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The shape of things to come

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Variations in pain sensitivity associate with different secondary structures of an enzyme mRNA.

The secondary structure of RNA may be of primary importance to its function. Secondary structure refers to the two-dimensional conformation formed by the base-pairing of nucleotides within an RNA sequence. The resulting folds and loops can aid or impede protein translation. Nackley *et al.* report that sequence variations associated with pain sensitivity affect cellular function by altering mRNA secondary structure in a recent article in *Science*.

The catechol-*O*-methyltransferase (COMT) enzyme breaks down catecholamines, like dopamine, epinephrine and norepinephrine. A single-nucleotide polymorphism (SNP) in COMT has previously been associated with differential performance in a cognitive task and with variations in the opioid response to pain. However, in this study, the authors found that an individual SNP in COMT did not account for differences in pain sensitivity. Instead, four COMT SNPs combined to form haplotypes that associated with low, average and high pain sensitivity.

Each haplotype mRNA had a different secondary structure, as shown by computer programs that fold RNA into energetically optimal structures. All three haplotypes formed stem loops. However, the low pain sensitivity haplotype had the most compact, and the high pain sensitivity haplotype had the most rigid structure. The stability of secondary structures is determined by Gibbs free energy: the less Gibbs free energy, the more stable the structure. The structure of the high pain sensitivity haplotype had less Gibbs free energy than did the structures for average or low pain sensitivity haplotype mRNA, suggesting that it was the most stable.

COMT activity differed among haplotypes. Cells transfected with the high pain sensitivity haplotype showed reduced COMT activity relative to cells expressing low pain sensitivity COMT, and cells expressing the average pain sensitivity haplotype showed intermediate activity compared to the other two COMT variants. Cells transfected with the high pain sensitivity haplotype also showed reduced COMT protein relative to those expressing the low pain sensitivity haplotype.

Would altering the secondary structure of high pain sensitivity haplotype mRNA rescue COMT activity? By mutating a single nucleotide in this mRNA, the authors converted its stable structure to a structure similar to that of the low pain sensitivity haplotype, but maintained the SNPs associated with high pain sensitivity. COMT activity and protein expression did not differ in cells expressing mutated high or low pain sensitivity haplotypes, suggesting that the secondary structure of COMT mRNA in the

high pain sensitivity haplotype impedes protein synthesis and therefore results in reduced enzymatic activity.

People with the high pain sensitivity haplotype were more likely to develop temporomandibular joint disorder than those with low or average pain sensitivity haplotypes, suggesting that haplotypes that alter the secondary structure of RNA may contribute to the susceptibility and progression of common diseases in people. Therefore, researchers should evaluate the secondary structure as well as the primary sequence of genes associated with disease.

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1. Nackley, A. G. *et al.* Human catechol-*O*-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* **314**, 1930–1933 (2006). | Article | PubMed | ChemPort |