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Genetics of Common Musculoskeletal Disordersin Adults

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Abstract

Common musculoskeletal disorders in adults are mostly degenerative and polygenic diseases influenced by both genetic and environmental factors.Hence, the identification of susceptibility genes may provide clues to their etiology and pathogenesis and this genetic study is demanded to gain better insight into advanced diagnosis and treatment for these disorders. Osteoarthritis (OA) of hip and knee joints, degenerative disc disease (DDD), and developmental dysplasia of the hip (DDH) are common musculoskeletal disorders in adults, and numerous genetic studies including genome-wide association studies have revealed several interesting predisposing candidate genes for these disorders along witha genetic overlap amongthose to date. However, only a few genes have far been associated with the above disorders at genome-wide significance levels. Accordingly, we have to discover additional susceptibility alleles for these disorders. This brief report describes the presence and future for geneticstudies of common musculoskeletal disorders in adults, especially focused on OA, DDH, and DDD, of which the genetics have been actively studied through advanced technique such as whole-genome sequencing recently.

Background and Significance

Technical evolutions in genetic studies in the past few years have substantially enhancedthe detection of the genetic alterations and our understandingof the genetic predisposition as well as the pathogenesis in musculoskeletal disorders.Although recent advances have not greatly affected our treatment options to date, those will be the cornerstone of better counseling, diagnostic tests and treatment options for patients in the future.

The genes responsible for Mendelian inherited orthopedic conditions, including many types of skeletal dysplasia andosteogenesis imperfect are already known. For other, more common, conditions such as osteoarthritis (OA), degenerative disc disease (DDD),developmental dysplasia of the hip (DDH), andosteoporosis that have a more complex inheritance pattern, the identification of genes involved in their pathogenesis is an ongoing project.

These musculoskeletal disorders pose major public health problems worldwide and the basis of a series of disabilities, especially in the elderly[1,2]. In addition, the public health burden imposed by these disabilities and their associated outcome is substantial in elderly patients. Most musculoskeletal disorders are polygenic disorders, with both genetic and environmental factors playing roles. The genetic influence may be more considerable than expected. The identification of susceptibility genes is becoming more important for understanding the etiology and pathogenesis of these disorders and the advent of new treatments.

Meanwhile, basic research about musculoskeletal disorders by other means is very difficult based on logistics of obtaining samples for analysis, and biochemical extractions being complex. Besides, the disease processes are very slow andanimal models have little value for most of these disorders. Therefore, genetic study is essential to gain better insight into advanced diagnosis and treatment for these disorders in the future.

We herein describe the presence and future of genetics of common musculoskeletal disorders in adults, especially focused on OA, DDH, and DDD of which the genetics have been actively studied through advanced technique such as whole-genome sequencing recently.

Recent Progress

OA is the most common form of arthritis worldwide, affecting about 40% of people older than 70 years[3].It is a complex disease of the musculoskeletal system with both genetic and environmental risk factors[4].From the results of heritability studies in twins, sibling pairs, and families, genetic factors are estimated to account for about 50% of the risk of developing OA in the hip or knee, although precise estimates vary according to sex, affected site, and severity of disorder[4-6].

To date, many association studies have been reported, including several genome-wide association studies (GWAS) and revealed many interesting genes and promising susceptibility variants [7-12].However, the research for OA susceptibility loci has not been as successful as many had anticipated. This reflects many factors, including the heterogeneous nature of the disorder, the tendency to use less severe phenotypes in genetic researches and the reliance on underpowered studies. Therefore, under the strict criteria of replication & functional data, GDF5 (encoding growth & differentiation factor 5) is the only truly associated gene [1].GDF5 known as CDMP1 (cartilage-derived morphogenetic protein 1) is a growth factor with high articular cartilage specificity and a member of BMP (bone morphogenetic protein)family within TGF-ß(transforming growth factor ß)superfamily. GDF5 is involved in joint formation and expressed in the region of future joints during early development [13-14].Many replication studies have reported a strong

association of GDF5 rs143383, which lies in the core promoter of GDF5, with OA of various joints [15-21].However, the genetic effects are consistent across different populations only for knee OA [16-22].Several significant functional data in humans and mice have indicated the relevance of GDF5 to OA susceptibility based on decreased GDF5 activitydue to decreased transcription activity and mRNA expression by this susceptibility allele, rs143383[1,17,23].

GDF5 single-nucleotide polymorphism (SNP) rs143383 is also associated with DDH as well as OA [1,24]. Dai et al. [25] found rs143383 to be associated with DDH. This finding was then reproduced in a French Caucasian population. Furthermore, GDF5 SNP has been reported to be associated with DDD in northern European women [26].

DDD is a common disorder that progresses with aging. DDD is characterized as morphological and biochemical changes of the disc[27,28].Magnetic resonance imaging (MRI) is the current gold standard to assess the integrity of the intervertebral disc. Since the end of the 20th Century, several studies have suggested that heredity is largely responsible for the development of lumbar disc degeneration and that environmental factors play a much smaller role than previously believed[29-31].This has led to the well-justified search for specific genetic risk factors[27].However, due to variation between study designs, sampling methods, populations, and phenotype definitions, the level of evidence of that association remains weak. To date, ASPN (asporin) (D-repeat), COL11A1 (collagen XI α1) (rs1676486), GDF5 (rs143383), SKT(Sickle tail) (rs16924573), THBS2(thrombospondin 2) (rs9406328), and MMP9(matrix metalloproteinase 9) (rs17576) have been known as genes related to DDD with a moderate level of evidence in the systemic literature review[26,28,32-35].However, clear definition of DDD phenotypes and large population-based cohorts are needed because the credibility of reported genetic associations is mostly weak[28].

DDH is a frequently disabling condition, which affect 20% to 80% of patients with end-stage arthritis of the hip [36].DDH is a complex disorder with both environmental and genetic causes [37]. This condition is especially believed to have a strong genetic basis based on its pattern of presentation in families [38].Based on the literature, the candidate genes for this disorder are HOXB9(HomeoboxB9), COL1A1(collagen typeI α1), andDLX3(Distal-less homeobox3) [4,10,38-40].HOXB9 is expressed in human embryo from 5 to 9 weeks, a period that coincides with primordial hip girdle formation. A polymorphism in COL1A1 might influence hip development, which can lead to osteogenesisimperfecta or Ehlers-Danlos syndrome. DLX3 is a member of a family of transcription factors, including Runx2, that regulate the expression of osteocalcin during fetal mouse development [39].

A recent study has reported that DDH shows genetic inheritance with an autosomal-dominant mode of transmission and the mutated gene linked to a region 4 Mb in size on chromosome 17q21by the linkage analysis of one multigeneration affected family [41].There are a number of attractive candidate genes in this region and the above candidate genes were also within the chromosome 17q21 region [40,42].In addition, another study has reported one shared variant, rs3732378 in CX3CR1, a 2.61 Mb candidate region on chromosome 3p22.2 co-inherited by all affected members of a large multi-generation family through genome-wide linkage analysis and whole exome sequencing [36].The above indicates the genetic heterogeneity of DDH; in other words, the activation of many genes are involved in hip formation during the time of development.In the study of Han Chinese, Shi et al [43] reported an association of D-repeat polymorphism of the asporin gene, ASPN, with DDH. This polymorphism (D-14 allele of ASPN) had originally shown an association with knee OA and subsequently with DDD, also in Asian cohorts [35,43-45].Functional studies have shown the number of D-repeats in asporin play a role in attenuating TGF-ß signaling [33,46,47].Members of the TGF- ß superfamily have different expression levels during development and in mature tissues. The D-repeat genotype and differences in the expression levels of members of TGF-ß superfamilyare likely to influence the affected skeletal sites and the subsequent phenotype.

As described, both ASPN and GDF5 are part of the TGF-ß pathway. GDF5 and ASPN have been replicated in different ethnic groups. It is difficult to find global genes such as GDF5 and ASPN because populations from different regions have different genetic backgrounds[43].Yet, intriguingly, there appears to be a genetic overlap between OA, DDD, and DDH[48]. This genetic overlap refers to the emerging concept of pleiotropy, in which a single gene or mutation in a gene influences multiple phenotypic traits depending on when and where it is expressed during the development and aging of the organism[49].The D14 allele of ASPN in Asiansand the GDF5 rs143383 SNP in European women are evidence in the literature of pleiotropy in the musculoskeletal system. Such evidence supports the notion that these genes affect the entire joint and not only the cartilage in OA and related diseases[49].Although these common susceptibility alleles suggest a common molecular pathology, we have to discover additional susceptibility alleles before conclusions can be made about how widespread the shared genetic risk is between OA, DDH, and DDD[48,49].

The Future for Genetic Studies

Although GWASs have revealed several interesting predisposing candidate genes for OA, DDH, and DDD,only a few genes have far been associated with the above disorders at genome-wide significance levels ($p \leq 5.0 \times 10\text{-}8$). This result might be attributed to several factors such as insufficient sizes in previous studies and disease heterogeneity that might result from different underlying causes, both genetic and environmental, depending on which joints are affected. In addition, phenotype definition in cases and controls is also a likely factor contributing to the dilution of power to detect strong signals.

To overcome the size limitation of the GWA approach, another existing approach called extreme trait sequencing can be effective. Compared to GWA studies, extreme trait sequencing is a cost effective strategy at identifying rare candidate variants for a phenotype. Variants of large effect are present at a low frequency in the general population. However, when whole genome sequencing is conducted on a small carefully selected population at one or both ends of the extremes of a phenotype, variants that contribute to the trait will be enriched in frequency [50].Afterthis strategy, candidate variants can then be genotyped for confirmation in a larger population.

An example of a group with an extreme end phenotype would be patients who have recurrent or multipleperiprosthetic joint infection (PJI). We are interested in identifying geneticsusceptibility causing variants in DNA that may lead to PJI even when all excluding criteria are absent. This approach will be fruitful in identifying susceptibility causing variants for musculoskeletal disorders as well as PJI.

A combination of multidimensional approaches with circumspection is needed in the future. It is important to use a

combination of information from different populations with a large-scale, multiethnic GWAS and interethnic comparison through international collaborative efforts. Next, we must consider gene-environment interactions and keep in mind that disorders with a similar phenotype would be likely to have common susceptibility genes, as is the case for GDF5 rs143383. These shared susceptibility genes would offer clues to novel pathogenesis pathway for common musculoskeletal disorders, which could give rise to the rational approaches to diagnosis and therapy. Next, functional analysis of susceptibility genes related to disorder pathogenesis is critical to identify causal variants and pathogenesis of the disorders. Improved definition of phenotype and reduced misclassification in such a prevalent disorder is demanded to enhance power. Finally, extreme trait sequencing which involves whole exome sequencing of small number of cases versus controls is a promising approach.

In the future, orthopaedicsurgeons should understand genetic predispositions in order to provide updated management, and provide the best advice to patients with prevalent musculoskeletal disorders. The efforts to discover the genetic basis of these musculoskeletal disorders would be an important step in understanding the etiology of those. Finally, by incorporating genetic knowledge and understanding in our diagnostic and therapeutic algorithms we can provide better care and cause promising outcomes.

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