points for the woman were 95 on the "Total Points" axis, giving an estimated 10-year average risk of hip fracture of ~12%.

Discussion

Although several candidate genes have been suggested to be associated with fracture, the replication of these findings has been poor [35], as is often seen in other fields of research [36]. Among the candidate genes of osteoporosis that have been studied, the association between *COL1A1* and fracture has been independently replicated in several studies [21]. However, the extent to which the genetic information could improve fracture prognosis is largely unknown. The present result confirmed that women carrying the *COL1A1* Sp1 *TT* genotype had an increased risk of fragility fracture, including hip and vertebral fracture, and that the use of this polymorphism could improve the predictive accuracy of fracture prognosis over and above that of age and FNBMD.

Our result is consistent with an earlier meta-analysis which found an additive association between the *COL1A1* gene variant and fracture risk [26]. In that meta-analysis, the risk of any fracture among *TT* carriers was increased by 1.78-fold compared to those with the *G* allele [26]; however, in a large-scale study on 20,708 Caucasian participants, the *TT* genotype was associated with a 33% increased risk of incident vertebral fracture, and this association was independent of BMD [37]. Taken together, these data suggest that the *COL1A1* gene is a suitable candidate gene for improving the predictive value of existing prognostic models of fracture. In this study, we have demonstrated a simple way to translate a genetic effect into such prognostic models for individualizing fracture risk.

Developing a genetic test for assessment of genetic predisposition to fracture is one of the goals in osteoporosis research. This means using genetic testing to identify individuals with higher risk of fracture, who could be encouraged either to change lifestyle factors or to take medications to reduce fracture risk. Prognosis based on our nomogram model could be helpful in fracture prediction by providing an absolute risk rather than placing individuals into risk-group strata usually expressed by relative risk. This absolute risk approach allows a better appreciation of fracture risk to an individual because it takes into account the time dimension of the risk.

There are some major advantages of using genetic markers as prognostic factors of fracture risk. First, since an individual's genotype is time-invariant, it is easier to estimate its effect size and to incorporate its information in a prognostic model. Second, as the association between *COL1A1* and fracture risk appears to be independent of clinical risk factors, the use of such a genetic marker can potentially improve the predictive value. Third, although there is no genetic therapy for individuals at high risk of fracture, the use of genetic markers could help segregate individuals at high risk from those with low risk of fracture and help manage the burden of osteoporosis in the community.

The potential usefulness of genetic testing for fracture risk prediction can be evaluated by comparing the discriminative accuracy of predictions based on models which do and do not include the genetic information. Traditionally, the increase in the area under the receiver operating characteristic curve was considered a measure of improvement; however, in recent years it has become clear that such a measure is not optimal because it is relatively insensitive, leading to omission of important prognostic factors [33]. In our study, for example, for hip fracture prediction, the area under the receiver operating characteristic curve for model with age, BMD T score, prior fracture, and fall was 0.86; when *COL1A1* genotypes were added to the model, the value increased to 0.88—a modest improvement. However, using the reclassification analysis, it was shown that the improvement of prognosis due to *COL1A1* genotypes was substantial, with ~5% reclassification for hip and vertebral fractures. Moreover, in a further analysis, the improvement was mainly in the specificity, not the sensitivity, of prognosis. This is perhaps not surprising because the relative frequency of the "risk genotype" (*TT*) is only 5% in the population and the magnitude of association between the genotype and fracture risk is modest.

The ultimate aim of developing a prognostic model is to provide clinicians and each individual with his or her risk estimate to guide clinical decisions. At present, individuals with low BMD (i.e., T scores less than −2.5) or with a history of low-trauma fracture are recommended for therapeutic intervention [38, 39]. This recommendation is logical and appropriate since these individuals have higher risk of fracture [40, 41] and treatment can reduce their risk of fracture [42–44]. However, because fracture is a multifactorial event, there is more than one way that an individual can attain the risk conferred by either low BMD or a prior fracture [45]. Indeed, as shown in this study, a 60-year-old woman with a T score of −2.3 could have the same risk of fracture as a 75-year-old woman with a T score of −1 if the two are carriers of genotype *TT*. These data support the informativeness of a multivariable prognostic model and the limitation of a risk stratification–based approach for risk assessment for an individual.

It has been suggested that treatment should be considered for postmenopausal women and men aged 50 years or

more [46] (1) with a preexisting hip or clinical vertebral fracture or a morphometric vertebral fracture, (2) with FN- or LSBMD T score ≤ -2.5 after excluding secondary cause of osteoporosis, and (3) with FN- or LSBMD T score between -1 and -2.5 and a 10-year risk of hip fracture $\geq 3\%$ or a 10-year risk of major osteoporotic fracture $\geq 20\%$. The nomogram presented here and the FRAX model [15] in conjunction with the above guidelines can help select suitable individuals for intervention.

A number of considerations should be taken into account in extrapolating the present findings to other populations. The present finding was based on an association—not linkage—analysis and, as such, does not necessarily show that the *COL1A1* gene is directly involved, rather than being a marker for nearby genes that are linked to hip fracture liability. The data were based on a sample of Caucasian women, whose lifestyles and environmental living conditions are relatively homogeneous; hence, they may not apply to women in other populations or to men. The number of fractures, particularly hip fracture, together with the low frequency of the *TT* genotype were modest, resulting in a rather wide confidence interval of the estimate of association between the gene and fracture. The sample size, as in most studies to date, was not sufficient to examine potential gene–environment interactions, which might improve fracture risk prediction. There are likely many other genes associated with fracture risk which were not considered in the present model.

Both prognosis and treatment decisions are concerned with an individual. Each individual is a unique case because there is no "average individual" in the population. The uniqueness of an individual can be defined in terms of the individual's environmental and genetic factors. The knowledge of genetics, in combination with environmental factors, can shift our current risk-stratification approaches to a more individualized evaluation and treatment of osteoporosis. To this end, these data indicate that a risk genotype of the *COL1A1* gene is associated with an increased risk of fracture and that the incorporation of this genetic information into a prognostic model could enhance its accuracy and predictive value for an individual. These data support the potential utility of genetic information in an individual's absolute fracture risk prediction.

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