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Original Article

TGF β1 gene polymorphisms correlate with the susceptibility of osteoarthritis

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Abstract: Purpose: We investigated the potential role of transforming growth factor beta 1 (*TGF β1*) gene polymorphisms (rs1800470 and rs1800469) in the occurrence of osteoarthritis (OA). Methods: Genotypes of *TGF β1* gene polymorphisms (rs1800470 and 1800469) were genotyped by TaqMan method in 111 OA patients and 129 healthy controls. The representativeness of case and control was inspected by Hardy-Weinberg equilibrium (HWE). Genotype and allele distribution differences between case and control groups were calculated by Chi-square test. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were utilized to emerge the relative risk of OA. Results: Genotype distributions of the two *TGF β1* gene polymorphisms were according to HWE examination. TT genotype of rs1800470 was significantly associated with the occurrence of OA (*P*=0.046, OR=2.093, 95% CI=1.009-4.340). For rs1800469, both TT genotype and T allele had significant association with the susceptibility of OA (*P*=0.000, OR=3.650, 95% CI=1.759-7.575; *P*=0.000, OR=1.957, 95% CI=1.360-2.817). Conclusion: TT genotype of rs1800470, TT genotype and T allele of rs1800469 were increased the risk of OA. We conjectured that the polymorphisms of *TGF β1* gene might increase the individual susceptible of OA.

Keywords: Transforming growth factor beta 1, polymorphism, osteoarthritis

Introduction

Osteoarthritis (OA), the most common form of arthritis, is a group of articular abnormalities, mainly implicated in regressive pathological changes of joints, including articular cartilage and subchondral bone. Recent years the incidence of OA present an upward trend worldwide, and OA is one of the most serious disease which could induce the disability in eastern Asia [1]. Symptoms of OA include slow development of joint pain, tenderness, stiffness, joint swelling, restricted movement, joint deformity and etc. OA is mainly caused by cartilage wear which is induced by imbalance mechanical stress distribution or excessive load. Recently it is believed that OA is an interaction between cartilage wear and low grade inflammatory processes [2]. Articular cartilage is a non-vascularized and non-innervated tissue, once damaged, cannot recovery.

So far, the precise pathogenesis of OA remains largely unknown. However increasing evidence showed that OA is mainly caused by overuse, hereditary, developmental and metabolic factors [3-6]. The disorder of articular homeostasis could lead to OA [7]. Recent cartilage repair research of OA demonstrate that transforming growth factor beta (TGF β) singling is essential for the autonomous formation of cartilage tissue [8]. TGF β1, a member of TGF β family, might contribute to the homeostasis and the cartilage formation [9]. TGF β1 is first identified in platelets, and has a potential role in wound healing [10]. Then it was found that TGF β1 has multiple functions such as regulate proliferation, differentiation, adhesion, migration, and other functions in many cell types. It is well known that gene polymorphisms could alter the gene expression and lead to some disorder in organism. Variants of *TGF β1* gene might relate to several diseases, including OA [11].

Now we carried out this study to analyze the single nucleotide polymorphisms (SNPs) of *TGF β1* gene (rs1800470 and rs1800469) in OA,

Table 1. Genotype and allele distributions of *TGF β1* gene polymorphisms

	Case n=111 (%)	Control n=129 (%)	*P* value	OR (95% CI)
Genotype				
Rs1800470				
CC	33 (29.73)	41 (31.78)	-	-
CT	46 (41.44)	69 (53.49)	0.532	0.828 (0.459-1.496)
TT	32 (28.83)	19 (14.73)	0.046	2.093 (1.009-4.340)
Rs1800469				
CC	23 (20.72)	43 (33.33)	-	-
CT	47 (42.34)	65 (50.39)	0.348	1.352 (0.720-2.539)
TT	41 (36.94)	21 (16.28)	0.000	3.650 (1.759-7.575)
Allele				
Rs1800470				
C	112 (50.45)	151 (58.53)	-	-
T	110 (49.55)	107 (41.47)	0.076	1.386 (0.966-1.989)
Rs1800469				
C	93 (41.89)	151 (58.53)	-	-
T	129 (58.11)	107 (41.47)	0.000	1.957 (1.360-2.817)

and detected the role of *TGF β1* SNPs in the occurrence of OA.

Materials and methods

Specimens

This case-control study was conducted according to the Helsinki Declaration, and approved by the ethic committee of Cangzhou Central Hospital. All subjects signed the written informed consent.

We recruited 111 OA patients (47 males and 64 females, mean age 56.7 years) between January 2010 and January 2015 who were diagnosed in Cangzhou Central Hospital. 129 healthy controls (54 males and 75 females, mean age 61.4) were enrolled from the healthy check-up center of the same hospital during the same period. Controls were according to the cases in age and gender. Demographic data and clinical information was collected from each individual. All participants were unrelated Chinese Han population.

Genotyping

Peripheral blood (5 ml) was collected from each participator. DNA was collected and purified from whole blood using a GenElute™ Blood Genomic DNA Kit (Sigma, USA) following the manufacture's introduction. Genotypes of rs1800470 and rs1800469 SNPs of *TGF β1* gene were genotyped by TaqMan method using the ABI-310 automated DNA sequencer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was used to detect the representativeness of cases and controls. Chi-square test was used to calculate the differences of genotype and allele distributions between case and control groups. Relative risk of OA was presented by odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). PASW 18.0 software was used to perform the calculation. $P<0.05$ showed a statistically significant result.

Results

Genotype distributions of rs1800470 and rs1800469 were in accordance with HWE examination ($P>0.05$). Genotype distributions of *TGF β1* gene polymorphisms were shown in **Table 1**. TT genotype of rs1800470 was obviously higher in case group than that in control group ($P<0.05$), indicating that TT genotype was a susceptible genotype for OA (OR=2.093, 95% CI=1.09-4.340). CT genotype and the alleles of rs1800470 had no significant association with the susceptibility of OA. Meanwhile, TT genotype and T allele of rs1800469 were significantly associated with the occurrence of OA (OR=3.650, 95% CI=1.759-7.575; OR=1.957, 95% CI=1.360-2.817).

Discussion

OA, the common arthritis in human, is a primary cause of decreased activity after middle age. It is characterized by degenerative changes of articular cartilage, destructive and secondary bone hyperplasia. Recent years with the extension of life expectancy, the incidence of OA has a rapidly rising trend. OA has high incidence

and disability rate, and the drain on manpower and material resources on therapy and recovery of OA lead to a heavy burden to the family and society [12-16]. On early stage, the symptoms of OA are not obvious. In order to find out an effective diagnosis method, the exploration of OA pathogenesis is necessary. Previous studies suggested that the occurrence and development of OA related to multiple factors [17-21]. In recent years, more and more studies have found that cytokines play important role in the development and progression of OA [18, 22].

Many studies have shown that *TGF β1* gene is related to the occurrence of OA [23]. Human *TGF β1* gene locates in 19q13.1, and has potential effect on the regulation of cartilage. Exogenous TGF *β1* could induce the formation of cartilage [9]. Meanwhile, animal model research showed that *TGF β1* gene expression level was enhanced in OA murine [24]. Polymorphisms in genes might change the expression of genes and lead to multiple disease. *TGF β1* gene polymorphisms relate to many disease [25-29], especially bone disease. A C to T variant at nucleotide position 29 of exon 1 of *TGF β1* gene (rs1800470) which lead to an amino acid change might increase the risk of spinal osteophytosis and protect against osteoporosis (OP) in Japanese women [30]. Lau et al. reported that the same SNP was also associated with bone mineral density (BMD) [31]. But another polymorphism +913 G/C (rs1800471) in exon 1 of *TGF β1* gene had no obvious association with bone and joint diseases [32]. C-509 T (rs1800469) was a polymorphism locating in the promoter region of *TGF β1* gene. -509 TT genotype was distinctly related to rheumatoid arthritis (RA) risk [33]. G-1639-A (rs1800468) and C788-T (rs1800472) polymorphisms of *TGF β1* gene were weakly associated with lumbar spine BMD [34]. It is reported that *TGF β1* gene polymorphisms might relate to the occurrence and development of OA [35, 36]. However, the researches focusing on the association of *TGF β1* gene polymorphisms and the OA risk were very less.

So we performed this study in order to get a reliable evidence to certify the association between *TGF β1* gene polymorphisms (rs1800470 and rs1800469) and OA risk. Then we find that the CT genotype distribution of rs1800470 between case and control groups had no distinctly difference, and the same results were found in the alleles of rs1800470. Meanwhile, TT genotype distribution was significantly different between the two groups. The result indicated that rs1800470 TT genotype was significantly related to the susceptibility of OA, and might have approximately 2.093 times increased risk of OA. At the same time, we find that both TT genotype and T allele distributions of rs1800469 polymorphism were obviously high in case group than that in control group. Rs1800469 polymorphism TT genotype and T allele may be enhanced the susceptibility of OA respectively, and no obvious association was found between rs1800469 CT genotype and the susceptibility of OA.

Above all we suggested that rs1800470 and rs1800469 polymorphisms of *TGF β1* gene were risk factor for the incidence of OA. Although we provided a positive result to understand the pathogenesis of OA, but the sample size was small and the ethnicity was few, so the result should be explained accurately. For this reason, a well designed study was necessary in the future.

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Disclosure of conflict of interest

None.

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