How do mutations affect STAT proteins?

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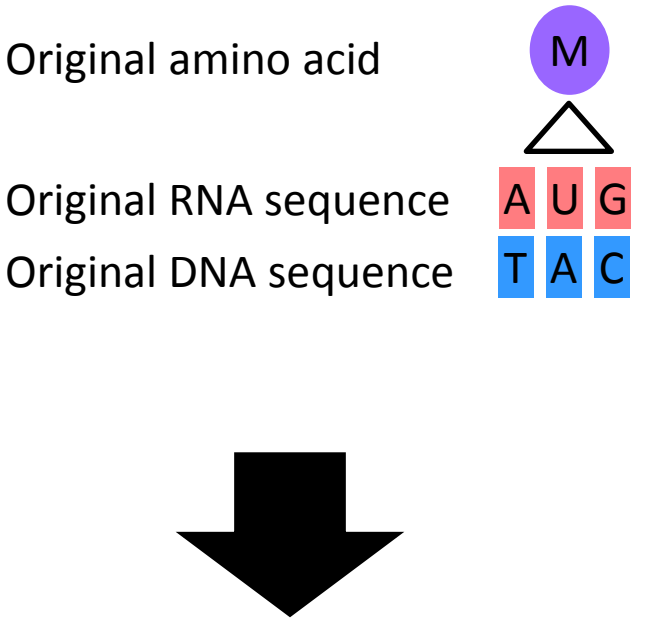

A mutation happens when a nucleotide in DNA is changed. These changes can be present in our DNA from birth (germline) or can be acquired (somatic), such as in a tumor.

In the diagram on the left, the term “original” can be also called “wild type.” This simply means it is the amino acid that most people in a population would have (it is the “normal” amino acid). In this example, the amino acid M (methionine) is the wild type amino acid in this sequence.

The example in this figure shows that the third nucleotide of DNA has changed from C in the original sequence to A in the mutated sequence. The RNA polymerase will incorrectly add a U instead of G due to this change in sequence. In this case, the M (methionine) is changed to I (isoleucine). The amino acids have differing structures, therefore the function of the protein may be altered.

The genetic code is redundant; sometimes the DNA mutation will not lead to an amino acid mutation. Future content will address this concept.

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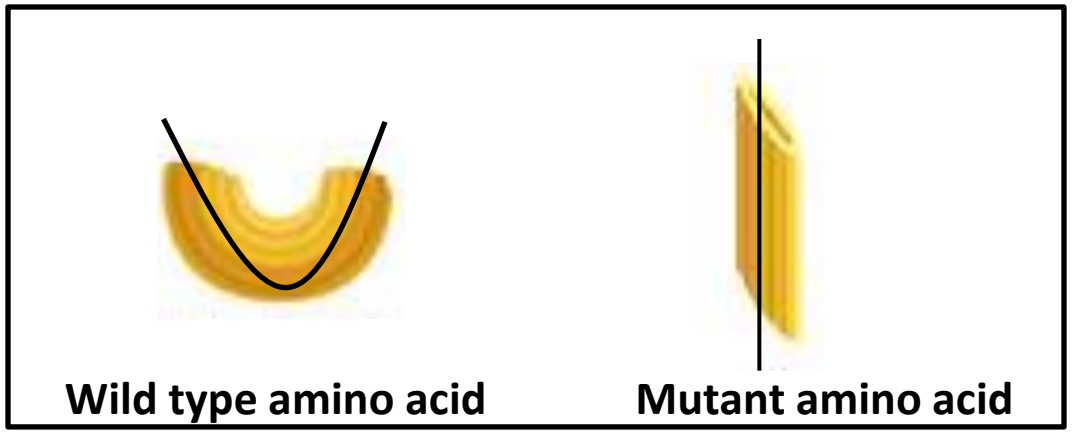
Analogy:

Another way to think of amino acids and how changes in them affect protein function is by using a pasta analogy, where a piece of pasta represents one amino acid. If you had macaroni on a wire, you would be able to bend it based in the shape of the macaroni. If you replaced a macaroni with a ziti, the ability to bend is now different. In our example, the amino acid change from methionine to isoleucine may cause a structural change in the protein. This could affect the protein's ability to function.



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Relevance of STAT mutations in LGL leukemia:

Previous research by Dr. Loughran's lab and collaborators showed that STAT3 and STAT5b are mutated in 30-40% and 2%, respectively, of LGL leukemia patients (Koskela et al 2012 *New England Journal of Medicine* 366:1905-1913, Rajala et al 2013 *Blood* 121(22)4541-4550). For example, one mutation that has been identified is called Y640F. This means that the 640th amino acid in the sequence of STAT3 is changed from an amino acid called tyrosine (Y) to phenylalanine (F). In this case tyrosine (Y) is the wildtype or normal amino acid and phenylalanine (F) is the mutant. This region of STAT3 is where the phosphorylation occurs. STAT3 monomers become phosphorylated and form a dimer which binds DNA and causes transcription. Research by our lab and others suggests that a mutation like Y640F may allow the phosphorylated dimer STAT to remain in dimer form longer, making it active longer. This means it may not be turned off as easily and can continually cause transcription of a gene. STAT3 can control transcription of many genes, so if it is activated for longer periods of time, it can potentially cause continual transcription of its target genes. Patients without the mutation may still have elevated transcription of STAT controlled genes due to higher levels of STATs present, or there could be increased or dysregulated signaling of the pathway. Future content will cover dysregulated STAT signaling and more detailed information about amino acids.

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