

Unrevealing the Genetic Pathways Involved with Bone Integrity Traits in Poultry

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Abstract:

The intense selection for heavier and faster growing birds led to some negative effects in avian species. As an example, turkeys are unable to reproduce by natural mating, and the amount chickens with locomotor problems have increased. Candidate gene approach, QTL mapping and GWAS have massively been used to identify chromosome regions and genes involved with specific traits. However, many of these studies have limited ability to consider multiple genetic factors that are influencing a particular phenotype of interest. The objective of this study was to integrate results from association studies with a functional annotation tool to investigate the mechanisms of action and pathways involving genes associated with bone-related traits in broilers. Sixteen candidate genes possibly involved with bone-related traits have been partially sequenced by our group for SNP identification in two chicken lines developed by Embrapa. Associations of SNPs with bone-related traits were tested. A gene set enrichment analysis (GSEA) was conducted using DAVID Bioinformatics Resources 6.7 to identify gene interactions and functional pathways. The evaluated genes were: ACTC1, BMP2, BMP3, BMP4, CALB1, CALM, COL1A2, GHRL, IBSP, RUNX2, SMAD1, SOST, SPARC, SPP1, TNFRSF11B, and TNFSF11. Associations were found with at least one bone related-trait ($P < 5.0 \times 10^{-2}$), indicating their importance with the phenotype. When gene-enrichment and functional analyses were conducted, three different gene pathways were significant ($P < 7.6 \times 10^{-2}$) using the KEGG_PATHWAY with the chicken genome background. Bone Morphogenetic Proteins (BMP2 and 4) were directly associated with the Hedgehog signaling pathway, that is linked with the TGF-Beta Signaling Pathway. A molecular interaction in this pathway between BMP2,4 and SMAD are involved in osteoblast differentiation ($P < 1.6 \times 10^{-2}$). The extracellular matrix (ECM)-receptor interaction was the pathway identified between genes COL1A2, IBSP and SPP1, consisting of a complex mixture of structural and functional transmembrane molecules with an important role in tissue and organ morphogenesis and in the maintenance of cell and tissue structure and function ($P < 1.5 \times 10^{-2}$). The ECM has a direct interaction with the Focal Adhesion Pathway, resulting in the regulation of the cytoskeleton and cell proliferation. The pathway involving Calmodulin (CALM) was related with Calcium Signaling Pathway and had an indirect effect on the Focal Adhesion Pathway, being associated as well with reproductive functions. Results from Gene Ontology (GO) identified 14 genes of those 16 studied to be involved with functional biological processes for ossification, bone mineralization and cartilage development ($P < 1.2 \times 10^{-4}$). The results indicate functional interactions among genes associated with bone traits in poultry. The use of pathway analysis incorporates important information regarding behavior and relationship among genes, and could help identifying additional functional candidate genes.