ABSTRACT

Background: Osteoarthritis (OA) is an age-related disease characterized by structural and functional failure of synovial joints. Risk factors include female gender, increased body mass index, reduced bone mass, history of injury and genetic susceptibility[1]. Although OA has a high heritability[2], a high discordance rate[3] in monozygotic (MZ) twins also suggests there is a strong environmental or epigenetic component. Increasingly, studies have examined the mechanism of epigenetic changes that alter gene expression without changes to the DNA sequence. The best-characterized epigenetic modification is DNA methylation, which has been implicated in the pathogenesis and etiology of several diseases, and differentially methylated regions (DMRs) have been identified in several diseases[4,5]. The present study aims to identify OA-related DMRs by comparing methylation levels between concordant and discordant OA MZ twins.

Material and Method: We examined DNA methylation levels in a total of 32 female MZ pairs comprising of two concordant and two discordant OA MZ pairs, and 28 OA-unaffected control pairs, whose age ranged from 33 to 68 years old as defined by the time of DNA extraction. Methylation was measured at 27,578 CpGs in the promoters of 14,459 genes using the Illumina HumanMethylation27 microarray, and resultant levels were transformed into beta scores. Data were subjected to quality control checks and quantile-normalization procedures prior to analysis of methylation differences. Methylation differences were calculated within twin pairs and compared between OA-discordant and phenotype-concordant pairs.

Results: Six differentially-methylated regions across the whole genome showed maximal differences ($|diff|>0.3$) between concordant and discordant OA pairs, where five of the CpGs were hypo-methylated and one CpG was hyper-methylated with OA. These sites were differentially-methylated specifically in OA, because all six probes shared similar methylation levels in the unaffected pairs and concordant OA pairs, and differed only within the OA discordant pair. The most significant site ($p<0.01$, $|diff|= 0.54$) was located on chromosome 1, proximal to the *OR2L13* gene, and the remaining five sites were in the promoters of the *CHFR, NPFF, PIK3R1*, and *SLC5A1* genes.

Conclusion: We compared genome-wide DNA methylation patterns in OA discordant MZ pairs to those in OA concordant and unaffected MZ pairs, and identified six methylation sites as differentially-methylated in osteoarthritis. These results require further validation and replication in independent cohorts.

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