Association Studies of Intervertebral Disc Disease with Genes in the Aggrecan Degradation Pathway

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You-Qiang Song completed his PhD studies in genetics at the University of Reading, UK. He did postdoctoral training in Prof Peter St George-hyslop's laboratory at the University of Toronto. He joined the University of Hong Kong in 2001. Research at his laboratory is aimed at understanding the molecular basis of human complex diseases, for example, Alzheimer's disease and degenerative disc disease. These complex diseases are caused by the interaction between genes and environmental factors. Using human and mouse models, several new disease genes were identified in his lab.

Low back pain is one of the most common problems seen in clinical and orthopaedic practices. It is usually a result of intervertebral disc degeneration. Sick leave arising from back pain is a significant burden on all industrialized societies. If poorly treated, patients frequently end up with chronic disability and with loss of their working ability. The cause of disc degeneration is not known. Epidemiological studies have suggested genetic factors, increasing age, and certain environmental factors are involved. We have previously established a Southern Chinese population dataset for genetic studies of IVD, diagnosed using magnetic resonance imaging (MRI) and demonstrated the Trp2 allele of *COL9A2* and the t allele of the VDR gene are risk factors for the development and severity of intervertebral disc disease. We also have identified a subgroup of 30 families with early onset (< 30 years) disc degeneration involving multiple members. It is likely that these families have a genetic cause.

In a degenerating disc, the major problem is a reduction in the water content, affecting its ability to resist compressive forces. Aggrecan (AGC1), through its many glycosaminoglycan side chains retains water, and is the major proteoglycan in the extracellular matrix of the intervertebral disc. Impairment in the structural property of aggrecan through enzymatic degradation will contribute to disc degeneration. Aggrecan degradation is thought to be initiated at two major sites of the core protein. A general MMP cleavage site (Asn^{341}-Phe^{342}) that can be cleaved by MMP1, 3, 7, 8, 9 and 13, and an aggrecanase cleavage site (Glu^{373}-Ala^{374}), cleavable by aggrecanase 1 (ADAMTS-4) and 2 (ADAMTS-5). Therefore, genetic variations in these genes of the aggrecan degradation pathway may affect the overall structural integrity of the disc contributing to the degenerative process.

Using this dataset, we performed studies for *MMPs, AGC1* and *ADAMTS-5*. SNP tags of these candidate genes were from HapMap and ABI SNPbrower databases. In addition, we performed a genome-wide scan of early-onset of familial IVD. We shall report our preliminary results for these studies. This work is supported by grants from the Research Grants Council of Hong Kong (HKU7230/01M), (HKU7509/03M) and (AoE/M-04/04).