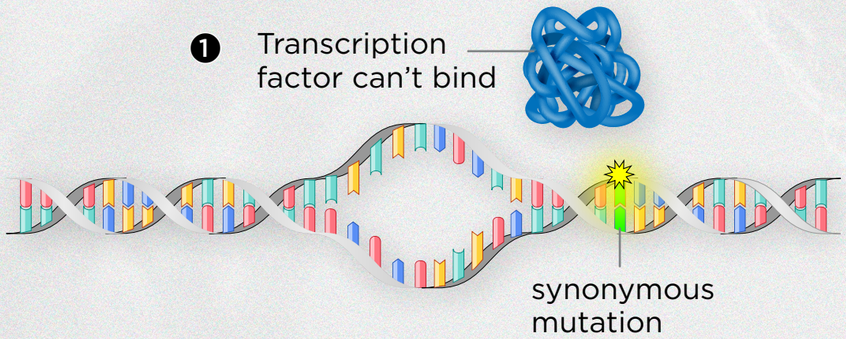
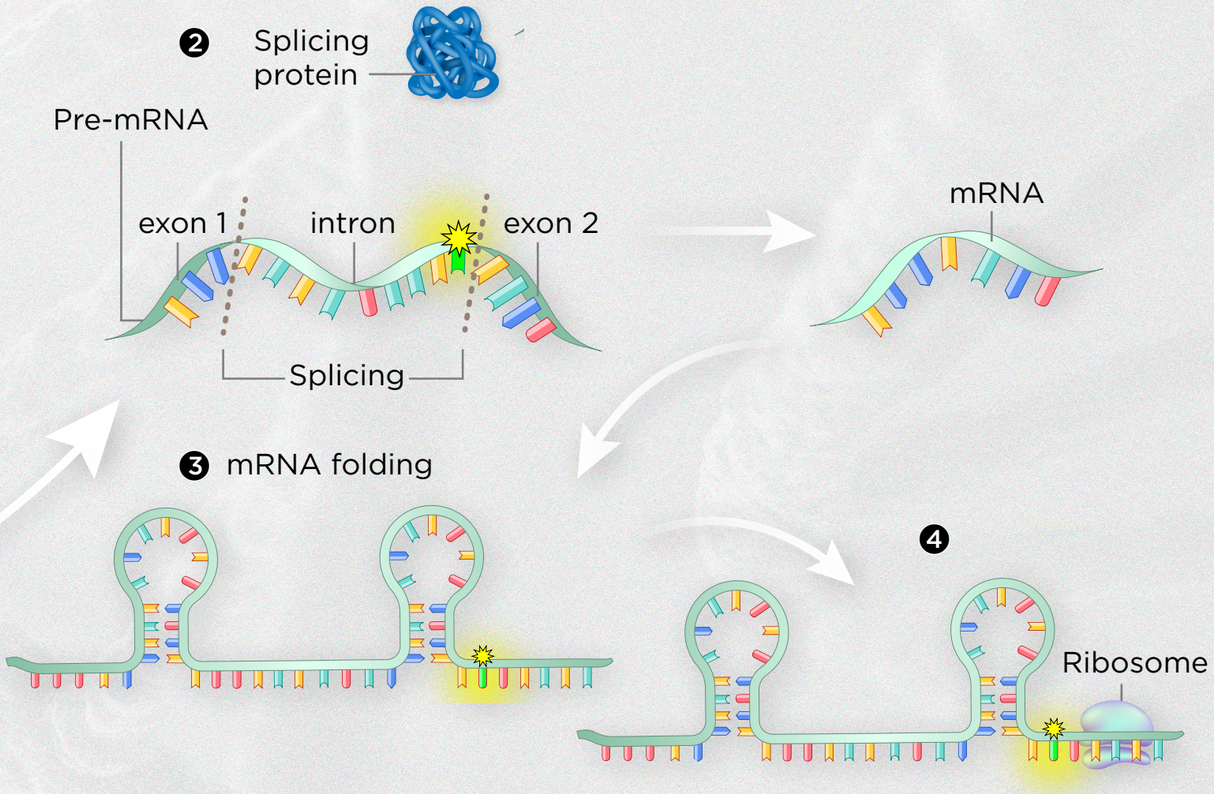
NOT SO SILENT AFTER ALL

Although scientists often assume that synonymous mutations don't cause any biological effects because they don't alter the amino acid sequence, recent research shows that they can influence transcription and translation in a variety of ways.





1 ALTERING REGULATORY BINDING SITES
Although a synonymous mutation may not alter the amino acid sequence of a protein, the change may still affect the binding of regulatory proteins that require specific sequences to interact with DNA. For instance, one not yet published study describes two synonymous mutations in the B-cell lymphoma (BCL2) gene in some lymphoma patients that appeared to prevent the binding of musculin, a transcription factor that represses expression of the gene.

2 DISRUPTING SPLICING PATTERNS
Synonymous mutations can remove binding sites for splicing proteins or create new ones, or change the rate of splicing overall. For instance, one recent study reported a synonymous mutation in the tumor suppressor gene BAP1 in a patient with a severe form of kidney cancer. The mutation likely causes the splicing machinery to miss a key piece of protein-coding DNA, effectively abolishing the protein that would normally help repress tumor growth.

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3 WARPING mRNA STRUCTURE
Chemical interactions between nucleotide bases cause mRNA to fold into three-dimensional structures that determine its overall stability. Synonymous mutations can affect binding sites on the mRNA for proteins and microRNAs, and also disrupt splicing or translation by affecting how the mRNA folds into three-dimensional structures. One 2003 study suggested that a synonymous mutation in the gene encoding the human dopamine receptor D2 makes the mRNA fold into a less stable conformation, causing less of it to be translated into protein.

4 EFFECTS ON TRANSLATION
Synonymous mutations can also influence the speed of translation because the precise codon used determines how quickly it's translated by ribosomes. For instance, one 2016 study reported that a handful of synonymous mutations in the *KRAS* oncogene changed a rare glycine-encoding codon into a commonly used one, potentially accelerating translation. Mutation-carrying cell lines had much higher protein levels than wild type cells and proliferated more quickly.