Genetics and its Impacts on Arthritis

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Editorial

Despite high prevalence and social impact, osteoarthritis (OA) is far behind other skeletal diseases like osteoporosis in the development of disease-modifying treatments. This is mainly because little is known about the underlying molecular mechanism that could be the therapeutic target. Since OA is a multifactorial disease caused by complex interplay between environmental and genetic factors with estimates of around 50% heritability depending on the site [1], numerous efforts and great expense have been spent on human genetic studies on OA worldwide. Although linkage studies have shown large areas of chromosomes associated with the disease, they have failed to detect the susceptible genes. Candidate gene studies have proposed over 100 genes as being responsible; however, most of them have not later been reproduced in larger meta-analysis studies. Recently, while genome-wide association studies (GWAS) have led to the discovery of over 600 gene loci in over 50 common multifactorial diseases, most of the gene variants are of only minimal individual effect. Even though the identified genes with such small effect sizes could possibly be therapeutic targets or at least prognostic markers, it is questionable whether or not these conventional OA genetic studies are worthy of such enormous investment. Aiming at a well-powered approach for this highly polygenic disease with multiple risk loci conferring small effects, consortium studies like Treat-OA and arcOGEN have been developed to enlarge the sample size. Considering the disease characteristics and prevalence, however, it is our opinion that not only the quantity but also the quality of studies is critical for identification of the genetic architecture. In this sense, the conventional OA genetic studies do not seem to us who are clinicians, although not genetic experts, to have been performed with sufficient scientific strictness, even as compared to those on other common diseases.

Several studies indicate that inconsistent and ambiguous definition of OA is a critical limitation of conventional genetic studies [2]. In addition to the stringency of disease definition raised by them, here we propose two other capital issues in the conventional studies: selection of appropriate controls and adjustment for environmental/clinical factors, from a clinician's point of view.

Stringency of Disease Definition

Although most conventional genetic studies determine OA on radiographs as Kellgren-Lawrence (KL) score=2 or higher [3-7], the KL grading is limited in reproducibility and sensitivity due to the subjective judgment of observers and the categorical classification into only a five-grade scale [8]. In the ROAD (Research on Osteoarthritis against Disability) study with a high-quality population-based cohort database of detailed environmental and genetic information of more than 3,000 participants [9], we delete the intermediate and ambiguous KL=2 subgroup for the case-control analysis to increase the detection power. For example, our as sociation analysis of the EPAS1 gene which was identified to be crucial for OA development in mice was able to detect a significant difference of the minor allelic frequency (mAF) of a SNP in the gene between KL=3 & 4 (case; mAF=11.1%) and KL=0 & 1 (control; mAF=15.2%) [10]. The mAF of the omitted KL=2 subgroup was 12.3%, confirming an inverse relationship between mAF of the SNP and KL scores. This clearly indicates that inclusion of the KL=2 subjects in the case group had caused a decrease in the detection power. In fact, this association was not reproduced by conventional Japanese and Chinese studies that include KL=2 in the case group [11]. Considering that prevalence of the KL=2 subgroup is shown to be fairly high in representative epidemiologic studies (17.3-41.3%; difference between KL ≥ 2 and KL ≥ 3 in), removal of this subgroup may inevitably cause a decrease in the total sample size. Generally, a lack of objective and quantitative measure for the disease definition remains a fatal limitation of clinical OA studies. The ROAD study has recently established the fully automatic program KOACAD (knee OA computer-aided diagnosis) to quantify the major OA parameters (joint space, osteophyte, etc.) on plain radiographs [8]. We believe that the KOACAD system as well as magnetic resonance image systems [12] will serve as optimal measures for the definition of OA in the near future, just as bone mineral density does in osteoporosis.

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