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**Title:** Insulin-like growth factor binding protein (Igfbp6) is a cross-species transcriptomic tendon marker.

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**Introduction**

Evaluation criteria of bioengineered tendon constructs are unclear partially due to the lack of specific markers of tendon development and differentiation. The aim of this study was to identify a panel of genes that exhibit clearly higher expression in tendon relative to cartilage and muscle and validate them across key model species utilised in tendon research.

**Materials and Methods**

Comprehensive gene expression profiling of rat tendon and cartilage was undertaken using two independent microarray platforms. Illumina RatRef v12 was used for analysing whole tissues while Affymetrix GeneST Rat for isolated primary tenocytes and chondrocytes. Processing of raw gene expression data and differential expression analysis was undertaken using software packages in R. Genes that demonstrated high correlation in expression levels across two studies were validated by qRT-PCR in whole rat tendon relative to cartilage and muscle. Five genes demonstrating the highest expression in validation experiment were selected for further evaluation by qRT-PCR across different musculoskeletal tissues in ovine and equine.

**Results**

Genes that demonstrated the highest tendon expression (log2 fold-change >1.5 ) in both microarray studies, relative to cartilage, included: *Tmnd*, *Serpinf1*, *Igfbp6*, *Cxcl13*, *Cpxm2*, *Mfap5* and *Aspn*. *Meox2*, *Mustn1*, *Thbs4*, *Thbs2*, and *Prrx1* demonstrated more variable expression between the two platforms. Genes showing higher expression in tendon were enriched for functional terms relating to ‘developmental processes’ and ‘extracellular matrix’. In qRT-PCR analysis of rat musculoskeletal tissues, significantly higher expression in tendon was detected for *Cpxm2*, *Myoc*, *Mfap5*, *Serpf1* (p<0.05) and *Aspn*, *Ecm1*, *Igfbp6*, *Tnmd* and *Thbs4* (p<0.001). Only *Igfbp6* and *Tnmd* demonstrated significantly higher expression in the tendon of all species relative to cartilage and muscle.

**Discussion**

The initial pool of tendon gene markers, identified by unbiased transciptomic analysis of musculoskeletal tissues in rat, demonstrated high variability in other model species. Insulin-like growth factor binding protein 6 (*Igfbp6*) was identified as the only universal tendon marker, comparable with that previously recognised; tenomodulin (*Tnmd*). Altered expression of *Igfbp6* has been described previously in animal models of tendon injury and human fibroblasts affected by Duptryen’s disease. *Igfbp6* may be considered a potential reference biomarker for evaluation of tendon physiological function and directed development of engineered tendon.