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Genetic clue to chronic pain could lead to new treatments for the condition

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Chronic pain is a serious medical problem, afflicting approximately 20% of adults. Some individuals are more susceptible than others, and the basis for this remains largely unknown. In a report published online today in *Genome Research*, researchers have identified a gene associated with susceptibility to chronic pain in humans, signaling a significant step toward better understanding and treating the condition.

The degree of pain experienced after injury or surgery is known to be highly variable between patients, even under nearly identical circumstances, prompting researchers to search for the contribution of genetics to chronic pain susceptibility. To accelerate research in this field, animal models are proving to be critical to understanding the underlying biology of chronic pain in human patients.

Recently, using a mouse model of chronic pain, Ariel Darvasi of the Hebrew University of Jerusalem and colleagues identified a region of mouse chromosome 15 that likely contained a genetic variant or variants contributing to pain. However, this region contains many genes and the responsible variant remained unknown.

Darvasi and an international team of researchers have now undertaken two fine-mapping approaches to narrow down the locus to an interval of 155 genes. Then, by applying bioinformatics approaches and whole genome microarray analysis, they were able to confidently identify a single gene, *Cacgn2*, as the likely candidate. This gene is known to be involved in cerebellar function and epilepsy, but a functional link to pain

had not been described previously.

To further test the potential role for *Cacgn2* in chronic pain, the authors utilized a mouse strain harboring a mutant version of the gene that had previously been used in epilepsy research. In testing the mice for behavioral and electrophysological characteristics of chronic pain, they found that, although modest, the observations were consistent with a functional role for *Cacgn2* in pain.

However, the question still remained as to whether the human version of the gene, *CACGN2*, also is important for chronic pain. Analyzing a cohort of breast cancer patients that had undergone removal or partial removal of a breast, they found known genetic polymorphisms in *CACNG2* were significantly associated with chronic pain experienced after surgery. The authors cautioned that although this association will need to be analyzed further, the result is encouraging.

"The immediate significance is the mere awareness that differences in pain perception may have a genetic predisposition," Darvasi explained. "Our discovery may provide insights for treating chronic pain through previously unthought-of mechanisms."

More information: Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, Dorfman R, Abitbul-Yarkoni M, Lu Y, Elahipanah T, delCanho S, Minert A, Fried K, Persson A, Shpigler H, Shabo E, Yakir B, Pisante A, Darvasi A. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res doi:10.1101/gr.104976.110

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