COMMENTARY & PERSPECTIVE

Toward a Genetic Crystal Ball for Patients with Rotator Cuff Disease

Commentary on an article by Elizabeth L. Yanik, PhD, ScM, et al.: “Identification of a Novel Genetic Marker for Risk of Degenerative Rotator Cuff Disease Surgery in the UK Biobank”

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As the population ages, patients desire the ability to remain active. However, injury and degeneration do occur, limiting the activities and satisfaction of patients. All else being equal, some people are more prone to injury and degeneration than others. If clinicians had access to a crystal ball that could help them predict which patients are most vulnerable to musculoskeletal damage or least likely to obtain repair of their injuries, it could transform orthopaedic surgical practice. Genetics represent a molecular crystal ball that permits identification of patients at risk for several biological traits.

In contrast to well-established genetic disorders that cause a range of obvious skeletal malformations, musculoskeletal degeneration only becomes evident with age, and genetic contributions are more subtle. Skeletal tissues are typically less well vascularized and less able to support tissue repair. Hence, degeneration may occur due to (1) time-and-use-dependent accumulation of tissue defects (e.g., macroscopic ruptures or microscopic tears), (2) diminished ability for stem-cell-based tissue healing due to cellular senescence, and (3) deregulation of repair processes that involve chronic cycles of inflammation and/or fibrosis. Tissue homeostasis and repair involve a precisely orchestrated balance between inflammation and stem cell differentiation that each involves multiple actively expressed genes and proteins. Thus, musculoskeletal tissue degeneration undoubtedly has a multifactorial genetic basis. Also, many genes have subtle quantitative rather than qualitative effects on tissue degeneration and repair. Furthermore, it is necessary to assess a lifetime’s worth of disease-modifying factors in each patient that can confound genetic analysis. Therefore, identification of genetic determinants of musculoskeletal degenerative diseases is a daunting task. Although major progress has been made in understanding genetic factors that contribute to bone and cartilage degeneration (e.g., osteoporosis and osteoarthritis), genetic studies that apply sophisticated genomic approaches to skeletal connective tissues and fibrosis remain limited in number.

Rotator cuff disease (RCD) is a major cause of shoulder pain and dysfunction that may have a genetic basis. Yanik and colleagues performed a population-based genome-wide association study (GWAS) of surgery for degenerative RCD in carefully selected cases. To characterize novel genetic markers for RCD, they leveraged the genomic information of approximately 500,000 patients in the UK Biobank, which is demographically biased for older patients (>40 years of age), who are more prone to develop tendon tears. The key finding of the study by Yanik et al. was the identification of single-nucleotide polymorphisms (SNPs) in the intron of the CREB5 gene (cyclic-adenosine-monophosphate [cAMP]-responsive element [CRE]-binding [CREB] protein 5). CREB5 is a transcription factor that contributes to skeletal development and is predicted to regulate genes involved in inflammation and fibroblast function. The key SNPs identified in the CREB5 gene do not map to the protein coding region. Therefore, the CREB5 SNPs may only represent genetic markers for RCD.

Strengths of this genetic study are that entries from the UK Biobank were stringently filtered with specific International Classification of Diseases (ICD) codes and patients were carefully matched. The execution of the statistical analysis and interpretations of the statistical findings both were robust and provide a solid foundation for future studies. The findings from this study on SNPs in the CREB5 gene complement those of several other studies (cited by Yanik et al.) that together identified about 2 dozen other SNPs associated with RCD in other patient cohorts. The main achievement of this work is the definition of novel genetic markers (SNPs) that account for at least some of the genetic variation that contributes to RCD, which is consistent with the polygenic nature of RCD. This excellent study provides a key example of what can and cannot yet be achieved by performing broad genome-wide analyses for degenerative musculoskeletal diseases.

Ultimately, for clinicians who treat a growing number of patients with shoulder pain and dysfunction, having access to a genetic “crystal ball” would inform their practice by predicting patient outcomes after surgery and help with patient management. Additional studies on susceptibility to degenerative RCD would permit conversations with genetically vulnerable patients about...
modifiable risk factors. Most excitingly, identification of genes involved in RCD may allow for development of new pharmacotherapies that would target causative disease-related pathways. The article by Yanik and colleagues represents a principal step toward achieving this challenging goal.

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References