Genetic mechanism helps explain chronic pain disorders

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Researchers at the University of North Carolina at Chapel Hill have discovered that commonly occurring variations of a gene trigger a domino effect in chronic pain disorders. The finding might lead to more effective treatments for temporomandibular joint disorder (TMJD) and other chronic pain conditions.

Catechol-O-methyltransferase (COMT), an enzyme that metabolizes neurotransmitters such as epinephrine, norepinephrine and dopamine and that has been implicated in the modulation of persistent pain, as well as cognition and mood, is regulated by a gene, also called COMT. Previous UNC-led research showed that common genetic variants of this gene are associated with increased pain sensitivity and the likelihood of developing TMJD.

Now, the researchers have discovered that specific variants of the COMT gene can dramatically affect the secondary structure of corresponding messenger RNA - which, in turn, leads to alterations in the amount of enzyme crucial for regulating pain processing. The discovery is published in the Dec. 22 issue of *Science*.

"TMJD is a complex pain condition that is frequently associated with other pain conditions such as fibromyalgia syndrome, chronic headaches and irritable bowel syndrome," said Dr. William Maixner, director of the Center for Neurosensory Disorders in UNC's School of Dentistry and a study co-author.

"This study has identified a new genetic mechanism that influences an individual's susceptibility to develop chronic pain conditions such as TMJD," Maixner said.

The study was conducted to understand the mechanism by which the identified genetic variants influence enzymatic activity and, ultimately, biological functions such as pain transmission. The researchers found that three major variants of COMT show significant differences in how they code for the secondary structure of messenger RNA, or mRNA. The differences lead to dramatic alterations in protein expression, which substantially influences pain sensitivity in humans.

These findings are clinically important because pain conditions resulting from low COMT activity or elevated catecholamine levels are likely to be susceptible to treatment with pharmacological agents that block beta 2- and beta 3-adrenergic receptors, which mediate COMT-dependent pain signaling, or that control mRNA secondary structure.

"Elucidating the genetic mechanisms that mediate pain perception will provide new insights into how chronic pain develops and will ultimately contribute to the identification of unique markers for diagnosing clinical pain conditions, as well as provide novel targets for the development of effective individualized therapeutics for TMJD and related conditions," said Dr. Andrea Nackley Neely, a research assistant professor in the Center for Neurosensory Disorders and the study's lead author.

"These data have broad medical and evolutionary implications regarding the analysis of variants common in the human population," Nackley Neely said. "It is believed that variants leading to altered protein structure have the strongest impact on gene function. However, this study demonstrates that combinations of common genetic variants that influence mRNA secondary structure may have even stronger effects and, thus, represent another key factor responsible for disease onset and

progression."

"This study provides additional evidence of a genetic, molecular and physiological basis for pain perception and human pain conditions and should help to remove the stigma associated with conditions such as TMJD and fibromyalgia," said Dr. Luda Diatchenko, an associate professor in the center and the study's chief investigator.

Other researchers were Dr. Inna Tchivileva, a postdoctoral research associate within the Center for Neurosensory Disorders; Kathryn Satterfield, a former research assistant within the center; Dr. Olex Korchynskyi, a former postdoctoral research associate within the UNC-Chapel Hill School of Medicine's Thurston Arthritis Research Center; Dr. Sergei S. Makarov, a former associate professor at the Center for Neurosensory Disorders and the Thurston center and now president and chief executive officer of Attagene Inc.; and Dr. Svetlana A. Shabalina, a staff scientist with the National Center for Biotechnology Information.

Source: University of North Carolina at Chapel Hill