Lack of associations between polymorphisms in \textit{SOD2} (rs2758331), \textit{NOS3} (rs1808593), \textit{PPAR\delta} (rs9794 and rs10865710) and the risk of osteoarthritis in a Chinese Han population: a case-control study

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To the Editor: Osteoarthritis (OA) is defined as a kind of chronic degenerative joint disorder, and it is generally accepted that genetic factors play an important role in the pathogenesis of OA.

Recently, increasing evidence suggested that the oxidative stress plays a critical role during OA development, and high levels of reaction oxygen species (ROS) could lead to greater lipid peroxidation, mtDNA damage, and signaling pathways' activation.\[^1\] All those changes could promote cartilage degradation and cause the cleavage of collagen and hyaluronan.\[^2\] \textit{SOD2}, \textit{eNOS}, and \textit{PPAR\delta} have been reported as important genes to influence ROS process.\[^3,4\]

However, no studies have yet evaluated the modifying roles of genetic variants in \textit{SOD2} (rs2758331), \textit{NOS3} (rs1808593), and \textit{PPAR\delta} (rs9794 and rs10865710) genes and their relationship with degenerative OA risk in a Chinese Han population. Therefore, we enrolled a set of OA patients, including knee OA and hip OA, and performed a case-control study, aiming to identify the possible associations between \textit{SOD2} (rs2758331), \textit{NOS3} (rs1808593), and \textit{PPAR\delta} (rs9794 and rs10865710) polymorphisms and OA risk in a Chinese Han population.

Patients were recruited from two hospitals (the First Affiliated Hospital of Anhui Medical University and the Anhui Provincial Hospital), including 189 patients with OA in the hip or knee and 199 healthy controls, from October 2016 to May 2017. The diagnosis of OA in the hip and knee was based on the criteria of the American College of Rheumatology. Rheumatoid arthritis (RA) or OA cases that were induced by inflammation, trauma, sepsis, or tuberculosis were removed from the current cohort. This study was approved by the Ethical Review Board of Anhui Medical University. All participants signed an informed consent form, and the study was also carried out in accordance with the principles of the Declaration of Helsinki.

SPSS 16.0 software was applied to conduct all the statistical analyses (SPSS Inc., Chicago, IL, USA). Logistic regression was applied to calculate the odds ratios (OR) and the corresponding 95% confidence intervals (95% CI), which could be used to evaluate OA risk. Hardy-Weinberg equilibrium (HWE) analysis was conducted by a Chi-squared test, and controls of each polymorphism were consistent with the HWE balance. \(P\) values <0.05 were regarded as statistically significant.

The purpose of this case-control study was to identify the associations between polymorphisms in \textit{SOD2} (rs2758331), \textit{NOS3} (rs1808593), and \textit{PPAR\delta} (rs9794 and rs10865710) and the risk of OA in a Chinese Han population. However, no associations were identified between the rs2758331, rs1808593, rs9794, and rs10865710 genetic polymorphisms and risk of OA. Furthermore, even stratified analysis had been conducted by unilateral/bilateral analysis of knee arthritis and hip arthritis, while negative results were also obtained [Table 1].

In the present study, we wanted to investigate a set of genetic polymorphisms in genes encoding enzymes regulating ROS and risk of OA, but we failed to identify any positive connection between these polymorphisms and risk of OA. There are several advantages that should be noted here. First, to our knowledge, although many functional studies have proved the functional roles of ROS-related enzymes in OA pathogenesis, this is the first study to reveal the connections between several ROS-related polymorphisms and the risk of OA in a Chinese Han population. Second, our study results provide some evidence for future work in which researchers seek to compare the differences between the genetic factors of OA pathogenesis in Asian-Chinese and other populations. However, the current work also has several limitations. First, the sample size is relatively small, which leads to a lower frequency of the homozygous wild type, which may cause potential bias.
Second, OA pathogenesis is a complex process, including hormonal factors, environmental factors, and many other factors, and we could not conduct further subtype analyses due to the lack of sufficient patient information. Finally, the current study failed to identify any positive predictors for OA screening.

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### Conflicts of interest

None.

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**Table 1: Difference between genetic polymorphisms and unilateral/bilateral in knee arthritis and hip arthritis subtypes of OA risk.**

| Items          | Knee arthritis (n) | Hip arthritis (n) | Control (n) | OR (95% CI) | OR (95% CI) |
|----------------|--------------------|-------------------|-------------|-------------|-------------|
|                | Unilateral | Bilateral | Unilateral | Bilateral |             |             |
| rs2758331      | CC       | 47       | 46         | 37         | 19         | 150         | 0.71 (0.24–2.14) |
|                | CA+AA    | 16       | 11         | 10         | 5          | 48          | 1.23 (0.38–3.91) |
| rs1808593      | TT       | 37       | 37         | 25         | 15         | 130         | 1.72 (0.65–4.55) |
| rs9794         | GT+GG    | 26       | 20         | 22         | 9          | 68          | 0.64 (0.23–1.75) |
| rs10865710     | CC       | 30       | 30         | 23         | 14         | 102         | 0.53 (0.20–1.38) |
|                | CG+GG    | 34       | 28         | 24         | 10         | 97          | 0.70 (0.26–1.83) |
|                | CC       | 35       | 28         | 27         | 13         | 115         | 1.09 (0.43–2.76) |
|                | CG+GG    | 329      | 29         | 20         | 11         | 83          | 1.28 (0.48–3.45) |

*Knee arthritis. †Hip arthritis. ‡Unilateral. §Bilateral. CI: Confidence interval; OA: Osteoarthritis; OR: Odds ratio.