Is Avascular Necrosis a Genetic Disease? A Genome-wide Association Study

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Introduction: Previous research has suggested that a genetic predisposition or epigenetic sensitivity to steroids may exist for patients that develop avascular necrosis (AVN). To identify novel genetic markers associated with AVN susceptibility, we conducted a large genome-wide association study (GWAS).

Methods: Phase I included collection and genotyping of DNA from 88 patients with AVN (50 steroid-induced) and from 176 controls (100 with a positive high-dose steroid history) that were also matched on age, sex, BMI, and ethnicity. Phase II involved incorporating genotype data from previous GWAS studies at our institution which included 102 AVN cases (22 steroid-induced) and 4,125 controls (1,813 with a positive steroid history). Testing was performed to identify differentially expressed single nucleotide polymorphisms (SNPs) in the genome that correlated with disease.

Results: For the entire cohort of Phase I patients, 11 genes contained 2 or greater SNPs that were significant at the $p<10\text{-}5$ level. For the steroid subcohort of Phase I patients, 39 genes contained 2 or greater SNPs that were significant at the $p<10\text{-}4$ level. The gene PPAR-γ was identified in both cohorts and was the focus of subsequent analysis with Phase I and II combination data. PPAR-γ had 7 SNPs significant at the $p<10\text{-}4$ level and 1 SNP significant at the $p<10\text{-}6$ level for the combination data.

Conclusions: To date, this study provides the most comprehensive dataset investigating genetic and epigenetic markers of AVN. PPAR-γ demonstrated several alterations in AVN patients, which is notable given its role in musculoskeletal tissue differentiation as well as lipid metabolism. Furthermore, patients treated with thiazolidinediones for diabetes management, which acts on PPAR-γ, are prone to an AVN-like syndrome, further suggesting a potential role in disease pathophysiology. Subsequent to further validation, these results can serve as the basis for potential risk-stratification diagnostics and pharmaceutical development.