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Background and objectives Progression of ankylosis in patients with ankylosing spondylitis is highly variable, suggesting that ankylosis is at least partially due to genetic factors. The authors used a murine ankylosing enthesitis mouse model (DBA/1) to search for disease-associated genes and limb bud pellet culture to examine differences in cartilage and bone formation between DBA/1 and BALB/c mice.

Materials and methods Male DBA/1 were crossed with female BALB/c mice. At 26 weeks, histomorphology was examined in male F2 mice from different litters. 159 markers with sequence-length polymorphisms on the autosomes were selected, with a median marker spacing of 6.9 cM. 162 F2 male mice were studied. Genes in regions of interests were linked to skeletal development pathways with the Gene Ontology database. Association was evaluated by χ^2 tests with a False Discovery Rate (FDR) algorithm. Limb bud pellet cultures were prepared from mesenchymal cells isolated from the forelimbs of 11.5 dpc BALB/c and DBA/1 embryos. High-density pellets were cultured in DMEM-F12 or GDF5 for 7 days. RNA was extracted and chondrogenic and osteogenic markers were assessed by qPCR.

Results Incidence of ankylosing enthesitis was lower in the F2 generation as compared to wild-type DBA/1 males (42% vs 72%; p<0.0001). When applying the FDR algorithm for 159 markers, associations with *D3MIT199* and *D3MIT160* were significant (p<0.016). Adjacent markers were additionally genotyped. In the associated region between markers *D3MIT42* and *D3MIT129*, 162 genes were found among which *Bmpr1b, Cxxc4, Lef1, Papss1, Pitx2*, and *Ube2d3*. Only BMP receptor type 1b (*Bmpr1b*) was specifically upregulated in mice with spontaneous arthritis as demonstrated by qPCR. Additionally, Bmpr1b ligand, GDF5, induces differential expression of osteogenic genes in cultures from BALB/c mice as compared to DBA/1 mice. Osterix (OSX), osteocalcin (OC) and bone siaoloprotein (BSP) are all significantly upregulated in BALB/c cultures after 5 days in the presence of GDF5.

Conclusions Using F2 mouse genetics in the analysis of joint ankylosis, The authors identified a locus on chromosome 3 that shows association to disease. Within this locus several genes may play a role in ankylosis, however, our functional data suggests that Bmpr1b is involved. The response to GDF5 in limb bud cultures highlights that differences exist in the GDF5-Bmpr1b pathway in BALB/c and disease-susceptible DBA/1 mice, further corroborating an essential role for BMPs in human and murine ankylosis.

11 PERIPHERAL JOINT ANKYLOSIS IN THE SPONTANEOUS MODEL OF ARTHRITIS IN DBA/1 MICE IS ASSOCIATED WITH A LOCUS ON CHROMOSOME 3 THAT CONTAINS THE BONE MORPHOGENETIC PROTEIN TYPE 1B RECEPTOR

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