

# 1) TITLE: Polymorphic Variation of the COMT and GCH1 Genes In Patients Undergoing Surgical Treatment For Lumbar Degenerative Disc Disease

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**INTRODUCTION:** Increasing evidence suggests that the experience of pain symptoms related to lumbar degenerative disc disease (DDD) is genetically determined. Two genes that have been linked to pain response seem of particular relevance to DDD: COMT and GCH1. The COMT (catecholamine-O-methyltransferase) gene codes for a critical enzyme in catecholamine metabolism and modulates dopamine, epinephrine, and norepinephrine-mediated neurotransmission as well as  $\mu$ -opioid system responses. COMT demonstrates a common functional genetic polymorphism (*val<sup>158</sup>met*) that, in human studies, appears to affect the response to sustained pain. GCH1, the GTP cyclohydrolase 1 gene, codes for the rate-limiting enzyme in synthesis of tetrahydrobiopterin, an essential cofactor for multiple biosynthetic pathways. Previous studies suggest that polymorphic variation of GCH1 may be associated with variable predisposition to chronic pain.

**PURPOSE/OBJECTIVE:** To determine whether patients presenting for surgical treatment of chronic low back pain due to degenerative disc disease demonstrate genetic variation with respect to COMT and GCH1. To determine whether the distributions of COMT and GCH1 genotypes vary significantly from that predicted for the general population.

**METHODS** Prospective genetic analysis of 100 patients presenting for surgical treatment of lumbar DDD based on clinical evaluation and MRI. Patients were 18 years and older with moderate to severe low back pain unresponsive to at least 6 months of non-operative treatment. A sample of venous blood was obtained from each patient for DNA extraction and sequencing. DNA sequence analysis of COMT was performed with respect to 5 single nucleotide polymorphisms in non-coding regions potentially associated with pain response.

**RESULTS:** The COMT analyses suggested that 5 of 5 COMT loci yielded informative results for the study population. Test for Hardy-Weinberg equilibrium (HWE) revealed 2 loci that diverged significantly from expected distributions. Specifically, carriers of COMT rs6269, (minor allele frequency, MAF, 50%) and rs4818, (MAF 46%) all in strong linkage disequilibrium ( $D'=0.95$ ), were less likely to be homozygous for minor allele and more likely to be heterozygous than expected under HWE. Chi-square analysis for these loci yielded p-values of 0.0488 and 0.0458 respectively.

The GCH1 analyses suggested that 14 of 15 GCH1 loci yielded informative results for the study population. Test for Hardy-Weinberg equilibrium (HWE) revealed 4 loci that diverged significantly from expected distributions. Specifically, carriers of GCH1 rs10483639, (minor allele frequency, MAF, 22%), rs752688 (MAF 22%), and rs4411417 (MAF 22%), all in strong linkage disequilibrium, were less likely to be homozygous for minor allele and more likely to be heterozygous than expected under HWE. In turn, homozygous carriers for minor allele of GCH1 rs12147422 (MAF 14%) were significantly overrepresented among our patients than expected under HWE. Chi-square analysis for these loci yielded p-values of 0.0319, 0.0300, 0.0319, and 0.0002, respectively.

**CONCLUSION:** As a group, patients presenting for surgical treatment of lumbar degenerative disc disease demonstrate significant deviation from HWE for a set of polymorphisms with respect to the pain-modulating genes COMT and GCH1. These results might suggest that allelic variations in COMT and GCH1 result in a predisposition to chronic pain and support results of previous studies in non-spine surgical patient populations.

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