

The Genetics of Intervertebral Disc Degeneration

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Introduction The molecular basis for degenerative disc disease (DDD) is poorly understood. This study aimed to test the contribution of genetics to DDD in the Southern Chinese population using a case-control approach.

Methods Since 2001, 804 volunteers between the ages of 18 and 55 were recruited from the general population. Symptoms and life-style were assessed by questionnaire, DNA was isolated from blood samples, and DDD was assessed by MRI for each level using the Schneiderman's classification and summated to provide a total DDD score. A DDD score of 0 was defined as no disc degeneration and these individuals were used as controls. Annular tears, disc and end-plate herniations were also objectively graded.

The frequencies of known predisposing genes such as Trp2 and Trp3 alleles in collagen IX; Taq I and Fok I alleles in Vitamin D receptor (VDR); the promoter polymorphism in metalloproteinase 3 (MMP3); as well as an additional 7 polymorphisms in 6 candidate genes (MMP3, MMP8, MMP13, aggrecanase 1, aggrecan and interleukin 1) were determined and correlated with MRI findings.

Results The prevalence of lumbar disc degeneration was 67%, lumbar disc herniation was 30%, annular tears were 30%, Schmorl's nodes was 10% and ossified yellow ligament was 6%. When stratified by age, lumbar disc degeneration was present in 40% of the population between 18 and 30 years, while 85% had disc degeneration by 50 years. Lumbar disc herniations occurred most commonly in the 18 to 30 age group, while the incidence of annular tears increases with age and were present in 33% of individuals between 50 to 55 years. There is no correlation between annular tears or mild disc degeneration with back pain.

The Trp2 allele was present in 20% of the population and was associated with a 4-fold increase in the risk of developing annular tears at

30-39 years and a 2.4-fold increase in the risk of developing DDD and end-plate herniations at 40-49 years. Affected Trp2 individuals had more severe degeneration. The Trp3 allele was absent from the Southern Chinese population.

The t allele of Taq I in VDR gene was significantly associated with DDD, with a relative risk of 2.61. Further subgroup analysis showed that under 40 years of age, the relative risk was even higher at 5.97. Similarly, disc herniation was significantly associated with t allele, with a relative risk of 4.64.

No additional significant associations could be identified in either type IX collagen, VDR, promoter region of MMP3, or the 7 other new polymorphisms.

Discussion

This is the largest-scale population study to date using MRI to precisely define DDD. For the first time, we demonstrated that the Trp2 allele is a significant risk factor for the development and severity of degeneration. The contrasting Trp allele frequencies between Finns and Chinese is the first indication that the genetic risk factors for DDD varies between ethnic groups. In addition, we were also able to demonstrate an age-dependent association between the t allele of VDR Taq I and a higher risk of developing DDD and disc herniation.

Such studies will provide a new angle to understand the underlying mechanism of DDD. Future work will focus on identifying additional candidate genes to test in a case-association study approach, finding early onset DDD families for linkage studies, and to understand the mechanism of disc degeneration using a proteomics approach and transgenic mouse models.

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