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*Original Article*

# Association between GDF5 rs143383 polymorphism and risk of congenital talipes equinovarus in a Chinese population

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**Abstract:** Congenital talipes equinovarus is a common musculoskeletal deformity in newborns. Growth differentiate factor (GDF)-5 is a member of (TGF)-β super families. GDF5 plays an important role in the formation of bone, cartilage and joint. Rs143383 is a common SNP in GDF5, which is reported to be associated with susceptibility to cartilage related diseases. Currently, no study reports the association between rs143383 and risk of congenital talipes equinovarus. We investigated the role of rs143383 in the susceptibility to congenital talipes equinovarus in a Chinese population. A total of 155 patients with congenital talipes equinovarus and 310 controls were collected in our study. The rs143383 polymorphic sequence was amplified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). In co-dominant model, we observed that individuals carrying the CC genotype of rs143383 had a 3.05 fold risk of congenital talipes equinovarus when compared with those with the TT genotype (OR=3.05, 95% CI=1.45-6.45; P=0.001). In dominant model, individuals harboring the TC+CC genotype of rs143383 had a significant higher risk of congenital talipes equinovarus in comparison with those with the TT genotype (OR=1.52, 95% CI=1.01-2.28, P=0.04). In recessive model, individuals carrying the CC genotype significantly increased the risk of congenital talipes equinovarus when compared with those with the TT+TC genotype (OR=2.68, 95% CI=1.32-5.49). In conclusion, our study shows that the GDF5 rs14338 polymorphism has a significant association with the risk of congenital talipes equinovarus in a Chinese population.

**Keywords:** GDF5, rs143383, polymorphism, congenital talipes equinovarus

## Introduction

Congenital talipes equinovarus is a common musculoskeletal deformity in newborns. It is estimated that the incidence rate of congenital talipes equinovarus is about 2-8/$10^3$ in newborns worldwide [1, 2]. The development of congenital talipes equinovarus includes many environmental and genetic factors. Previous studies have shown that the skeletal dysplasia, neuromuscular disorders, abnormal soft tissue contracture, blood vessel abnormality and prenatal exposure to smoke and solvents play an important role in the risk of congenital talipes equinovarus [3, 4]. A previous twin study shows that the concordance rate of identical twins suffering from congenital talipes equinovarus is 32.5%, while the concordance rate of non-identical twins is only 2.9% [5]. A recent twin study has reported that 30% of patients with congenital talipes equinovarus attribute to the heritability factors [6]. Thus, we hypothesized that the heritability played a critical role in the pathogenesis of congenital talipes equinovarus. Currently, many studies have shown that many genetic factors contribute to the development of congenital talipes equinovarus, such as COL9A1, T-box 4, CHST3, CAND2 and WNT7a [7-10].

Growth differentiate factor (GDF)-5 is a member of (TGF)-β super families, and it plays a vital role in the formation of bone, cartilage and joint. In a vivo experimental study, the GDF5 could promote the differentiation of one progenitor cells to cartilage cells [11-13]. Single

nucleotide polymorphism (SNP) are DNA sequence polymorphism caused by a single nucleotide variation. The genetic polymorphisms could affect the expression and activities of proteins. Rs143383 is a common SNP in GDF5, which is identified to be associated with the risk of cartilage related diseases, such as osteoarthritis and symptomatic lumbar disc herniation [14, 15]. Currently, no study reports the association between rs143383 and risk of congenital talipes equinovarus. Therefore, we performed a 1:2 matched case-control study to investigate the role of rs143383 in the risk of congenital talipes equinovarus in a population of China.

## Materials and methods

Each investigated subject signed an informed consent form prior to enrollment. This study was performed with the permission of Luoyang Orthopedic Hospital of Henan Province/Orthopedic Hospital of Henan Province the ethics committee of Luoyang Orthopedic Hospital of Henan Province/Orthopedic Hospital of Henan Province. The performance of this study was according to the Declaration of Helsinki.

### *Subjects*

A total of 155 patients with congenital talipes equinovarus and 310 controls were recruited from the Department of Orthopaedics of Luoyang Orthopedic Hospital of Henan Province/Orthopedic Hospital of Henan Province between October 2013 and October 2015. The congenital talipes equinovarus was diagnosed through clinical presentation and X-ray examination. The exclusion criteria were congenital talipes equinovarus caused by spina bifida, cerebral palsy or multiple joint contractures.

The 310 control subjects were healthy individuals, and they collected from the Luoyang Orthopedic Hospital of Henan Province/Orthopedic Hospital of Henan Province during the same time period. The controls were free of any food deformities. Two controls were selected after recruitment of one patient with congenital talipes equinovarus. Two controls were matched with one patient by sex and years. The control subjects were confirmed to be free of congenital anomalies, congenital arthrogryposis, and myopathy as well as neuromuscular diseases.

The environmental risk factors and clinical factors related to congenital talipes equinovarus were collected from medical records and a questionnaire. They involved age, sex, maternal smoking habit, maternal drinking habit, family history of congenital talipes equinovarus, clinical situation of this disease. Maternal drinking habit was defined as drinking alcohol drinking more than 50 ml while wine, 250 ml beer, or 50 ml red wine per week. Maternal smoking habit was defined as smoking more than 20 cigarettes per week.

### *DNA extraction and genotyping*

At recruitment, five milliliters of peripheral venous blood was obtained from each subject for DNA extraction. The blood samples were kept in vacuum tubes with 0.5 mol/L EDTA. The DNA was extracted from the QIAamp DNA Blood Mini Kit. The rs143383 polymorphic sequence was amplified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The primers of rs143383 were designed by Primer premier 5.0 software. The primers sequences of rs143383 were based on a previous study [15]. The forward and reverse primers were 5'-CAGCAATTCGCCACCATTCC-3' and 5'-CGCTGAATGACACCTTTCACA-3', respectively. PCR was amplified in a 25 μL reaction mixture, which contained 2.5 μL 2 mmol/L dNTP, 2 μL 10 pmol/L each primer, 1.5 μL 2 mmol/L $MgCl_2$, 1.5 U Taq DNA *Taq* polymerase enzyme and 100 ng template DNA. The PCR amplification was done in PCR-Cycler, and it started with denaturation at 94°C for 5 min; and then 35 cycles of annealing at 58°C for 35 s and extension at 72°C for 45 s; and a finally extension at 72°C for 7 min. The PCR products of rs143383 was confirmed through 8% polyacrylamide gel and verified by ultraviolet light.

### *Statistical analysis*

All statistical analyses were done by IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp., IBM Corp., China). The continue data were expressed by mean and standard deviation, and categorical data were expressed by frequencies and percentage. The age, sex, maternal smoking status, maternal drinking status, family history of congenital talipes equinovarus and feet of talipes equinovarus were compared by Chi-square ($\chi^2$) test or student t

**Table 1.** Baseline information of patients with congenital talipes equinovarus and controls

| Variables | Patients | % | Controls | % | $\chi^2$ value or t value | *P* value |
|---|---|---|---|---|---|---|
| Age, years | 3.36 ± 1.45 | | 3.55 ± 1.50 | | 1.30 | 0.10 |
| Sex | | | | | | |
| Female | 55 | 35.48 | 109 | 35.16 | | |
| Male | 100 | 64.52 | 201 | 64.84 | 0.005 | 0.95 |
| Maternal smoking situation | | | | | | |
| No | 138 | 89.03 | 295 | 95.16 | | |
| Yes | 17 | 10.97 | 15 | 4.84 | 6.06 | 0.01 |
| Maternal drinking situation | | | | | | |
| No | 140 | 90.32 | 292 | 94.19 | | |
| Yes | 15 | 9.68 | 18 | 5.81 | 2.35 | 0.13 |
| Family history of congenital talipes equinovarus | | | | | | |
| No | 146 | 94.19 | 310 | 100.00 | | |
| Yes | 9 | 5.81 | 0 | 0.00 | 18.36 | <0.001 |
| Talipes equinovarus | | | | | | |
| Single foot | 72 | 46.45 | | | | |
| Both feet | 83 | 53.55 | | | | |

**Table 2.** Genotype distributions of rs143383 between patients with congenital talipes equinovarus and controls

| rs143383 | Patients | % | Controls | % | $\chi^2$ value | *P* value | $\chi^2$ value for HWE | *P* value | $\chi^2$ value for HWE | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | In patients | | In controls | |
| TT | 80 | 51.61 | 129 | 41.61 | | | | | | |
| TC | 66 | 42.58 | 138 | 44.52 | | | | | | |
| CC | 9 | 5.81 | 43 | 13.87 | 8.40 | 0.02 | 0.94 | 0.33 | 0.39 | 0.53 |

test. Whether the genotype distributions of rs143383 were deviation from the Hardy-Weinberg equilibrium was evaluated by comparing the actual values with predicted value through Chi-square test. The association of rs143383 genetic polymorphism with the development of talipes equinovarus was evaluated through multiple logistic regression analysis, and the results were expressed by the odds ratios (ORs) and 95% confidence intervals (CI). The dominant, co-dominant and recessive genetic models were used to express the results. A *P* value less than 0.05 was considered as statistically significant.

## Results

Comparison of the demographic and clinical variables between patients with congenital talipes equinovarus and controls were shown in **Table 1**. When compared with the controls, patients with congenital talipes equinovarus are more inclined to have a habit of maternal smoking ($\chi^2$=6.06, P=0.01) and a family history of congenital talipes equinovarus ($\chi^2$=18.36, P<0.001). However, there was no significant differences between patients with congenital talipes equinovarus and controls in terms of age (t=1.30, P=0.10), sex ($\chi^2$=0.005, P=0.95) and maternal drinking habit ($\chi^2$=2.35, P=0.13). Of the included patients, 72 (46.45%) patients were reported to have single foot talipes equinovarus and 83 (53.55%) patients have both feet talipes equinovarus.

The genotype frequencies of rs143383 in the two investigated groups were presented in **Table 2**. The TT, TC and CC genotypes of rs143383 accounted for 51.61%, 42.58% and 5.81% in patients with congenital talipes equinovarus, respectively; and they accounted for 41.61%, 44.52% and 13.87% in controls, respectively. A significant difference was reported to be found between the two investigated

**Table 3.** Correlation between rs143383 polymorphism and risk of congenital talipes equinovarus

| rs143383 | Patients | % | Controls | % | Adjusted OR (95% CI)[1] | *P* value |
|---|---|---|---|---|---|---|
| Co-dominant | | | | | | |
| TT | 64 | 41.61 | 160 | 51.61 | 1.0 (Ref.) | - |
| TC | 69 | 44.52 | 132 | 42.58 | 1.31 (0.85-2.01) | 0.20 |
| CC | 22 | 13.87 | 18 | 5.81 | 3.05 (1.45-6.45) | 0.001 |
| Dominant | | | | | | |
| TT | 64 | 41.61 | 160 | 51.61 | 1.0 (Ref.) | - |
| TC+CC | 91 | 58.39 | 150 | 48.39 | 1.52 (1.01-2.28) | 0.04 |
| Recessive | | | | | | |
| TT+TC | 133 | 86.13 | 292 | 94.19 | 1.0 (Ref.) | - |
| CC | 22 | 13.87 | 18 | 5.81 | 2.68 (1.32-5.49) | 0.002 |

[1]Adjusted for maternal smoking situation and family history of congenital talipes equinovarus.

groups in terms of the genotype distributions of rs143383 ($\chi^2$=8.40, P=0.02). We observed that the genotype frequencies of rs143383 conformed to the HWE in both patients ($\chi^2$= 0.94, P=0.33) and controls ($\chi^2$=0.39, P=0.53).

The correlation between rs143383 polymorphism and risk of congenital talipes equinovarus was shown in **Table 3**. In co-dominant genetic model, we observed that the CC genotype of rs143383 had a 3.05 fold risk of congenital talipes equinovarus when compared with the TT genotype (OR=3.05, 95% CI=1.45-6.45; P=0.001). In dominant model, we found that individuals harboring the TC+CC genotype of rs143383 had a higher risk of developing congenital talipes equinovarus in comparison with those with the TT genotype (OR=1.52, 95% CI=1.01-2.28, P=0.04). In the recessive model, we found that individuals carrying the CC genotype significantly increased the risk of congenital talipes equinovarus when compared with those with the TT+TC genotype (OR=2.68, 95% CI=1.32-5.49).

## Discussion

The candidate-gene approach has been increasingly adopted to identify genes that may trigger the initiation and progression of congenital talipes equinovarus. Single nucleotide polymorphism, which means the replacement, deletion, or insertion of a single nucleotide within the genome, may alter the expression and quantities of proteins in individuals of the same species. In the present study, we carried out a case-control study to investigate the role of rs143383 polymorphism in the risk of congenital talipes equinovarus, and the rs143383 polymorphism showed a significantly increased risk of congenital talipes equinovarus in all genetic models.

GDF5 is located at chromosome 20q11.2 with a length of 488 kb, including 502 amino acids. The GDF5 is a cartilage tissue factor in osteogenesis, and it induces and promotes the cartilage formation [16, 17]. GDF5 is involved in the formation of long bone and joint [16, 17]. The GDF5 could promote the differentiation of chondral progenitor cells in the cartilage and joint areas to chondroblast through adhesiveness and aggregation, and regulate the growth of endochondral ossification [18-22]. Many in vitro and in vivo studies have indicated that over-expression of GDF5 could promote chondrogenesis and osteogenesis [22]. Many previous experimental studies have shown that GDF5 not only promotes the chondrogenesis, development of long bone and formation of cartilage bone and arthroplasty, but also is involved in repairing damaged tendons, nerves, ligaments, dental tissue, blood vessels and intervertebral discs [23-28].

Previous studies have reported a significant association between GDF5 rs143383 polymorphism and many cartilage related diseases, such as lumbar disc herniation and knee osteoarthritis [14, 15, 29-31]. Tawonsawatruk et al. done a study with 90 knee osteoarthritis and 103 controls in Thai population, and reported that the TT genotype of GDF5 rs143383 polymorphism conferred an increased risk of knee osteoarthritis in Thai people [29]. Williams et al. performed a study in 5 population cohorts from Northern Europe, and reported that GDF5 rs143383 gene was a risk factor for lumbar disc degeneration in women [30]. Mu et al. reported that the GDF5 rs143383 polymorphism increased the susceptibility to lumbar disc herniation in the Chinese Han population [15]. However, some studies reported negative association of GDF5 rs143383 with the risk of

cartilage related diseases [31-33]. Syddall et al. indicated that individuals with the rs143383 T allele was correlated with risk of osteoarthritis in comparison to those carrying the C allele [14]. Shin et al. performed an investigation of 725 subjects, and reported that the GDF5 rs143383 could not influence the risk of osteoarthritis in the Korean population [32]. Bijsterbosch et al. reported that GDF5 rs143383 was not associated with the progression of hand osteoarthritis [31]. Raleigh et al. reported that the GDF5 rs143383 variant could not influence the risk of anterior cruciate ligament rupture [33].

Up to now, no study reported their association between GDF5 rs14338 and congenital talipes equinovarus. Our study firstly reported that the CC genotype and TC+CC genotype of rs143383 were correlated with the risk of this disease. Further studies are greatly required to confirm our results. Two limitations should be considered in this study. First, the patients and controls were recruited from only one hospital, which may not be sufficiently representative of other population. The selection bias cannot be avoided in this study. Second, other genes except for GDF5 rs14338 may contribute to the risk of congenital talipes equinovarus, and the possibility of gene-gene or SNP-SNP interactions or linkage disequilibrium between polymorphisms should be taken into analysis in further studies. Third, this study had limited statistical power because of the relative small sample size of our study.

In conclusion, our study shows that the GDF5 rs14338 polymorphism has a significant association with the risk of congenital talipes equinovarus in a Chinese population, suggesting that the GDF5 rs14338 is a potential genetic risk factor in the etiology of congenital talipes equinovarus.

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## Disclosure of conflict of interest

None.

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## References

[1] Chapman C, Stott NS, Port RV and Nicol RO. Genetics of club foot in maori and pacific people. J Med Genet 2000; 37: 680-683.

[2] Chung CS, Nemechek RW, Larsen IJ and Ching GH. Genetic and epidemiological studies of clubfoot in hawaii. General and medical considerations. Hum Hered 1969; 19: 321-342.

[3] Dodwell E, Risoe P and Wright J. Factors associated with increased risk of clubfoot: a Norwegian national cohort analysis. J Pediatr Orthop 2015; 35: e104-109.

[4] McConnell L, Cosma D, Vasilescu D and Morcuende J. Descriptive epidemiology of clubfoot in Romania: a clinic-based study. Eur Rev Med Pharmacol Sci 2016; 20: 220-224.

[5] Wynne-Davies R. Genetic and environmental factors in the etiology of talipes equinovarus. Clin Orthop Relat Res 1972; 84: 9-13.

[6] Engell V, Nielsen J, Damborg F, Kyvik KO, Thomsen K, Pedersen NW, Andersen M and Overgaard S. Heritability of clubfoot: a twin study. J Child Orthop 2014; 8: 37-41.

[7] Shyy W, Dietz F, Dobbs MB, Sheffield VC and Morcuende JA. Evaluation of CAND2 and WNT7a as candidate genes for congenital idiopathic clubfoot. Clin Orthop Relat Res 2009; 467: 1201-1205.

[8] Unger S, Lausch E, Rossi A, Mégarbané A, Sillence D, Alcausin M, Aytes A, Mendoza-Londono R, Nampoothiri S, Afroze B, Hall B, Lo I, Lam ST, Hoefele J, Rost I, Wakeling E, Mangold E, Godbole K, Vatanavicharn N, Franco LM, Chandler K, Hollander S, Velten T, Reicherter K, Spranger J, Robertson S, Bonafé L, Zabel B and Superti-Furga A. Phenotypic features of carbohydrate sulfotransferase 3 (CHST3) deficiency in 24 patients: congenital dislocations and vertebral changes as principal diagnostic features. Am J Med Genet A 2010; 152A: 2543-2549.

[9] Liu LY, Jin CL, Jiang L and Lin CK. [Expression of COL9A1 gene and its polymorphism in children with idiopathic congenital talipes equinovarus]. Zhongguo Dang Dai Er Ke Za Zhi 2011; 13: 478-481.

[10] Lu W, Bacino CA, Richards BS, Alvarez C, VanderMeer JE, Vella M, Ahituv N, Sikka N, Dietz FR, Blanton SH and Hecht JT. Studies of TBX4 and chromosome 17q23.1q23.2: an uncommon cause of nonsyndromic clubfoot. Am J Med Genet A 2012; 158A: 1620-1627.

[11] Coleman CM and Tuan RS. Growth/differentiation factor 5 enhances chondrocyte maturation. Dev Dyn 2003; 228: 208-216.
[12] Koyama E, Ochiai T, Rountree RB, Kingsley DM, Enomoto-Iwamoto M, Iwamoto M and Pacifici M. Synovial joint formation during mouse limb skeletogenesis: roles of Indian hedgehog signaling. Ann N Y Acad Sci 2007; 1116: 100-112.
[13] Shim JH, Greenblatt MB, Xie M, Schneider MD, Zou W, Zhai B, Gygi S and Glimcher LH. TAK1 is an essential regulator of BMP signalling in cartilage. EMBO J 2009; 28: 2028-2024.
[14] Syddall CM, Reynard LN, Young DA and Loughlin J. The identification of trans-acting factors that regulate the expression of GDF5 via the osteoarthritis susceptibility SNP rs143383. PLoS Genet 2013; 9: e1003557.
[15] Mu J, Ge W, Zuo X, Chen Y and Huang C. A SNP in the 5'UTR of GDF5 is associated with susceptibility to symptomatic lumbar disc herniation in the Chinese Han population. Eur Spine J 2014; 23: 498-503.
[16] Plett SK, Berdon WE, Cowles RA, Oklu R and Campbell JB. Cushing proximal symphalangism and the NOG and GDF5 genes. Pediatr Radiol 2008; 38: 209-215.
[17] Fujimura K, Terai Y, Ishiguro N, Miya M, Nishida M and Okada N. Heterotypy in the N-terminal region of growth/differentiation factor 5 (GDF5) mature protein during teleost evolution. Mol Biol Evol 2008; 25: 797-800.
[18] David L, Feige JJ and Bailly S. Emerging role of bone morphogenetic proteins in angiogenesis. Cytokine Growth Factor Rev 2009; 20: 203-212.
[19] Daans M, Lories RJ and Luyten FP. Dynamic activation of bone morphogenetic protein signaling in collagen-induced arthritis supports their role in joint homeostasis and disease. Arthritis Res Ther 2008; 10: R115.
[20] Loiselle AE, Frisch BJ, Wolenski M, Jacobson JA, Calvi LM, Schwarz EM, Awad HA and O'Keefe RJ. Bone marrow-derived matrix metalloproteinase-9 is associated with fibrous adhesion formation after murine flexor tendon injury. PLoS One 2012; 7: e40602.
[21] Panda DK, Goltzman D and Karaplis AC. Defective postnatal endochondral bone development by chondrocyte-specific targeted expression of parathyroid hormone type 2 receptor. Am J Physiol Endocrinol Metab 2012; 303: E1489-1501.
[22] Jin L and Li X. Growth differentiation factor 5 regulation in bone regeneration. Curr Pharm Des 2013; 19: 3364-3373.
[23] Storm EE and Kingsley DM. GDF5 coordinates bone and joint formation during digit development. Dev Biol 1999; 209: 11-27.
[24] Tsumaki N, Nakase T, Miyaji T, Kakiuchi M, Kimura T, Ochi T and Yoshikawa H. Bone morphogenetic protein signals are required for cartilage formation and differently regulate joint development during skeletogenesis. J Bone Miner Res 2002; 17: 898-906.
[25] Brederlau A, Faigle R, Kaplan P, Odin P and Funa K. Bone morphogenetic proteins but not growth differentiation factors induce dopaminergic differentiation in mesencephalic precursors. Mol Cell Neurosci 2002; 21: 367-378.
[26] Lehmann K, Seemann P, Silan F, Goecke TO, Irgang S, Kjaer KW, Kjaergaard S, Mahoney MJ, Morlot S, Reissner C, Kerr B, Wilkie AO and Mundlos S. A new subtype of brachydactyly type B caused by point mutations in the bone morphogenetic protein antagonist NOGGIN. Am J Hum Genet 2007; 81: 388-396.
[27] Miura S, Hanaoka K and Togashi S. Skeletogenesis in Xenopus tropicalis: characteristic bone development in an anuran amphibian. Bone 2008; 43: 901-909.
[28] Upton PD, Long L, Trembath RC and Morrell NW. Functional characterization of bone morphogenetic protein binding sites and Smad1/5 activation in human vascular cells. Mol Pharmacol 2008; 73: 539-552.
[29] Tawonsawatruk T, Changthong T, Pingsuthiwong S, Trachoo O, Sura T and Wajanavisit W. A genetic association study between growth differentiation factor 5 (GDF5) polymorphism and knee osteoarthritis in Thai population. J Orthop Surg Res 2011; 6: 47.
[30] Williams FM, Popham M, Hart DJ, de Schepper E, Bierma-Zeinstra S, Hofman A, Uitterlinden AG, Arden NK, Cooper C, Spector TD, Valdes AM and van Meurs J. GDF5 single-nucleotide polymorphism rs143383 is associated with lumbar disc degeneration in Northern European women. Arthritis Rheum 2011; 63: 708-712.
[31] Bijsterbosch J, Kloppenburg M, Reijnierse M, Rosendaal FR, Huizinga TW, Slagboom PE and Meulenbelt I. Association study of candidate genes for the progression of hand osteoarthritis. Osteoarthritis Cartilage 2013; 21: 565-569.
[32] Shin MH, Lee SJ, Kee SJ, Song SK, Kweon SS, Park DJ, Park YW, Lee SS and Kim TJ. Genetic association analysis of GDF5 and ADAM12 for knee osteoarthritis. Joint Bone Spine 2012; 79: 488-491.
[33] Raleigh SM, Posthumus M, O'Cuinneagain D, van der Merwe W and Collins M. The GDF5 gene and anterior cruciate ligament rupture. Int J Sports Med 2013; 34: 364-367.