Reading the genetic code depends on context

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The so-called central dogma of molecular biology states the process for turning genetic information into proteins that cells can use. "DNA makes RNA," the dogma says, "and RNA makes protein." Each protein is made of a series of amino acids, and each amino acid is coded for by sets of "triplets," which are sets of three informational DNA units, in the genetic code.

University of Utah biologists now suggest that connecting amino acids to make proteins in ribosomes, the cell's protein factories, may in fact be influenced by sets of three triplets - a "triplet of triplets" that provide crucial context for the ribosome. Their results are published in *Proceedings of the National Academy of Sciences*.

The DNA alphabet is composed of four letters: A, C, G and T. DNA sequence can be represented by a series of these four letter combinations such as GCACCACCT, with each letter corresponding to one of the four chemical components of DNA. RNA copies the DNA sequence and communicates it to the ribosome, which reads the sequence and generates the appropriate proteins. Biologists have long accepted that sets of three letters, called triplets or codons, are the fundamental unit of instruction telling the ribosome which particular amino acid to add to the growing protein chain.

"We know it's a triplet code," says biologist Kelly Hughes. "That's been established since 1961. But there are certain things that happen in making protein from RNA that don't quite make sense."

Hughes and Fabienne Chevance worked with a gene in *Salmonella* that codes for the FlgM protein, which is a component of the bacteria's flagellum. A mutation that was defective in "reading" a specific codon in the *flgM* gene only affected FlgM protein production and not other genes that contained the same codon.

"That got us thinking—why is that particular codon in the *flgM* gene affected and not the same codon in the other genes?" Hughes says. "That's when we started thinking about context."

Changing the codon on one side of the defective codon resulted in a 10-fold increase in FlgM protein activity. Changing the codon on the other side resulted in a 20-fold decrease. And the two changes together

produced a 35-fold increase. "We realized that these two codons, although separated by a codon, were talking to each other," Hughes says. "The effective code might be a triplet of triplets."

Hughes and Chevance say that a triplet of triplets code might reframe how biologists study cancer genetics, for example, or other human genetic diseases for which triplet codon context may be more important than previously recognized.

More information: Fabienne F. V. Chevance el al., "Case for the genetic code as a triplet of triplets," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1614896114

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