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Genetic association between bone mineral density and the fracture of distal radius

A case-control study

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Abstract

Low bone mineral density (BMD) was significantly related to the fracture of distal radius. Serum brain-derived neurotrophic factor (BDNF) level was closely related to BMD in spine and osteoporotic fractures. In this study, we aimed to explore the association of BDNF polymorphisms (rs6265 and rs7124442) with BMD and the fracture of distal radius.

This retrospective study included 152 patients with distal radius fractures and 148 healthy controls. BDNF polymorphisms were detected via TaqMan allelic discrimination assay. BMD was evaluated through X-ray. Difference in features between cases and controls were compared adopting Chi-square test or *t* test. The associations of BDNF polymorphisms with fracture risk of distal radius and BMD were assessed employing χ^2 test and expressed by odd ratios (ORs) with 95% confidence intervals (95% CIs).

BMD was significantly decreased in patients with the fracture of distal radius than in healthy controls. The polymorphism rs6265 significantly increased the risk of distal radius fracture (adjustment: GA: OR = 1.724, 95%CI = 1.003 –2.951, P = .049; GG: OR = 2.415, 95%CI = 1.0219 –3.674, P = .005). Moreover, rs6265 genotypes GA (OR = 4.326, 95%CI = 1.725 –11.896, P = .003) and GG (OR = 13.285, 95%CI = 3.659 –51.072, P = .001) significantly increased BMD reduction. However, BDNF polymorphism rs7124442 had no obvious correlation with BMD or fracture risk.

BMD was associated with BDNF rs6265 polymorphism. BDNF polymorphism rs6265 could elevate the risk of osteoporosis and distal radius fracture.

Abbreviations: 3'-UTR = 3'-untranslated region, 95% CIs = 95% confidence intervals, BDNF = Brain-derived neurotrophic factor, BMD = Bone mineral density, BMI = Body mass index, GWAS = Genome-wide association study, HWE = Hardy–Weinberg equilibrium, ORs = Odds ratios, PCR = Polymerase chain reaction, SNP = Single nucleotide polymorphism.

Keywords: BDNF, bone mineral density, fracture of the distal radius, polymorphisms

1. Introduction

The fracture of distal radius is a general injury caused by aging. With the increasing of aging population, its incidence is increased in recent years.[1,2] It has been found that the fracture of distal radius was significantly associated with low bone mineral density (BMD).[3] BMD is a general indicator for fractures in osteoporosis.[4,5] Low BMD usually induces fractures and finally leads to death, functional debility and decreased life quality.[6] Many risk factors are related to the occurrence of distal radius fracture.[7–9] Previous studies suggested that BMD has strong association with heredity. Various genetic mutations have been considered to contribute to BMD alterations.[10] Although many therapeutic methods have been used for osteoporosis, the outcomes of the patients are still poor.[11,12] Therefore, it is necessary to find genetic factors associated with BMD and osteoporosis fracture.

Genome-wide association study (GWAS) showed that serum brain-derived neurotrophic factor (BDNF) was obviously associated with BMD in spine and osteoporotic fractures. Human BDNF gene is located at 11p14.1, and contains 12 exons.[13] BDNF is an important regulator of nervous system,[14,15] and also participates in the regulation of bone tissues.[16,17] Nose and coworkers found that serum BDNF level was positively correlated with BMD, and that it was elevated by estradiol therapy in female osteoporosis patients.[18] BDNF knockout could inhibit osteoblast differentiation.[19] Polymorphisms in BDNF gene might alter the expression and function of the protein. Deng et al, indicated that G allele of BDNF rs6265 polymorphism caused significantly high total protein phosphorylation level, NAD then influenced osteoblast differentiation and BMD.[20] Liu and colleagues suggested that rs712444 C allele carriers had significantly higher serum BDNF levels than TT carriers in Chinese patients with ischemic stroke.[21] Thus, we speculated that BDNF polymorphisms rs6265 (5' promoter region, Val66Met) and rs7124442 (3'-untranslated region, 3'-UTR) might be correlated with BMD and osteoporosis fracture.

Editor: Arjun Ballal.

The authors have no funding to disclose.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Li H, Fu M, Gao J, Fu J, Li T, Niu G. Genetic association between bone mineral density and the fracture of distal radius: A case-control study. Medicine 2021;100:36(e27116).

Received: 23 March 2021 / Received in final form: 27 July 2021 / Accepted: 15 August 2021

http://dx.doi.org/10.1097/MD.0000000000027116

In this study, we aimed to explore the association of BDNF polymorphisms rs6265 and rs7124442 with the risk of osteoporosis and distal radius fracture in Chinese Han population.

2. Materials and methods

2.1. Study population

A total of 152 adults who were in Foshan Hospital of Traditional Chinese Medicine for fractures were included in our study. All the cases were diagnosed with low- to moderate-energy based on physical examination and X-ray. With any one of the following conditions, patients would be excluded:

1. suffering renal failure and/or liver diseases;
2. with more than one fracture;
3. having acute or chronic inflammatory diseases;
4. with malignancy;
5. having other metabolic disorders that might influence bone metabolism, including diabetes mellitus, hyperthyroidism, hypothyroidism, and pituitary gland diseases; and
6. suffering psychiatric disorders.

Clinical data of the cases were recorded, and summarized in an Excel form. In addition, 148 healthy individuals who were matched with the cases in gender and age were recruited as controls. The controls received medical examinations in the same hospital, and all of them reached normal physical examination results. Moreover, individuals with the history of malignancy, diabetes, renal disease, hepatic disease, or severe osteoprosis were excluded from the current study. All of the study subjects were Chinese Han people.

The current study was approved by the Ethics Committee of Foshan Hospital of Traditional Chinese Medicine. All of the participants singed written informed consents. The process of sample collection was consistent with the national ethics criteria for human genome research.

2.2. BMD measurement

Peripheral BMD (distal and proximal radius and calcaneus) was estimated through single-photon absorptiometry using the Osteon Osteoanalyzer (Dove Medical Group, Los Angeles, CA). BMD values were corrected for age and gender. Based on World Health Organization criteria, BMD reduction was defined as T-score values lower than −1.5, while T-score less than -2.5 was confirmed as osteoporosis. In addition, T-score values above −1.5 indicated normal BMD.

2.3. DNA extraction and single nucleotide polymorphism (SNP) analysis

After a 12h-fasting, blood samples were collected from all participants in the morning. Genetic DNA extraction was performed utilizing QIAamp DNA Mini Kit (Qiagen, Hilden, Germany), and experiment procedures were conducted following the instructions of the manufacturers. Obtained DNA samples were diluted in nuclease-free water and stored at −80°C for subsequent analysis.

BDNF polymorphisms rs6265 and rs7124442 were selected for the current study, and analyzed using TaqMan allelic discrimination assay (Applied Biosystems, San Diego, CA, USA). Amplification system, a volume of 20 μl, contained 30ng genetic DNA sample (2 μl), 0.5 μl forward primer, 0.5 μl reverse primer, 2 μl 10 × Buffer, 1 μl dNTP, 0.5 μl MgCl2, 1 μl Taq DNA polymerase and 12.5 μl deionized sterile water. Polymerase chain reaction (PCR) cycle was as follows: 95°C initial denaturation for 5 min; followed by 32 cycles of denaturing at 95°C for 30 s, annealing at 60°C for 30 s and extension for 30 s at 72°C; and final extension at 72°C for 5 min. SDS 2.3 software was adopted to analyze the distributions of the polymorphisms.

2.4. Statistical analysis

Data analysis was performed using SPSS.18 statistical software. Genotype and allele frequencies between two groups were compared applying χ^2 test. The correlation of BDNF polymorphisms with the fracture of distal radius was reflected by odds ratios (ORs) and 95% confidence intervals (95% CIs). Multiple analysis was performed using logistic regression model. All tests were two-tailed, and *P* values less than .05 indicated statistical significance of results.

3. Results

3.1. Baseline characteristics of the cases and healthy individuals

Baseline characteristics of the study subjects were shown in Table 1. The case group contained 72 males and 80 females, and their average age was 54.83 ± 9.10 years old. There were 65 men and 83 women in control group, with a mean age of 55.74 ± 9.21 years old. The case and control groups were matched in age and gender. In case group, smokers accounted for 40.13%, while there were 56 smokers in healthy control group. Alcohol drinking was observed in 45 cases and 48 healthy individuals. The case and control groups did not show significant differences in BMI values, smoking or drinking. Based on BMD measurement, 64 cases were confirmed with low BMD, and 26 cases were diagnosed with osteoporosis. In control group, 35 individuals showed BMD reduction, and 10 persons were confirmed with osteoporosis. BMD showed significant differences between case and control groups ($P < .001$).

3.2. BDNF polymorphisms were correlated with the risk of distal radium fracture

Genotype and allele distributions of BDNF polymorphisms rs6265 and rs7124442 in case and control groups were shown in Table 2. According to Chi-square test, the frequencies of these two tested variants did not deviate from Hardy–Weinberg equilibrium (HWE) ($P > .05$ for both), indicating the representativeness of the participants.

For rs6265 polymorphism, AA, GA and GG genotypes in case group was 26 (17.11%), 68 (44.74%) and 58 (38.16%), respectively. In control groups, the carriers of AA, GA and GG genotypes were 45 (30.41%), 64 (43.24%) and 39 (26.35%), respectively. Chi-square analysis showed that GA (OR = 1.839, 95%CI = 1.018–3.322, $P = .042$) and GG (OR = 2.574, 95%CI = 1.370–4.837, $P = .003$) genotypes were obviously correlated with the risk of distal radium fracture. After adjustment via logistic regression model, the associations were still significant (GA: OR = 1.724, 95%CI = 1.003–2.951, $P = .049$; GG: OR = 2.415, 95%CI = 1.0219–3.674, $P = .005$). Through allele analysis, we

Table 1

The comparisons of baseline characteristics between case and control groups.

Characteristics	Case group (n=152)	Control group (n=148)	*P* values
Age	54.83±9.10	55.74±9.21	.391
Sex			
Male	72 (47.37%)	65 (43.92%)	.549
Female	80 (52.63%)	83 (56.08%)	
BMI (kg/m^2)	23.07±3.48	23.16±2.10	.773
Smoking status			
Yes	61 (40.13%)	56 (37.84%)	.684
No	91 (59.87%)	92 (62.16%)	
Alcohol drinking			
Yes	45 (29.61%)	48 (32.43%)	.597
No	107 (70.39%)	100 (67.57%)	
BMD			<.001
Normal	32 (21.05%)	103 (69.59%)	
Low BMD	120 (78.95%)	45 (30.41%)	
Osteoporosis	26 (17.11%)	10 (6.76%)	

BMD=bone mineral density, BMI=Body mass index.

found that the distribution of G allele was significantly higher in case group than in control group (60.53% vs 47.97%), revealing its association with increased risk of distal radium fracture (OR=1.663, 95%CI=1.203–2.299, *P*=.002). After adjustment, G allele was still correlated with the risk of distal radium fracture (OR=1.557, 95%CI=1.165–2.187, *P*=.007).

For rs7124442 polymorphisms, its distributions showed similarity between case and control groups (*P*>.05 for all), revealing that the SNP had no significant association with the risk of distal radium fracture.

3.3. BDNF polymorphisms enhanced the risk of distal radium fracture via influencing BMD

According to BMD measurements, the cases with distal radium fracture were divided to normal (n=32) and low (reduced BMD and osteoporosis) BMD groups. We analyzed the relationship between BDNF polymorphisms and BMD in case group. As shown in Table 3, we found that rs6265 GA (OR=4.751, 95% CI=1.805–12.500, *P*=.001) and GG (OR=14.875, 95%CI=4.149–53.329, *P*<.001) genotypes significantly increased the risk of BMD reduction. After adjustment, GA (OR=4.326, 95% CI=1.725–11.896, *P*=.003) and GG (OR=13.285, 95%CI=3.659-51.072, *P*=.001) genotypes were still correlated with low BMD. In allele analysis, we found that the presence of G allele significantly increased the risk of low BMD (round: OR=3.747, 95%CI=2.096-6.700, *P*<.001; adjustment: OR=3.215, 95% CI=2.875–6.599, *P*=.002). While rs7124442 polymorphism had no significant influences on BMD (*P*>.05 for all).

4. Discussion

In the present study, we explored the influence of *BDNF* rs6265 and rs7124442 polymorphisms on BMD and the risks of osteoporosis and distal radius fracture in Chinese Han population. Firstly, we compared basic data between distal radius fracture patients and healthy individuals without fracture, and results showed that distal radius fracture was obviously associated with age, BMD and irregular calcium supplements, but not with gender, BMI, smoking or drinking status. This conclusion was consistent with that from a previous study.[22] But Xu reported that high BMI was a risk factor for distal radius fracture in postmenopausal women.[9] The association of *BDNF* polymorphisms with the risk of distal radius fracture was

Table 2

The distributions of BDNF polymorphisms rs6265 and rs7124442 in case and control groups.

Genotype/Allele	Case (n=152,%)	Control (n=148,%)	*P*	OR (95% CI)	*P**	OR* (95% CI)
rs6265						
AA	26 (17.11)	45 (30.41)	–	1.00	–	1.00
GA	68 (44.74)	64 (43.24)	.042	1.839 (1.018–3.322)	.049	1.724 (1.003–2.951)
GG	58 (38.16)	39 (26.35)	.003	2.574 (1.370–4.837)	.005	2.415 (1.219–3.674)
A	120 (39.47)	154 (52.03)	–	1.00	–	1.00
G	184 (60.53)	142 (47.97)	.002	1.663 (1.203–2.299)	.007	1.557 (1.165–2.187)
HWE		0.140				
rs7124442						
CT	10 (6.58)	15 (10.14)	–	1.00	–	1.00
TT	142 (93.42)	133 (89.86)	.265	1.602 (0.695–3.689)	.325	1.574 (0.548–3.257)
C	10 (3.29)	15 (5.07)	–	1.00	–	1.00
T	294 (96.71)	281 (94.93)	.276	1.569 (0.694–3.552)	.413	1.409 (0.517–2.986)
HWE		0.516				

95% CI=95% confidence interval, BDNF=Brain-derived neurotrophic factor, HWE=Hardy–Weinberg equilibrium, OR=odds ratio.

* The results were adjusted to the potential confusing factors using logistic regression model.

Table 3

The association of BDNF polymorphisms rs6265 and rs7124442 with low BMD in case group.

Genotype/Allele	Low BMD (n=120,%)	Normal BMD (n=32,%)	P	OR (95% CI)	P*	OR* (95% CI)
rs6265						
AA	12 (10)	14 (43.75)	–	1.00	–	1.00
GA	57 (47.5)	14 (43.75)	.001	4.750 (1.805–12.500)	.003	4.326 (1.725–11.896)
GG	51 (42.5)	4 (12.5)	<.001	14.875 (4.149–53.329)	.001	13.285 (3.659–51.072)
A	81 (33.75)	42 (65.63)	–	1.00	–	1.00
G	159 (66.25)	22 (34.38)	<.001	3.747 (2.096–6.700)	.002	3.215 (2.875–6.599)
rs7124442						
CT	7 (5.83)	3 (9.37)	–	1.00	–	1.00
TT	113 (94.17)	29 (90.63)	.473	1.670 (0.407–6.859)	.503	1.523 (0.326–6.025)
C	7 (2.92)	3 (4.69)	–	1.00	–	1.00
T	233 (97.08)	61 (95.31)	.480	1.637 (0.411–6.517)	.514	1.508 (0.326–6.027)

95% CI=95% confidence interval, BDNF=Brain-derived neurotrophic factor, BMD=bone mineral density, OR=odds ratio.
* The results were adjusted to the potential confusing factors using logistic regression model.

investigated and outcomes indicated that *BDNF* rs6265 polymorphism was significantly correlated with increased risk of distal radius fracture, but not rs7124442. This was the first study exploring the correlation of *BDNF* polymorphisms with the risk of distal radius fracture.

Moreover, we further checked the influence of *BDNF* polymorphisms on BMD in patients with distal radius fracture and found that rs6265 was obviously associated with BMD in fracture patients, which suggested that *BDNF* polymorphism rs6265 might increase the risk of distal radius fracture through influencing BMD. In a previous study, Deng reported that rs6265 in *BDNF* could impact hip BMD in humans.[20] However, in the study of González-Peña, *BDNF* rs6265 polymorphism was not significantly associated with BMD in females in northern México.[23] These inconsistent results may attribute to different study populations and sample sizes, which are important factors for the distribution of gene polymorphisms. The rs7124442 did not influence BMD in fracture patients.

In our study, *BDNF* polymorphism rs6265 significantly increased the risk of osteoporosis, which was also consistent with previous findings. Yang reported that *BDNF* served as a susceptibility gene for osteoporosis and impacted BMD in Chinese Han population and other populations.[24] However, no obvious association between *BDNF* rs7124442 polymorphism and osteoporosis susceptibility was found in our study. Certainly, our study firstly investigated the role of *BDNF* polymorphism rs7124442 in BMD, the risk of distal radius fracture and osteoporosis development.

Although we obtained some achievements about the association of BMD with distal radius fracture, some shortcomings should be mentioned here. Firstly, the relatively small sample size might influence statistical power. Moreover, only Han population was included in our study, which might limit practical application of our conclusion. Exact mechanism of *BDNF* polymorphisms influencing BMD and the risks of distal radius fracture and osteoporosis was not revealed. In a previous study, rs6265 was found to influence hip BMD by regulating the phosphorylation of BDNF protein and osteoblast differentiation.[20] Cattaneo reported that *BDNF* polymorphism Val66Met (rs6265) might influence amniotic fluids (AF) risk through regulating BDNF protein levels.[25] Rs7124442 is located in the 3' untranslated region (3'UTR) of *BDNF* and affects BDNF expression.[21] But rs6265 did not impact serum BDNF concentration.[26] So, *BDNF* polymorphisms may participate in the occurrence of some diseases through influencing BDNF protein level or gene structure, which will be verified in further study. The occurrence of osteoporosis and fracture and BMD alteration are complex polyfactorial processes regulated by genetic and environmental factors.[27–29] However, in the present study, gene-environment, gene-gene and polymorphism-polymorphism interactions were not investigated. Therefore, further study is needed to verify our findings, based on better design, larger sample sizes and multiple populations.

In conclusion, *BDNF* polymorphism rs6265 contributes to the risk of distal radius fracture and osteoporosis in Chinese Han population and it may influence distal radius fracture through changing BMD.

Acknowledgments

None.

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