A Polymorphism in the BMP2 Gene is Associated with Whole Skeletal Muscle Volume and Subcutaneous Fat Volume in Caucasian Males

Laura L. Tosi1, Melissa B. Rogers2, Cinzia Brandoli1,3, Heather A. Gordish-Dressman3, Andrew H. Gordon4, Eric P. Hoffman3, Joseph M. Devaney3

1Orthopaedic Surgery and Sports Medicine, Children's National Medical Center, Washington, DC; 2UMDNJ-NJ Medical School, Newark, NJ; 3Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC; 4School of Medicine And Health Sciences, The George Washington University, Washington, DC
cbrandoli@cnmcresearch.org

Introduction: Bone Morphogenetic Protein 2 (BMP2) expression and activity is precisely regulated and is indispensable for normal development and physiology in general, and for bone development and fracture healing in particular. Polymorphisms in both coding and non-coding regions have been associated with changes in bone mineral density and osteoporosis susceptibility, suggesting that alterations in BMP2 activity and/or gene expression may influence bone biology. Several hundred nucleotides within the 3' untranslated regions (UTR) of BMP2 genes from mammals to fishes are extraordinarily conserved indicating that the region is under stringent selective pressure. Biochemical and tissue culture analyses indicate that this region controls BMP2 expression by post-transcriptional mechanisms. Furthermore, an A to C single nucleotide polymorphism (SNP, rs15705) disrupts a putative post-transcriptional regulatory motif (an AU-rich element, ARE) within the human ultra-conserved sequence and destabilizes the RNA in vitro. Specific proteins and potentially micro-RNA bind the A or C allele RNAs with different affinity. We have hypothesized that polymorphisms in or trans-acting regulatory factors that bind this powerful regulatory element might alter BMP2 expression levels and thus be associated with identifiable phenotypes associated with both health and disease.

Materials and Methods: Using DNA samples (blood) and MRI images from the Functional Polymorphisms Associated with Muscle Size and Strength (FMS) study, (a multi-center program designed to study the influence of genetic polymorphisms on bone geometry, fat volume and skeletal muscle size and strength in response to exercise), we sought to identify significant associations between the BMP SNP, rs 15705 and our baseline and training phenotypes. Our genotyping protocol used an allelic discrimination assay that included a specific, fluorescent, dye-labeled probe for each allele. A semi-automated MRI analysis tool, RAPIDIA®, calculated fat, whole arm, whole muscle and bone volumes pre and post a three months exercise protocol. Analysis of covariance (ANOVA) statistical analysis determined significantly different mean levels of the different phenotypes among genotypes.

Results: For the BMP2 variant (+A1123C; rs15705), the C allele was found to be significantly associated with lower baseline subcutaneous fat volume (p=0.012) as well as with greater increases in whole muscle volume (p=0.0081) following resistance training in a cohort of young Caucasian males.

Discussion: BMP2 play critical roles in adipogenesis and osteogenesis. Our study suggests that a non-coding SNP in the BMP2 gene (+A1123; rs 15705) may not only play a role in determining subcutaneous fat volume but may also influence the response of muscle to exercise. Further validations in other populations as well as functional studies are needed. Identifying genetic markers associated with health risks may accelerate the development of clinical tools that facilitate early diagnosis, treatment, and/or prevention of disabling diseases associated with poor fitness.