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To determine non-HLA-B27 risk genes/variants underlying axial spondyloarthritis

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Keywords

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease, that affects the sacroiliac joints and spine, with inflammation in either gut, eye, and/or skin, and a strong association with the human leukocyte antigen (HLA)-B27 allele. AxSpA affects approximately 1-1.5% (~3.3 million) individuals in the USA. However, 20-30% of axSpA patients do not carry HLA-B27, and most individuals with HLA-B27 remain healthy. Furthermore, genome-wide association studies (GWAS) on ankylosing spondylitis
(AS/radiographic axSpA) have revealed more than 115 disease-associated genes. This in addition to the strong genetic overlap between axSpA and inflammatory bowel disease
(IBD), points towards axSpA being a polygenic disease. Therefore, we aim to determine the risk genes/variants required in addition to HLA-B27 for disease development. To achieve this, we bred disease susceptible HLA-B27 transgenic (Tg) Fischer rats with disease-resistant wild-type DA (Dark Agouti) rats. The F1 litter mixed rats were all susceptible to disease, suggesting the dominant nature of the Fischer alleles. Therefore, we aim to further backcross the mixed F1 HLA-B27 Tg rats with wild-type DA rats to decrease the amount of Fischer genetic contribution and to dissect disease phenotype from HLA-B27. Interestingly, we observed the presence of gut inflammation in WT mixed rats in F2 generations, suggesting that the gut inflammation can indeed be dissected from HLA-B27., and are currently performing backcrosses at F4 generation. This will be followed by whole genome sequencing of HLA-B27 Tg rats with and without the disease to determine risk genes. The resulting risk genes/variants from the rat and GWAS studies will be used to develop targeted gene panel to determine their interplay in axSpA subjects. Thus, the proposed study has the potential to define the additional risk genes/variants required in axSpA, leading to genetic stratification of the disease, and unraveling novel targets for axSpA treatment and prevention strategies.