Carbohydrate sulfotransferase 3 (CHST3)

An enzyme that catalyzes proteoglycan sulfation, as a susceptibility gene for lumbar disc degeneration (LDD). The strongest genome-wide linkage peak encompassed CHST3 from a Southern Chinese family-based data set, while a genome-wide association was observed at rs4148941 in the gene in a meta-analysis using multiethnic population cohorts. rs4148941 lies within a potential microRNA-513a-5p (miR-513a-5p) binding site. Interaction between miR-513a-5p and mRNA transcribed from the susceptibility allele (A allele) of rs4148941 was enhanced in vitro compared with transcripts from other alleles. Additionally, expression of CHST3 mRNA was significantly reduced in the intervertebral disc cells of human subjects carrying the A allele of rs4148941. Together, our data provide new insights into the etiology of LDD, implicating an interplay between genetic risk factors and MicroRNA [1)].

Their search strategy involved an initial search for linkage and association loci by means of genome-wide approaches in families affected by earlier, and more severe lumbar disc degeneration. It is well known that in complex, multifactorial diseases like LDD, multiple genetic variants may each contribute only a small to moderate effect on disease progression, thus reducing the power of linkage analysis compared with association studies. Thus, focusing initially on families burdened by accelerated and severe disease would theoretically reduce heterogeneity working on the hypothesis that some variants are common within these families. They next focused on utilizing a large genome-wide association study (GWAS) meta-analysis using several population samples to fine-tune regions within significant linkage/association signals.

Their 2-stage approach enabled the filtering of potential false positives and provided a candidate region within chromosome 10. After studying the findings from linkage and association studies on a total of 32 642 subjects consisting of 4043 LDD cases and 28 599 control subjects, they were able to identify carbohydrate sulfotransferase 3 (CHST3), an enzyme that catalyzes proteoglycan sulfation, as a susceptibility gene for LDD. The strongest genome-wide linkage peak encompassed CHST3 from a Southern Chinese family-based data set, while a genome-wide association was observed at rs4148941 in the gene in a meta-analysis using multiethnic population cohorts (5 Japanese, 5 Chinese and 3 Finnish cohorts). rs4148941 lies within a potential microRNA-513a-5p (miR-513a-5p) binding site in CHST3. Interaction between miR-513a-5p and mRNA transcribed from the susceptibility allele (A allele) of rs4148941 was enhanced in vitro compared with transcripts from other alleles. Additionally, expression of CHST3 mRNA was significantly reduced in the intervertebral disc cells of human subjects carrying the A allele of rs4148941.

In theory, it makes sense that CHST3 should be implicated in the pathogenesis of LDD. CHST3 is known to play a key role in proper hydration and function of cartilaginous tissues. The proteoglycan aggrecan is concentrated in disc matrix and chondroitin sulphate glycosaminoglycan side chains are abundant. Appropriate sulfation of glycosaminoglycan side chains is important for water retention to maintain proper osmotic pressure to resist compressive forces within the nucleous pulposus. It seems to follow that activity of CHST3, an enzyme that catalyzes proteoglycan sulfation, would be important for intervertebral disc function, and that mutations of the gene could result in accelerated disc degeneration.

Overall, their data suggest an interplay between genetic risk factors and MicroRNA, and provide new insights into the etiology of LDD. While these results are fascinating, their translation into clinical practice is limited at this time. But, in an effort to one day modify the risk factors of developing LDD, we must first come a long way in understanding the etiology behind the disease. In that sense, the work of Song et al brings us one step closer to that goal, opening up new targets for therapeutic

intervention in the future [2].

[1]
Song YQ, Karasugi T, Cheung KM, Chiba K, Ho DW, Miyake A, Kao PY, Sze KL, Yee A, Takahashi A, Kawaguchi Y, Mikami Y, Matsumoto M, Togawa D, Kanayama M, Shi D, Dai J, Jiang Q, Wu C, Tian W, Wang N, Leong JC, Luk KK, Yip SP, Cherny SS, Wang J, Mundlos S, Kelempisioti A, Eskola PJ, Männikkö M, Mäkelä P, Karppinen J, Järvelin MR, O'Reilly PF, Kubo M, Kimura T, Kubo T, Toyama Y, Mizuta H, Cheah KS, Tsunoda T, Sham PC, Ikegawa S, Chan D. Lumbar disc degeneration is linked to a carbohydrate sulfotransferase 3 variant. J Clin Invest. 2013 Oct 8. pii: 69277. doi: 10.1172/JCI69277. [Epub ahead of print] PubMed PMID: 24216480; PubMed Central PMCID: PMC3809787.

[2]
Gologorsky Y, Chi J. Genetic predisposition to lumbar disc degeneration. Neurosurgery. 2014 Feb;74(2):N10-1. doi: 10.1227/NEU.0000000000000275. PubMed PMID: 24435142.

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